DIAGNOSIS OF HEART FAILURE WITH PRESERVED EJECTION FRACTION

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INTRODUCTION

Heart failure (HF) remains a major public health problem and significant burden for patients and health care providers in most parts of the world.[1] HF is commonly classified as "diastolic" (preserved ejection fraction) or "systolic" (reduced ejection fraction), and currently heart failure with preserved or normal ejection fraction (HFNEF) accounts for more than 50% of all HF patients.[2,3] Although the revised American College of Cardiology/American Heart Association guidelines for the diagnosis and management of HF adopted the term "heart failure with preserved" or normal "ejection fraction" rather than "diastolic HF,"[4] the later term is still preferred by several investigators and certainly prevails in current diagnostic billing codes. Both terms are used interchangeably in our own institution.

Recent clinical studies have provided sufficient data to develop standardized diagnostic criteria to define HFNEF.[1,5,7] HFNEF is a clinical syndrome characterized by symptoms and/or signs of fluid retention with preserved left ventricular (LV) ejection fraction and evidence of abnormal diastolic function. The purpose of this article is to provide perspective on the clinical and diagnostic (nonechocardiographic) aspects of HFNEF.

CLINICAL ASPECTS OF HFNEF

Proposed Diagnostic Criteria

Recently, the European Society of Cardiology published revised criteria for the diagnosis of HFNEF (Table 1). Similar to the criteria published by Vasan and Levy (Table 2), the European criteria mandate objective documentation of clinical congestion, preserved LV systolic function, and evidence of abnormal LV diastolic function. Multiple consensus documents propose an LV ejection fraction >50% as a cut-off for normal or mildly abnormal systolic function.[5,6,8] Although echocardiography has assumed the primary role in the noninvasive assessment of LV systolic function and volume, acceptable alternatives include cardiac radionuclide ventriculography and cardiac magnetic resonance (CMR) imaging.

In contrast to the Vasan and Levy criteria, the European criteria recommend excluding concomitant LV enlargement (LV end-diastolic index <97 ml/m^2) in the presence of preserved LV systolic function and include echocardiographic indices, alone or in combination with biomarker elevation (NT-proBNP and BNP), and cardiac catheterization as acceptable evidence of LV diastolic dysfunction.[5] While it is true that patients with HFNEF have normal or even small LV volume,[9] the criteria proposed by Vasan and Levy provide a framework for developing a "consensual standard" for HFNEF that is applicable in routine clinical practice, epidemiological studies, and clinical trials.

A recent study by Zile et al. applied the proposed Vasan and Levy criteria for

European criteria to diagnose heart failure with preserved ejection fraction. All three criteria are required for the diagnosis of HFNEF.5
1) Clinical symptoms or signs of heart failure
2) Normal or mildly reduced LV systolic function and normal LV chamber size (LVEF >50% and LVEDVI <97 ml/m2)
3) Evidence of abnormal LV relaxation, filling, diastolic distensibility, and diastolic stiffness: invasive hemodynamic measurements: a) pulmonary capillary wedge pressure >12 mmHg, or left ventricular end-diastolic pressure >16 mmHg, or b) time constant of LV relaxation (tau) >48 msec, or c) diastolic LV stiffness modulus >0.27, or d) echocardiographic data alone or combined with biomarkers

Table 1. Revised criteria for the diagnosis of HFNEF published by the European Society of Cardiology. Multiple consensus documents propose an LV ejection fraction >50% as a cut-off for normal or mildly abnormal systolic function.[5,6,8]

definite HFNEF; using cardiac catherizarion, they demonstrated abnormal active relaxation and increased passive stiffness as the predominant pathophysiologic cause of HF in those patients.[10] Although there is an almost uniform presence of elevated ventricular filling pressures and abnormal filling patterns as detected on Doppler echocardiography in patients with HFNEF,[12,20] the European Cardiology Society's recommendation of including noninvasive indices ω confirm diastolic dysfunction remains controversial. Some authorities believe that the diagnostic Doppler abnormalities seen in patients with HFNEF mainly reflect elevated LV filling pressures and not the specific underlying intrinsic myocardial diastolic abnormalities that define this patient population.[11]

Patient Characteristics

Multiple studies have examined the clinical features of patients with HFNEF (Table 3).[2,3,6,12,19] A significant percentage of these patients are women and are relatively older (mean age 73 years). Compared to patients with systolic HF, patients with HFNEF are more likely to have a history of hypertension and atrial fibrillation - two clinical features that are common precipitants of acute decompensation. In the largest placebo-controlled, morbidity-mortality trial to date in patients with HFNEF (I-PRESERVE), approximately 80% were overweight or obese, and between 25-33% had diabetes.[18] While coronary artery disease is a major cause of systolic HF with reduced ejection fraction, several studies cite prior myocardial infarction as less common in patients with HFNEF. However, it remains important to determine the contributing etiologic mechanisms in HFNEF (LV hypertrophy and/or ischemia) ω target treatment at the underlying cause.

The earliest manifestations of HFNEF, dyspnea on exertion, paroxysmal nocturnal dyspnea, and orthopnea are due to pulmonary congestion and are similar to those of systolic heart failure.[1] Data from the two largest registries of hospitalized patients with HFNEF demonstrate that the physical exam surrogates of elevated filling pressures (i.e., rales and peripheral edema) occur with the same relative frequency compared to patients with systolic heart failure.[3,11] These findings confirm that a bedside clinical assessment is not adequate ω determine underlying ventricular function in the setting of decompensated HF.

EVIDENCE OF DIASTOLIC DYSFUNCTION (NON EC HOC ARDIOGRAPHICI

Cardiac Catheterization

While Doppler echocardiography has assumed the k_{ey} role in noninvasive assessment of LV diastolic function , cardiac catheterization remains the gold standard for demonstrating impaired relaxation and abnormal filling because it directly measures ventricular diastolic pressure.[i,7,20] Invasive measurements of diastolic dysfunction can be divided into those that demonstrate impairment of active relaxation or those that reflect an increase in passive stiffness; they include measurement of the time constant of LV relaxation (tau), LV end-diastolic pressure, left atrial pressure, or assessment of the LV stiffness modulus.".[20]

A commonly used invasive measurement to demonstrate diastolic dysfunction in the setting of HFNEF is a mean pulmonary capillary wedge pressure (PCWP) >12 mmHg or an LV end-diastolic pressure (LVEDP) >16 mmHg. An elevated PCWP or LVEDP in the presence of a normal LV end-diastolic index is consistent with reduced LV diastolic distensibility, which refers to the position on a pressure-volume plot of the LV diastolic pressure-volume relarionship.'i

Tau, a reliable index of myocardial relaxation activity, is determined by fitting a mono-exponential curve to the isovolemic period of the ventricular pressure curve.[2,1n] To measure tau, a high-fidelity micromanometer catheter is placed in the left ventricle, and digitized pressure data is acquired at fixed time intervals (i.e., 4 or 5 msec) ω create a plot of ventricular pressure on a logarithmic scale beginning at maximum negative dP/dt to the point where pressure declines to the level of LV end-diastolic pressure. The time-

Vasan and Levy criteria to diagnose heart failure with preserved ejection fraction.
1) Definite evidence of HF: Clinical symptoms and signs of heart failure, supporting laboratory tests (i.e., CXR), and a typical clinical response to treatment with diuretics, with or without documentation of elevated LV filling pressure
2) Normal LV systolic function (LVEF ◆0.50 within 72 hours of HF event)
3) Evidence of abnormal LV relaxation, filling, distensibility indices on a cardiac catheterization

From the National Heart, Lung, and Blood Institute's Framingham Heart Study

Table 2. All three criteria are required for the diagnosis of "definite" diastolic heart failure versus "probable" diastolic heart failure in the absence of cardiac catheterization data demonstrating LV diastolic dysfunction.[20]

Clinical Characteristics	Mean Value
Age (yr)	73
Female sex	58%
Previous myocardial infarction (MI)*	28%
Hypertension	74%
Atrial Fibrillation**	29%
Diabetes	32%
Obesity (BMI >30 kg/m2)***	40%
SBP (mmHg)****	146
DBP(mmHg) *****	77

The percentages and i•alues giz.en are approximate and rounded mean figures based on data al'4ilablefrom 11 hospital- or community-based HFNEF studies u•ith a total o/68,013 patients/ patient episodes (includes 26,322 patient episodes adoptedfrom the ADHERE databaseY·3·6·'·!•19

BM! = body mass index, SBP = syrto/ic bloodpressure, DBP = diastolic bloodpressure

- *Previous]\,ff or ischemic etiologyfrom 62,248 patient/patient episodn·6·12·13 ,,.r.,o*

** *Atrialfibrillation or atrial arrh_ythmiafrom 6?; 83 patient/patient episodes2·3·6·12·19*

*** *Obesity defined as a BM! >30 k-glnr f ρm 9,3'>3 patients-·'18!9*

**** *SBPfrom 55,944patientlpatient episodes3·6·12·". 18.19*

" " ' *DBPfrom 55,064 patient/patient episodes3·6•13·"·18•19*

Table 3. Clinical characteristics associated with heart failure with preserved ejection fraction.

course of isovolume pressure fall after maximum negative dP/dt is characterized by tau and by definition equals 1/ slope of the linear relationship between ln P and time in s-1.[21]

In 47 patients with HFNEF based on the Vasan and Levy criteria, Zile et al. demonstrated a mean tau value of 59 + 14 msec compared to a control (patients without HF) value of 35 + 10 msec.[10] Alchough tau fundamentally characterizes active diastolic ventricular properties, tau increases with all forms of hypertrophy during the normal aging process, is influenced by loading conditions, and is not always associated with elevated mean left atrial pressure and heart failure.23

Another invasive indexofLV diastolic $d_{y\,s}$ function is the nonlinear end-diastolic pressure-volume relationship (EDPVR), which characterizes passive LV chamber properties. Changes in the passive component of diastole (i.e., shift in the EDPVR) have been associated with HFNEF.[24,25] The slope of the EDPVR at a given volume (dP/dV) reflects ventricular stiffness. The diastolic LV stiffness modulus (>0.27) is the constant of an exponential curve fit to the diastolic LV pressure-volume points when a common level of LV filling pressure cannot be defined due to divergent LV filling pressure.'

Cardiac Magnetic Resonance

Cardiac magnetic resonance (CMR) is considered by some to be the gold standard for LV and left atrial (LA) volume and LV mass measurements.[26] In patients with suspected HFNEF, CMR can demonstrate preserved LV systolic function, normal LV volume, LV hypertrophy, and an enlarged LA volume. Although several studies have shown that diastolic dysfunction is almost uniform in hypertrophic myocardium,[8,20] CMR is still considered a research tool and therefore should not be included in diagnostic flowcharts for patients with HFNEF. As the clinical use of CMR expands, and as newer tissue-tagging techniques address LV longitudinal, radial, and circumferential indices of diastolic function,[27] CMR will likely be included in future diagnostic strategies.

Heart Failure Biomarkers

Plasma levels of B-natriuretic peptide {BNP) and NT-pro BNP are elevated in patients with systolic HF and HFNEF. In patients with HFNEF, BNP and NT-proBNP have been shown to correlate with invasive indices ofLV diastolic dysfunction, the time constant of relaxation, LV end-diastolic pressure, and the LV stiffness modulus.[5,28,29] BNP and NT-proBNP also correlate with the severity of LV diastolic dysfunction and LV filling pressure as estimated by Doppler echocardiography.[30,31] Nacriuretic peptides, however, can vary with age and body mass index and can be influenced by coexisting pulmonary disease, liver failure, or kidney failure:'[2,31] Therefore, elevated natriuretic peptides do not provide direct evidence of HFNEF. The European criteria recommend that natriuretic peptides, when used for diagnostic purposes, be implemented with echocardiographic indices of LV diastolic dysfunction, but they also can be used for exclusion purposes based on the high negative predictive value (96% and 93% when using a cut-off value of 100 pg/ml and 120 pg/ml for BNP and NT-proBNP, respectively).'

CONCLUSION

HFNEF remains a significant public health problem, accounting for more than 50% ofall HF patients. All recently published criteria for definitive HFNEF require clinical evidence ofHF based on

widely accepted symptoms and signs of congestion, documentation of an LVEF >50%, and reliable evidence of abnormal LV diastolic dysfunction. Clinical characteristics associated with HFNEF include advanced age, a predominance of female gender, and a high rate of hypertension and obesity. While LV chamber size is usually normal or small, mild to moderate LV enlargement does not rule our a diagnosis of HFNEF. Doppler echocardiography is the primary tool for noninvasive assessment of LV diastolic function, while cardiac catheterization remains the gold standard for demonstrating impaired relaxation and abnormal filling. Categorizing patients with HFNEF according to published diagnostic guidelines is recommended to identify an etiologically homogenous group that can guide future clinical trials and treatment.

REFERENCES

1. Zile /1fR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part I: diagnosis, prognosis, and measurements of diastolic junction. Circulation. 2002;105(11): 138.-1393.
2. Owan TE, Hodge DO, Herges RM.Jacobsen SJ, R$_{oge}$r Vl, Redfield MJ\f. Trends in prevalence and outcome of heart failure with preserz,ed ejection fraction. N Engl J Med. 2006;355(3):251-259.
3. fonry CU". Lopatin M, Stevenson LW, De Marco T, Fonarow C C ADHERE Scientific Adviso$_{ry}$ Committee and Im•estigators. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with presen•ed systolic junction: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. J Am Coll Cardiol. 2006;47(1):76-84.
4. Hunt SA. ACCIAHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and /l-fanagement of Heart Failure). J Am Coll Cardiol. 2005;46(6):el-82.
5. Paulus WJ, Tschiipe C, Sanderson JE, et al. How to diagnose diastolic heart failure: a comemus statement on the diagnosis of heart failure u•ith normal left ventricular ejection fraction by the Heart Failure and Echocardiograph_y Associations of the European Society of Cardiology. Eur Heart J 200;28(20):2539-2550.
6. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK. Levy D. Congestive heart failure in subjects with normal versus reduced left z,entricular ejection fraction: prevalence and mortality in a populmion-based cohort. J Am Coll Cardiol. 1999;33e}:1948-1955.
7. Yturralde RF, Gaasch WH. Diagnostic criteria for diastolic heart failure. Prog Cardiovasc Dis. 2005;47(5):314-319.
8. Zile MR, Gaasch WH, Carroll JD, et al. Heart failure with a normal ejection fraction: is measurement of diastolic Jimction necessary to make the diagnosis of diastolic heart failure? Circulation. 2001:J04D::'79-a2.
9. Zile /1fR, Lewinter MM. Left i•entricular end-diastolic volume is normal in patients with heart failure and a normal ejection .fraction: a renewed comensus in diastolic heart failure. J Am Coll Cardiol. 2007;49(9):982-985
10. Zile MR, Baicu CF, Gaasch ·wH. Diastolic heart failure--abnormalities in active relaxation and passii•e stiffness of the left ,•entricle. N Engl J Med. 2004;350(19): 1953-1959.
11. Maurer MS, Spevack D, Burkhoff D, Kronzon l Diastolic dysfonction: can it be diagnosed by Doppler echocardiograph_y? J Am Coll Cardiol. 2004;44(8): 15<13-1549.
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;355(3):260-269.
13. Fonarow GC, Stough WG, Abraham WT, et al.; OPTIMIZE-HF Investigators and Hospitals. Characteristics, treatments, and outcomes of patients with preserved systolic junction hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol. 2007;50(8): 768-777.
14. Gottdiener JS, McClelland Rl, Marshall R, et al. Outcome of congestive heart failure in elder(y persom: influence of left ,•entricular ystolic Junction. The Cardiovascular Health Study. Ann Intern /1fed. 2002;Jr(8):631-639.
15. Hobbs FD, Roa/ft AK. Dai•is RC, Davies MK. Hare R; /l-fidlands Research Practices Comortium (.MidReC). Prognosis of all-cause heart failure and borderline left z•entricular systolic dysjimction: 5 _year mortality follow-up of the Echocardiogr,1phic Heart of England Screening Study (ECHOES). Eur Heart J. 2007; 28(9):1128-1134.
16. Lenzen MJ, Scholte op Reimer Vlj, Boersma E, et al. Differences between patients u•ith a preserz,ed and a depressed left ventricular fonction: a report from the EuroHeart Failure Sun•ey. Eur Heart J 2004;25(14):1214-1220.
17. Masoudi FA, Havranek EP, Smith G, et al. Gender, age, and heart failure with presen•ed left ventricular systolic fonction. J Am Coll Cardiol. 2003;41(2):217-223.
18. McMurra_y JJ, Carson PE, Komajda M, et al. Heart failiire with presen•ed ejection fraction: clinical characteristics of 4133 patients enrolled in the I-PRESERVE trial. Eur J Heart Fail. 2008;10(2):149-156.
19. Yusuf S, Pfeffer MA, Swedberg K, et al.; CHAM! Investigators and Committees. Effects of candesartan in patients with chronic heart failure and presen•ed left-z,entricular ejection fraction: the CHARAf-Presen•ed Trial. Lancet. 2003; 362(9386):.77-781.
20. i-asan RS, L$_{evy}$ D. Defining diastolic heart failure: a call for standardized di$_{agn}$ostic criteria. Circulation. 2000; 101(17):2118-2121.
21. Weiss JL, Frederiksen JW, Weisfeldt ML. Hemodynamic determinants of the time-course of fall in canine left i•entricular pressure. J Clin Invest. 1r6.-58(3):751-760.
22. Yellin EL, Nikolic S, Frater RW Left i•entricular filling dynamics and diastolic function. Prog Cardiovasc Dis. 1990; 32(4):247-271.
23. Hirota }JI. Clinical study of left ventricular relaxation. Circulation. 1980;62(4):756-763.

24. Grossman U: Di,1stolic dysfimction and congestiz,e he,1rt failure. Circu/,1tion. 1990;81(2 Suppl):IIll-7.
25. Zile MR. Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part II: causal mechanisms and treatment. Circul,uion. 2002; 105(12): 1503-1508.
26. Rademakers FE. A-fagnetic resonance imaging in cardiology. Lancet. 2003;361 (9355):359-360.
27. Gotte 1Ljf. Germans T. Riissel IK. et al. /1,{yocardial strain and torsion quantified 'I cardiovasmlar magnetic resonance tissue tagging: studies in normal and impaired left ventricular function. J Am Coll Cardio!. 2006;48(10):2002-2011.
28. Tschope C. Kamer J,,,f, U:stermann D, Gaub R, Poller WC, Schultheiss HP. The role of NT-proBNP in the diagnostics of isolated diastolic dysfunction: correlation with echocardi$_{o\ g}$rap hic and inmsfre measurements. Eur Heart]. 2005: 26(21):227-228'-I.
29. Watan,ibe S, Shite], Takaoka H. et al. /I, yocardial stiffness is an important determinant of the plasma bmin natriuretic peptide concentration in patients with both diastolic and systolic heart failure. Eur Heart J. 2006;2 7(;'):832-838.
30. Dokainish H, Zoghbi WA, Lakkis NM, et al. Optimal nonim•asive assessment of left ventricular filling pressures: a comparison of tissue Doppler echocardiography and B-type natriuretic peptide in patients with pulmonary artery catheters. Circulation. 2004;!09(20):2432-2439.
31. Lubien E, DeA-faria A, Krishnaswamy P, et al. Utility of B-natriuretic peptide in detecting diastolic dysfimction: comparison with Doppler velocity recordings. Circulation. 2002; 105(5):595-601.
32. Horwich TB, Hamilton MA, Fonarow GC. B-type natriuretic peptide levels in obese patients with advanced heartfailure. j Am Coll Cardiol. 2006;47(1):85-90.
33. Tsutamoto T. Wada A, Sakai H, et al. Relationship between renal function and plasma brain natriureticpeptide in patients with heart failure. J Am Coll Cardiol. 2006;4 (3):582-586.