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Heart Failure with a Normal Ejection Fraction: Treatments for a Complex Syndrome?

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Opinion statement

Heart failure with a normal ejection fraction (HFNEF) now comprises more than 50% of all patients with heart failure. As the population ages, HFNEF will continue to be a growing public health problem. Recent studies highlight the heterogeneity of this syndrome with regards to underlying pathophysiologic mechanisms. It has been recognized that multiple physiologic domains of cardiovascular function are abnormal in afflicted subjects resulting in a reduced reserve capacity which contributes in an integrated fashion to produce the observed phenotype. Additionally, the realization that differing aspects of this syndrome (e.g. exercise limitations, pulmonary edema and labile blood pressure) likely each have distinct physiologic causes further adds to the complexity. As a result of the heterogeneous nature of the pathophysiologic processes and comorbid illnesses in this population, there is a wide range of clinical outcomes. Accordingly, appreciation of the global nature of HFNEF will ideally better inform optimal design for future diagnostic and therapeutic strategies. Completed clinical trials have not resulted in any evidence-based treatments available for improving survival. Given the disappointing results of these investigations, there has been renewed interest in developing interventions that target underlying comorbidities and peripheral mechanisms. Additionally, non-pharmacologic interventions such as diet and exercise have shown promise in early, small clinical investigations. Finally, methods to more rationally subgroup patients in order to identify cohorts who could respond to targeted intervention are essential. Recognizing the success achieved in the treatment of systolic heart failure, or heart failure with a reduced ejection fraction (HFREF) by addressing neurohormonal and renal mechanisms, new therapies for HFNEF may be achieved by a similar shift in attention away from the heart.

Introduction

Heart failure with a normal ejection fraction (HFNEF) has now supplanted heart failure with a reduced ejection fraction (HFREF) as the most common cause of heart failure, accounting for over 50% of all cases [1–3]. These patients are typically elderly and female, and have a high incidence of medical comorbidities including hypertension, diabetes, renal dysfunction, obesity, anemia, frailty, and coronary artery disease [4–6]. Despite its well-elucidated epidemiology, however, there is still considerable controversy over the pathophysiology of HFNEF.

HFNEF was formerly referred to as *diastolic heart failure*, as many investigators thought the primary disorder was that of diastolic, rather than systolic function [7–10]. Indeed, these patients were noted to have myocardial hypertrophy and interstitial fibrosis associated with

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increased ventricular stiffness and prolonged ventricular relaxation [10]. As such, diagnostic algorithms were generated to evaluate these variables both by cardiac catheterization and non-invasively through echocardiography utilizing patterns of blood flow and tissue velocities [11, 12]. However, these properties have also been noted in patients with HFREF as well as those without heart failure [13]. To confirm the presence of *diastolic dysfunction*, the end-diastolic pressure-volume relation (EDPVR) can be utilized, which should shift upwards demonstrating both elevation of left ventricular end diastolic pressures as well as decreased ventricular capacitance [5]. While precisely this abnormality was presumed to occur in patients with HFNEF, more recent studies have indicated that the majority of HFNEF patients have either no or *rightward* shifting of the EDPVR curve (as do those with HFREF), whereas left and upwards shifts occur in those patients with true diastolic dysfunction (e.g. amyloidosis or restrictive cardiomyopathy) [14, 15]. Moreover, recent investigations examining exercise intolerance in HFNEF patients have concluded that these limitations are likely not due to diastolic dysfunction, but rather are secondary to peripheral, non-cardiac factors [16].

As such, the scope of HFNEF research has broadened in recent years in an attempt to define the pathophysiologic mechanisms that underlie this disease. One of the larger contributing factors to this entity is volume overload and a documented sensitivity to sodium-induced expansion of the intravascular and extravascular space that occur in HFNEF as well as HFREF patients [17, 18]. Such intravascular volume expansion can result in statistically significant differences in left ventricular end diastolic volumes [15, 19, 20]. In one large trial, in comparison to normal subjects, HFNEF patients had markedly greater left ventricular end-diastolic volumes ($145 \pm 40\text{mL}$ versus $67 \pm 12\text{mL}$) [21]. Further, the multiple comorbidities typically found in HFNEF (obesity, renal dysfunction, anemia) are associated with volume overload, and indeed multiple studies investigating human and animal models have indicated that HFNEF patients are chronically volume overloaded despite normal ejection fractions [22–24]. Other potential non-diastolic mechanisms include chronotropic incompetence [25], altered ventriculovascular coupling [14, 26, 27], LA dilation and concomitant atrial systolic failure [28], endothelial dysfunction [17, 29] and altered skeletal muscle oxidative capacity.

Unlike HFREF where evolving medical treatments and treatment regimens have slowed down mortality and hospitalizations, hospitalizations for HFNEF have increased over the past 15 years from 38% to 54% and mortality rates remain high at greater than 50% over 5 years from the time of diagnosis [2]. While pharmacologic treatment is the mainstay of HFREF management, medical therapy has thus far shown no mortality benefit in patients with HFNEF in large randomized controlled trials (Candesartan in Heart Failure-Assessment of Reduction of Mortality and Morbidity [CHARM-Preserved][30], Irbesartan in HF with Preserved EF [I-Preserve][31], Perindopril in Elderly People with Chronic Heart Failure [PEP-CHF][32], Digitalis Investigation Group [DIG-PEF][33], Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure [SENIORS][34]). Only diuretics have demonstrated improvements in quality of life and symptomatic dyspnea, albeit in smaller trials or sub-studies of large randomized controlled trials [17, 35, 36]. With medical therapy showing no clear benefit in this population up to this point, other studies have focused on improving quality of life and minimizing exacerbations through medical comorbidity control and exercise therapy. Indeed, the only current Class I, level of evidence A recommendation for patients with HFNEF at this time is control of systolic and diastolic hypertension [36].

TREATMENT

Diet and Lifestyle

- According to the 2005 ACC/AHA guidelines for the diagnosis and management of chronic heart failure in the adult, reduction of systolic and diastolic blood pressure is the *only* Class I, level of evidence A recommendation for HFNEF management [36].
- Given the high prevalence of medical comorbidities associated with HFNEF and the important role of volume overload in HFNEF exacerbations, dietary and lifestyle changes are central to patient management. This is reflected in the 2010 Heart Failure Society of America Comprehensive Heart Failure Practice guidelines, which recommend dietary instruction for management of medical comorbidities (Grade B evidence) and sodium restriction (Grade C evidence) [1].
- The majority of HFNEF patients are concomitantly affected by obesity, renal dysfunction and insulin resistance, if not frank diabetes. Diet and weight loss through the DASH diet in combination with exercise has been shown to decrease systolic and diastolic hypertension, combat elevated cholesterol, control diabetes, and promote weight loss [37, 38]. Such interventions are actively being pursued in HFNEF.
- In HFNEF patients with EF 50% who were admitted for acute decompensations, a recent study showed decreased odds of 30-day combined death and readmission with sodium restriction to 3g (odds ratio 0.43, 95% confidence interval, 0.24–0.79; $p = 0.007$). This same study noted that HFNEF patients were significantly less likely than HFREF patients to receive discharge recommendations for weight monitoring (33% vs. 43%) and sodium-restricted diets (42% vs. 53%) [39].
- Alcohol in excess has also been linked to elevated blood pressures, and should be limited to 10 – 20 grams per day (one “standard drink” is equal to 13.6g of alcohol; this includes 12oz of beer, 8oz of malt liquor, 5oz of wine or 1.5oz of 80-proof distilled spirits or liquor [i.e. “a shot”]) [40].
- While no prospective studies have examined the impact of smoking on HFNEF, animal studies have reported that myocardial hypertrophy is accelerated in the setting of smoking, and continued smoking has been linked to increased re-hospitalizations and mortality in all types of heart failure [41, 42].
- Due to the significant contribution of medical comorbidities to the development and exacerbation of volume overload and HFNEF and that more than half of the subjects with HFNEF are readmitted because of non-cardiac reasons, their continued management is a critical component of treatment [19, 43].

Pharmacologic Treatment

- Large randomized controlled trials for pharmacologic agents have thus far shown no improvement in mortality for patients with HFNEF. Current recommendations for the use of all medications listed below (except diuretics) are Class IIb, level of evidence C [36].

Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

- Targets of the renin-angiotensin-aldosterone system (RAAS) have intrigued HFNEF investigators for some time, given its prominent role in hypertension myocardial hypertrophy, interstitial fibrosis, and vascular dysfunction [44, 45].

Given the efficacy of angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in patients with HFREF, these drugs were evaluated for their use in HFNEF [46, 47].

- The largest randomized controlled trial investigating ACEIs was that of PEP-CHF, which looked at the effect of perindopril on mortality and hospitalizations in 850 patients > 70 years old with EF > 45% [32]. The study revealed no mortality benefit in HFNEF patients over a median follow-up of 2.1 years, but noted decreased hospitalizations at 1 year (53 vs. 34, $p = 0.033$)
- Two randomized controlled trials were performed to evaluate ARBs. The first, CHARM-Preserved, evaluated candesartan in NYHA functional class II – IV patients with EF > 40% [30]. It revealed no mortality benefits, but an overall decrease in hospitalizations over the 36.6 months of follow-up (230 vs. 279, $p = 0.017$). The more recent I-PRESERVE trial looked at irbesartan in NYHA functional class II – IV HFNEF patients with LVEF < 45% who were > 60 years old, and showed neither a benefit in mortality or hospitalizations when compared to patients not on irbesartan over the course of 49.5 months [31].
- A small study by Warner et al. suggests ARBs may improve exercise tolerance in HFNEF patients. In 20 patients with EF > 50% and echocardiographic evidence of diastolic dysfunction, the addition of losartan to their regimen showed a significant improvement in exercise tolerance versus placebo [48]. It was suggested that perhaps this was secondary to blunted peaks and rate of change of systolic blood pressure during exercise.
- ACEIs and ARBs are encouraged as treatment for the comorbidities associated with HFNEF (e.g. diabetes, renal dysfunction) which are thought to contribute to volume overload and HFNEF exacerbation, however, has little supporting evidence as HFNEF-specific therapy [36].

Beta Blockers

- Beta blockers have been suggested as useful treatments in HFNEF as their rate control effects lengthen diastole and filling time, and thereby mediate against diastolic dysfunction [49]. However, as previously discussed, ventricular overfilling and not inability to fill (e.g. diastolic dysfunction) is a predominant mechanism and as such beta-blocker use in these patients is of unclear benefit.
- In the SENIORS trial, a large randomized controlled trial examining the effect of nebivolol on mortality and hospitalization in patients > 70 years old with a hospitalization for heart failure within the past year or an EF < 35%, a sub-analysis of patients with EF > 35% showed no improvement in the primary outcome of combined mortality and hospitalizations when nebivolol was used versus controls over an average 21 month period [34].
- The ACC/AHA has recommended rate control for HFNEF patients with concomitant atrial fibrillation given its high prevalence in this population (30% – 40%), as well as its association with worse function class, quality of life, 6-minute walking distance, and left atrial enlargement [30, 50]. This is thought to be secondary to increasing heart rates, loss of atrial systole, irregular cycle lengths, and its periodicity in nature [50].
- Conversely, however, chronotropic incompetence is thought to play a central role in the pathophysiologic mechanism of HFNEF, and is a known contributor to decreased exercise tolerance in these patients, calling beta-blocker use into question [17, 27].

- As a HFNEF therapy, beta-blockers have yet to demonstrate a mortality or hospitalization benefit in this population [36].

Calcium Channel Blockers

- Calcium channel blockers were suggested for treatment of HFNEF patients for their rate control effects, but also as a way to increase lusitropy based on reported benefits in those with hypertrophic cardiomyopathy [51, 52]. However, no large randomized controlled trials have examined their efficacy in HFNEF.
- A small study examined the effects of verapamil on 20 male patients, aged 68 ± 5 years old with EF > 45%. It showed a benefit in exercise capacity by 33% and peak filling rates by 30% [53]. However, in addition to the small sample size of this study, the patients examined in earlier studies often unintentionally included younger patients with restrictive or hypertrophic cardiomyopathies [3].
- The benefit of rate control afforded by calcium channel blockers was previously discussed in the beta-blockers section and applies here as well.
- While calcium channel blockers remain a Class IIb, level of evidence C recommendation in HFNEF, no clear benefit has been demonstrated in their use at this time [36].

Diuretics

- Diuretics are a mainstay of symptomatic treatment for fluid overload and acute pulmonary edema in HFNEF patients, and also concomitantly contribute to reduction of elevated blood pressures [17, 35, 36].
- Given the prominent role of volume overload in HFNEF, volume reduction via diuretics (intravenous loop diuretics, in particular) has reproducibly demonstrated reductions in dyspnea and improvement in quality of life [24, 54, 55].
- Sub-analysis of the ALLHAT trial has also shown the benefits of diuretics in preventing the occurrence of HFNEF in patients with hypertension [56]. In comparison with amlodipine, lisinopril, and doxazosin, the hazard ratios of developing HFNEF were 0.69 (95% confidence interval [CI], 0.53 to 0.91; $p = 0.009$), 0.74 (95% CI, 0.56 to 0.97; $p = 0.032$), and 0.53 (95% CI, 0.38 to 0.73; $p = 0.001$), respectively.
- Similarly, thiazide diuretics were investigated in the recent HYVET trial, wherein 3845 patients 80 years old with hypertension were evaluated for the benefits of pharmacologic hypertensive control [57]. Notably, there was a 64% reduction in the incidence of heart failure (95% CI, 42 to 78, $p < 0.001$) in this cohort, although HFNEF v. HFFREF was not delineated. Recall, however, that elderly patients are more typically characteristic of the HFNEF population.
- Concern regarding “overdiuresis” exists within the HFNEF population due to the notable preload sensitivity of patients with true upward and leftward shifts of the EDPVR. This has not borne out in the broader HFNEF population however, as even with aggressive diuresis as is typical of treatment for acute pulmonary edema, the majority of patients do not need blood pressure support [8, 24, 58]. Worsening renal function in HFNEF subjects when prescribed diuretics may be more attributable to alterations in ventricular vascular coupling with age, which has been shown to result in greater alterations in blood pressure in older as compared to younger individuals [59, 60].

- Repeat exposure and chronic diuretic use has been associated with decreased efficacy, residual pulmonary congestion, and electrolyte abnormalities, which can result in increased hospitalizations and mortality [24, 61].

Digoxin

- Digoxin is a well-studied and widely used pharmacologic agent in HFREF. It was historically thought of as contraindicated in patients with HFNEF, however, based solely on anecdotal reports or prior nonrandomized trials [62].
- However, like beta-blockers and calcium channel blockers, digoxin has been postulated to provide potential benefits in those patients with HFNEF and concomitant atrial fibrillation.
- In conjunction with the widely known Digitalis Investigation Group (DIG) study, the DIG ancillary study evaluated digoxin in 988 patients with EF > 45%. There were no significant reductions in the amount of hospitalizations or mortality secondary to heart failure, although trends towards decreased hospitalization and improved exercise tolerance were noted [33].
- As such, according to the ACC/AHA digoxin has not been shown to minimize symptoms of heart failure, and therefore remains a Class IIb, level of evidence C recommendation in HFNEF [36].

Aldosterone Receptor Antagonists

- Despite the absence of data supporting ACEIs and ARBs in HFNEF, the RAAS system has still been of considerable interest in HFNEF treatment, in particular the role of the aldosterone receptor.
- Aldosterone has specifically been associated with renal, vascular, and myocardial fibrosis and is noted as a critical component in resistant hypertension [63, 64]. Further, aldosterone antagonism has shown significant benefit in patients with HFREF [65–67].
- Two large randomized control trials are currently underway to investigate the efficacy of aldosterone receptor antagonists in HFNEF. This includes the TOPCAT trial, which is evaluating 3515 patients with EF < 45%, and the Aldo-DHF trial, which is looking at 420 patients > 50 years old, EF < 50%, NYHA II/III and echocardiographic evidence of diastolic dysfunction [68, 69]. The results of both studies, however, are anxiously awaited.
- Given the lack of evidence in this group of medications thus far, no formal recommendations have been made regarding their use in HFNEF.

Interventional Procedures

Percutaneous Coronary Intervention and Coronary Artery Bypass Surgery

- The link between coronary artery disease and HFNEF has been well established, but its role remains controversial [70, 71]. Some studies support the role of myocardial ischemia resulting in increased stiffness and upward shifting of the EDPVR curve [72, 73]. Others suggest that HFNEF represents early compensation for myocardial dysfunction which ultimately progresses into HFREF, the initiators of which are coronary artery disease and myocardial infarction [74–76].
- Kramer et al examined 46 patients hospitalized with flash pulmonary edema in the setting of poorly controlled hypertension. It was noted that recurrence of pulmonary edema (or death) was not only similar between patients with ejection

fractions less than and greater than 40%, but also between those patients who were and were not revascularized despite the presence of coronary artery disease [77].

- As such, the ACC/AHA recommends pursuit of revascularization if symptomatic myocardial ischemia is judged to be contributing to the worsening of cardiac function in HFNEF patients [36], however, no long-term randomized investigations have been performed for this specific population.

Aortic Valve Replacement

- It is well established that the development of heart failure in aortic stenosis portends a poor prognosis, with a median survival of 2 years [78].
- Approximately 60% of these patients develop heart failure with a preserved ejection fraction (> 50%), thought to be due to myocardial hypertrophy and the deterioration of ventricular compliance [79, 80].
- According to the ACC/AHA, in the setting of severe aortic stenosis (aortic valve area < 1.0cm², mean aortic valve gradient > 40mm Hg, or aortic jet velocity > 4.0m/s), symptomatic HFNEF should be managed with aortic valve replacement [81, Class I]. Symptom and survival improvement are similar to those patients with reduced ejection fractions.
- For those patients with severe aortic stenosis, HFNEF and paradoxically low flow states, prognosis has actually been shown to be worse when compared to HFNEF patients with normal flow states. One study looked at 331 patients with EF > 50% and an aortic valve area < 0.6cm², and it was noted that low flow states were associated with lower 3-year survivals (76% v. 86%, p = 0.006) [82].
- Transcatheter aortic valve replacement (TAVR) is an evolving therapy for aortic stenosis. Although no studies have examined outcomes in HFNEF patients specifically, subgroup analysis of patients with high-risk aortic stenosis and EF > 55% show no difference in survival whether undergoing TAVR or surgical replacement [83].
- HFNEF is not only relegated to aortic stenosis, but may also be seen in aortic insufficiency. While mortality rates of >20% annually have been reported for patients with aortic insufficiency, these studies did not measure LV function specifically, and therefore the effect of EF on prognosis is unclear [84, 85]. However, subsequent data has shown poor outcomes for medically treated patients regardless of EF [86, 87].
- Like severe aortic stenosis, in symptomatic aortic regurgitation, aortic valve replacement is indicated regardless of ejection fraction [81, Class I].

Physical/speech therapy and exercise

- Exercise intolerance (manifested by exertional dyspnea, fatigue, or anergia) in HFNEF patients is not only the most common symptom of HFNEF, but is also a cause of decreased quality of life and a predictor of mortality [2, 19, 88, 89].
- It has been demonstrated that peak exercise oxygen uptake (VO₂) is a valid and reproducible target for assessing exercise intolerance in patients with heart failure, and notably is consistently decreased in HFNEF patients compared with age-matched healthy volunteers, and to a similar degree as in HFREF [16, 90]. This is further compounded by the observation that VO₂ declines by up to 10% per decade in health older adults [91, 92].

- The decline in VO₂ could be secondary to either a decreased CO or a decline in arterial-venous extraction, as predicted by the Fick equation. The declines in CO with exercise have been postulated to result as result of a blunted chronotropic response, whereas decreases in the arterial-venous extraction has been attributed to multiple potential sources including impaired peripheral vascular function and/or musculoskeletal function [16].
- A recent study noted benefits of 16 weeks of exercise training performed 3 days a week in 53 HFNEF patients aged 70 ± 6 years old. Specifically, when compared to controls, these patients had significantly better VO₂, peak power output, exercise time, 6-minute walk distance, and ventilator anaerobic threshold [88]. Of note, there was also a significant improvement in physical aspect of the quality of life score, but not in the total. Similar studies by Gary et al [93] and Smart et al [94] have also demonstrated improvements in exercise tolerance, as well as quality of life in conjunction with exercise therapy. The increase in VO₂ in this cohort was predominately mediated by peripheral effects and not changes in CO with exercise.
- Exercise training can therefore be utilized with symptomatic benefit as well as improvement in quality of life in the HFNEF population.

Emerging therapies

- The benefit of cardiac resynchronization therapy (CRT) in HFREF is well established in those with mechanical and electrical ventricular dyssynchrony [95, 96]. However, the role of the aforementioned in HFNEF is only now being examined as a potential therapeutic target, with small studies suggesting that it is less prevalent than in HFREF, but is still significant [97, 98]. Currently, the KaRen study is being conducted to evaluate potential CRT benefits in the HFNEF population [99].
- Given the greater activity of the sympathetic nervous system in the elderly, and its contributions to hypertension, renal dysfunction, vascular stiffness, and myocardial ischemia, its role in HFNEF is currently under evaluation [100]. The Rheas system, an implantable electrical device linked to the carotid baroreceptor, is currently being studied to determine if this system can impact outcomes in HFNEF patients. Prior studies have already shown benefit in reducing arterial pressures, heart rate, and left ventricular mass [101].
- Similarly, there has been an increasing focus on renal sympathetic innervation, as it is linked to the renal vasculature, tubules and juxtaglomerular apparatus and consequently to sodium reabsorption and the RAAS [102]. Some experiments have utilized renal denervation in resistant hypertension and shown favorable changes in blood pressure, renal function and cardiac hypertrophy. The SIMPLICITY-HTN3 trial is currently ongoing to evaluate radiofrequency ablation in resistant hypertension, but may have use in HFNEF in the future.
- Given the prominent role of hypertension in HFNEF, the RESPeRATE device may also prove to have some benefit. This device utilizes biofeedback in combination with slower respiration rates to manipulate cardiac and pulmonary sympathetic outflow to decrease blood pressure. Preliminary studies have shown reliable decreases in both systolic and diastolic blood pressures and may ultimately show benefit in HFNEF patients [103].

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