Published in final edited form as:

J Card Fail. 2009 September ; 15(7): 561–564. doi:10.1016/j.cardfail.2009.04.004.

Heart Failure with a Normal Ejection Fraction (HFNEF): Embracing Complexity

Mathew S. Maurer, MD

Department of Medicine, Division of Cardiology, Columbia University Medical Center, New York, New York

During the two hours allotted for rounds, my co-attending and I[†] had eight new admissions to review with the housestaff on the cardiology service. The medical students, interns and residents began their well orchestrated presentations delineating the chief concerns and what led up to our new patients need to search out our services; exams findings were highlighted and the litany of previous non-invasive testing either previously performed or planned was outlined. The house officers and students seemed genuinely happy to have me there, as six of the admissions were admitted for decompensated heart failure and four had preserved systolic function. While my co-attending seemed surprised at the magnitude of the heart failure epidemic, I was not. Not only have patients with acute decompensated heart failure overwhelmed our cardiology units, but the phenotype has changed. During the time between his training (mid 1980s) and now, we have seen that the percentage of patients admitted with heart failure and a normal ejection fraction (HFNEF), increase from ~30% of all cases of heart failure to >50%.¹ While our new patients shared some similarities, they were older adults (mean age of 77 years), mostly women and had ejection fractions of >45%, that is where one's ability to recognize a pattern ended. Indeed, what was most striking was the phenotypic heterogeneity.

Geriatricians have long recognized the striking heterogeneity found among chronically ill older adult persons with respect to physiologic function in addition to health status, belief systems, cultural and ethnic backgrounds, values, and personal preferences. It is often stated as "if you seen one octogenarian, then you have seen one octogenarian" and nothing could be more true of older adults with HFNEF. The clinical heterogeneity suggests that multiple pathophysiologic mechanisms underlie the development of the phenotype. Not only is HFNEF a common and progressive condition, it also has its underpinnings develop decades before the clinical manifestations are apparent.^{2, 3} Indeed the differences between individuals are manifested not as much by the presence or absence of a condition such as HFNEF but by the presence of other contributing conditions that affect the progression (see Figure 1). By the end of rounds, we had concluded that too little is known about potential differences among clinical subgroups of the syndrome we called heart failure with a normal ejection fraction and how we could alter the trajectory of its course.

Address for correspondence: Mathew S. Maurer, Clinical Cardiovascular Research Laboratory for the Elderly, Columbia University Medical Center, Allen Pavilion of New York Presbyterian Hospital, 5141 Broadway, 3 Field West Room 035, New York, N.Y. 10034, Phone: (212) 305-9808, Fax: (212) 305-7439.

[†]The Department of Medicine at Columbia University Medical Center has maintained a two attending system for rounds despite the time and financial pressures of modern medicine. For the attendings, this remains one of the best experiences as it provides for exchange of ideas and ongoing professional development.

What did we agree upon?

While there has been much healthy debate into the underlying pathophysiologic mechanisms^{4, 5} and a renewed interest in defining these factors^{6–10}, we acknowledged that we don't do a very good job of managing this condition. As highlighted by Hummel and colleagues in this issue of the *Journal of Cardiac Failure*¹¹, patients with this condition whose average age was 74 years have a high mortality (>50% at five years), with a significant proportion dying from cardiovascular causes. Perhaps even a greater burden to the patients, their caregivers and the healthcare system is the high recidivism rate at which they return to the acute care setting with recurrent or worsening symptoms.¹² Indeed national data suggests that ~20–50% of Medicare beneficiaries are readmitted within 6 months, and at the top of the list are older adults with heart failure.¹³ If this was a test that we faced in medical school, we all agree that a 60–70% success rate simply wouldn't cut it.

We discussed the new terminology used to delineate this syndrome, “heart failure with a normal or preserved EF” or “heart failure with normal or preserved systolic function” that had replaced the former term “diastolic heart failure”. While the latter rolled off the tongue more easily, the newer terms highlight the need to be open minded about the multitude of potential therapeutic targets that include both diastolic and non-diastolic mechanisms (see Table) as we evaluate patients with this clinical. The need for the name change is highlighted by the high prevalence in this population of co-morbid conditions that can impact on myocardial systolic, ventricular, vascular, renal, and extra-cardiovascular properties, on outcomes, and on symptoms not related to diastolic ventricular properties; these co-morbid conditions include hypertension, diabetes, coronary artery disease, obesity, renal dysfunction, and anemia.

Finally, we agreed that recent large scale clinical trials for this population have not demonstrated effectiveness of any specific therapy. Indeed the recent reported clinical trials of I-Preserve¹⁴, PEP-CHF¹⁵ and CHARM-Preserve¹⁶ have failed to demonstrate significant benefits in terms of hard endpoints for this population. These therapies were tested on the belief that some of the same strategies used in systolic heart failure would be beneficial for those with HFNEF. We acknowledged that that belief was based largely on assumptions, and most of our patients that morning with HFNEF were already receiving treatment for hypertension with the standard therapies used for systolic heart failure. Most important, we concluded that without a better understanding of the pathophysiology of HFNEF, opportunities for novel and ideally more effective strategies could be missed.

What is still left to do?

In short, a lot!! Others have highlighted the difficulties in recruiting and retaining older adults with multiple complex co-morbid conditions in clinical trials.¹⁷ Designing novel methods for assessing the impact of interventions is required. We thought that collaboration with our geriatric colleagues on methodologies including bringing research to non-traditional settings such as the home and long term care settings might accomplish our mutual goals.¹⁸

Recognizing the success achieved in the treatment of systolic HF by addressing neurohormonal and renal mechanisms, new therapies for HFNEF were likely to be achieved by a similar shift in attention away from the heart. It is plausible that addressing non-diastolic mechanisms of HFNEF may provide further answers and, more importantly, lead to more therapeutic advances. Enthusiasm was initially high for using clinical tools to rationally subgroup patients based on operative pathophysiologic mechanisms. Nevertheless, despite the multitude of patients admitted and readmitted with this clinical syndrome they are rarely subjected to exercise testing or, invasive hemodynamic monitoring and

endomyocardial biopsy is rarely performed. Given the unknown yield of these tests, how they might impact on diagnostic probabilities and/or aid in prognosis, these gaps in knowledge, coupled with the complexity added by the frail nature of the population, has resulted in a profound uncertainty about the value of invasive testing. However, what about all the non-invasive tests that already are being performed? Is there potential but overlooked value in the data already being collected as part of routine clinical care?

In this issue of the Journal of Cardiac Failure, Hummel et al¹¹, demonstrate a routine pre-discharge EKG can add to our prognosticating the outcomes of patients with HFNEF regarding subsequent mortality. The strengths of the study are the large, representative sample size and the near complete ascertainment of data for all variables included in their model. Despite the limitations of this analysis, the authors have directed us in an interesting a potentially worthwhile direction. The finding that a prolonged QRS duration among subjects with HFNEF is an independent predictor of long term mortality provides a simple and easily obtainable prognostic marker. This is one of multiple risk factors that in the proposed susceptibility model (see figure 1) fits prevalent health problems such as HFNEF. In this model, as risk factors are modified, the slope of the progression is decreased. As the slope decreases, the date of crossing the symptomatic threshold can be postponed, perhaps indefinitely, the severity of symptoms experienced can be decreased; and death due to the disease can be delayed or possibly even prevented;

While the association of a prolonged QRS with subsequent mortality was strong and consistent across multiple subgroups it was more predictive in those <75 years of age. This may reflect the fact that prolonged QRS is a specific marker of an increased risk of cardiac mortality. However, as recent data suggest the leading cause of death in patients with HFNEF is non-cardiovascular,¹⁹ the utility of this variable could be limited in the oldest patients. For such patients, the goal is often not extension of life, but rather the intense focus on the preservation and restoration of function. When questioned about fears of growing old, older adults usually do not cite fear of death, but rather they describe a dread of chronic illness, intractable symptoms and an inability to physically get around that can result in a state of total dependence upon others. These are relevant endpoints for our therapeutic endeavors. The paradigm of preservation of vitality with the consequent compression of morbidity into a shorter period prior to the end of life, offers a framework within which to view the syndrome of HFNEF and within which we may begin to develop some effective interventions that can alter the rate of decline in such patients (Figure 1).

Perhaps most intriguing about the findings of Hummel and colleagues, is not that QRS duration is an independent predictor of subsequent mortality but that it might point to an underlying life threatening mechanism that if identified could be a target for intervention. The authors propose that ventricular dyssynchrony, infiltrative diseases, fibrosis and concomitant coronary artery disease could be explanations for the excess risk attributable to a prolonged QRS. Those risks could be modifiable. The therapeutic challenge then is to identify modifiable mechanisms, as well as to prevent any entrenchment by initiating therapeutic interventions early in adult life and continuing them throughout life.

Heart failure cardiology is a cognitive discipline. Accordingly, as cognitive cardiologists we need to embrace the complexity underlying the syndrome of HFNEF. Identifying distinct subgroups of patients with HFNEF based on phenotype is potentially vital, because the mechanism(s) of disease, prognosis and optimal treatment can differ between groups. Until this is disproved, it is important to continue the search for underlying mechanisms and prognostic factors that contribute to the morbidity and mortality of the HF syndrome in the setting of preserved systolic function, especially for the purpose of clinical intervention and

future clinical trials. Many effective therapies might be deemed a failure because they are not applied to the appropriate population.

The underlying premise of this commentary is that the practice of the heart failure specialist and geriatric medicine are more similar than distinct. They both represent more than caring for old people; both involves a mind-set, a way of thinking that can be incorporated into clinical practice to improve the health and well-being of patients with HFNEF taking into consideration its relation to the life course and its complex causes, mechanisms, progression and outcomes.

Reference List

1. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006 July 20;355(3):251–259. [PubMed: 16855265]
2. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a "set up" for vascular disease. *Circulation* 2003 January 7;107(1):139–146. [PubMed: 12515756]
3. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part II: the aging heart in health: links to heart disease. *Circulation* 2003 January 21;107(2):346–354. [PubMed: 12538439]
4. Burkoff D, Maurer MS, Packer M. Heart failure with a normal ejection fraction: is it really a disorder of diastolic function? *Circulation* 2003 February 11;107(5):656–658. [PubMed: 12578861]
5. Maurer MS, King DL, El-Khoury RL, Packer M, Burkoff D. Left heart failure with a normal ejection fraction: identification of different pathophysiologic mechanisms. *J Card Fail* 2005 April; 11(3):177–187. [PubMed: 15812744]
6. Lam CS, Roger VL, Rodeheffer RJ, et al. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota. *Circulation* 2007 April 17;115(15):1982–1990. [PubMed: 17404159]
7. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure--abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med* 2004 May 6;350(19):1953–1959. [PubMed: 15128895]
8. Melenovsky V, Borlaug BA, Rosen B, et al. Cardiovascular features of heart failure with preserved ejection fraction versus nonfailing hypertensive left ventricular hypertrophy in the urban Baltimore community: the role of atrial remodeling/dysfunction. *J Am Coll Cardiol* 2007 January 16;49(2):198–207. [PubMed: 17222731]
9. Borlaug BA, Melenovsky V, Russell SD, et al. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. *Circulation* 2006 November 14;114(20):2138–2147. [PubMed: 17088459]
10. Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. *Circulation* 2003 February 11;107(5):714–720. [PubMed: 12578874]
11. Hummel SL, Skorcz S, Kollering TM. Prolonged electrocardiogram QRS duration independently predicts long-term mortality in patients hospitalized for heart failure with preserved systolic function. *J Card Fail*. 2009
12. Bhatia RS, Tu JV, Lee DS, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med* 2006 July 20;355(3):260–269. [PubMed: 16855266]
13. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. *N Engl J Med* 2009 April 2;360(14):1418–1428. [PubMed: 19339721]
14. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 2008 December 4;359(23):2456–2467. [PubMed: 19001508]
15. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 2006 October;27(19):2338–2345. [PubMed: 16963472]

16. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003 September 6;362(9386):777–781. [PubMed: 13678871]
17. Lee PY, Alexander KP, Hammill BG, Pasquali SK, Peterson ED. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. *JAMA* 2001 August 8;286(6):708–713. [PubMed: 11495621]
18. Norris SL, High K, Gill TM, et al. Health care for older Americans with multiple chronic conditions: a research agenda. *J Am Geriatr Soc* 2008 January;56(1):149–159. [PubMed: 18047493]
19. Henkel DM, Redfield MM, Weston SA, Gerber Y, Roger VL. Death in Heart Failure: a Community Perspective. *Circ Heart Fail* 2008 July 1;1(2):91–97. [PubMed: 19300532]
20. Fries JF. The Compression of Morbidity. *The Milbank Quarterly* 2005;83(4):801–823. [PubMed: 16279968]

Figure 1.

Panel A: Model of Chronic Disease such as HFNEF, in which risk factors that cause/contribute to syndrome are characterized by early age of onset, progression at various rates, and pass a symptomatic threshold at which time a clinical diagnosis is made. Factors such as a prolonged QRS are adverse prognostic markers while effective interventions alter the progression in a favorable manner. Panel B and C: Compression of Morbidity in HFNEF can be realized in which by delaying or eliminating contributing/causal factors, the period of adult vigor prior to infirmity is prolonged in the panel C as compared with B. (Modified from Fries JF20)

Table 1

Differential diagnosis of mechanisms and factors contributing to heart failure in the setting of normal ejection fraction (HFNEF)

Diastolic heart failure (DHF)
Restrictive cardiomyopathy
Infiltrative cardiomyopathy
Amyloid
Hemochromatosis
Hypertrophic cardiomyopathy
Hypertensive Heart Disease
Hypertensive heart disease with myocardial factors not related to diastolic dysfunction
Subclinical myocardial systolic dysfunction with neurohormonal activation
Volume Overload State with the following causal or contributing factors:
Chronic Renal Dysfunction
Diabetes
Salt/Water Handling Abnormality
Anemia
Obesity
Ventricular Vascular Coupling Abnormality
Excessive Venoconstriction
Chronotropic Incompetence
Right heart failure
Primary (precapillary pulmonary hypertension)
Right ventricular infarct
Arrhythmogenic right ventricular dysplasia
Atrial septal defect
Pericardial disease
Cardiac tamponade
Constrictive pericarditis
Intracardiac mass
Atrial myxoma
Pulmonary vein stenosis
Valvular heart diseases
Significant valvular stenosis
Significant valvular regurgitation