Heart Failure With Normal Ejection Fraction

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INTRODUCTION

Approximately 30-50% of patients with Heart Failure (HF) have normal or near normal left ventricular (LV) systolic function. This condition was earlier called as Diastolic Heart Failure (DHF) based on physiologic description and currently referred to as “HF with Normal LV Ejection Fraction” (HFNEF) by ACC/AHA criteria - a more descriptive term. Although there is still much controversy about the underlying pathophysiology of HFNEF, the clinical profile and circulating neurohormonal elevations are similar to the patients of HF with impaired systolic function. Some have argued that since the exact cut off values for “normal” EF are somewhat controversial and variable, a better term would be “HF with preserved EF”. For clinical purpose, patients with HF are currently classified into two categories: 1. HF with low EF (<50%), 2. HF with normal EF (>50%) from academic point of view. In contrast to patients with HF & impaired LVEF (typically with LV dilatation, eccentric LVH & low relative wall thickness), patients with HFNEF are characterized by a nondilated LV, concentric LVH & normal LVEF (See Fig 1). From practical experience, it is not infrequent to see the overlap of systolic abnormalities in patients of HFNEF and vis-versa and hence HFNEF is more a heterogeneous syndrome.

PATHOPHYSIOLOGICAL BASIS

The patients of HFNEF have any or all of the following pathophysiological processes:

1. Diastolic Dysfunction
   Diastolic Dysfunction due to impaired LV relaxation, increased LV diastolic stiffness or both; In other words there is an inability of the LV to fill adequately at normal filling pressures. The LV loses its normal ability to suction blood from the left atrium. When the LV relaxes abnormally, filling is delayed and the left atrial emptying is incomplete.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HF with Impaired LVEF</th>
<th>HFNEF</th>
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</thead>
<tbody>
<tr>
<td>LV morphology</td>
<td></td>
<td></td>
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<tr>
<td>Pressure-volume loop</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDV</td>
<td>↑</td>
<td>normal</td>
</tr>
<tr>
<td>LV mass</td>
<td>eccentric LV hypertrophy</td>
<td>concentric LV hypertrophy or concentric LV remodeling</td>
</tr>
<tr>
<td>Left atrium</td>
<td>dilated</td>
<td>dilated</td>
</tr>
<tr>
<td>LVEF</td>
<td>↓</td>
<td>normal</td>
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<tr>
<td>dp/dt</td>
<td>↓</td>
<td>normal</td>
</tr>
<tr>
<td>LVEDP</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>β</td>
<td>normal</td>
<td>↑</td>
</tr>
<tr>
<td>E/E</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>BNP/NT-proBNP</td>
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Fig.1: Comparison of the Characteristics of LV Morphology and Function Reduced LVEF and HFNEF
abnormally stiff LV worsens the problem by also impeding the left atrial emptying. The end result is abnormally high LA and LV diastolic pressures. The LV loses its suction and instead of “pulling” blood from the LA & pulmonary veins, it now relies heavily on the LA contraction so that LV can fill and distend appropriately and recoil in systole. Atrial fibrillation (AF) if it occurs in such patients is tolerated very poorly since it further increases LA pressure, pulmonary vascular congestion and results poor Cardiac Output (CO). In patients of HFNEF, the LV diastolic pressure - volume curve (loop) is shifted up & to the left consequent to gross LV diastolic dysfunction. Such patients have high relative LV wall thickness, high LV mass, increased fibrosis & scar of LV myocardium and impaired active relaxation of the myocardium (See Pressure - Volume Loop in Fig 1;5). The product of LA volume & LV mass index has been shown to have a high accuracy of predicting the HFNEF particularly in patients of hypertensive LVH who are asymptomatic.

2. LV enlargement, LV hypertrophy (LVH) & increased intravascular volume
LV enlargement is a key predictor of HF regardless of EF. However, patients with isolated DHF are often thought to have small LV volumes, but when the underlying cause is myocardial ischemia there could be mild LV enlargement, DHF & still later systolic HF. Besides, many patients with LV enlargement have increased intravascular volume due to comorbid conditions such as anemia, chronic kidney disease and obesity. LVH is an important risk factor for HFNEF. LVH limits coronary flow reserve, increases LV diastolic stiffness and impairs LV relaxation. Patients with LVH suffer from inability to adequately utilize the Frank-Starling mechanism and therefore inadequate preload and chronotropic incompetence can lead to decreased CO with its consequent symptoms of dizziness, light headedness, fatigue etc. Finally sub - endocardial ischemia is a consequence of chronic LVH and this also leads to both LV systolic & diastolic dysfunction & thus may exacerbate HFNEF.

3. Interaction between ventricular stiffness and central arterial stiffness
These two are always well matched in healthy individuals to maintain optimal cardiac efficiency. But if ventricular stiffness rises out of proportion to arterial stiffness as it happens in older age & in patients of HFNEF, the cardiac efficiency goes down. These patients have high pulse pressure. This so called abnormal ventriculo-vascular coupling i.e., stiff heart ejecting into a stiffer vascular tree is a major pathophysiological abnormality underlying DHF.

4. Role of atrial fibrillation (AF) and coronary artery diseases (CAD)
AF is quite frequent in patients of HFNEF. AF worsens the functional class & quality of life and also reduces the walking capacity. Irrespective of the baseline LVEF, the AF is associated with adverse cardiovascular outcomes. Increased LA size, higher heart rate with irregular cycle lengths and loss of atrial systole are probably responsible for the worse prognosis of such patients 3.

In CAD patients ischemia affects early diastole by causing calcium sequestrations in diastole which results in impaired LV relaxation and increased LV filling pressures. In areas of prior infarction or ongoing ischemia, regional systolic dysfunction and dysynchrony can further exacerbate abnormal loading conditions and create a mixture of systolic and diastolic dysfunction. Non - infarcted areas may get hypertrophied and may be hyperdynamic also resulting in the preservation of overall LVEF.

ETIOLOGIES OF HFNEF
I. HFNEF with abnormal diastolic function
1. Hypertensive Heart Disease,
2. Coronary Artery Disease: Prior MI, severe chronic stable CAD, inducible myocardial ischemia
3. Hypertrophic cardiomyopathy: Obstructive or Non obstructive.
4. Restrictive Cardiomyopathy: Diabetic Cardiomyopathy, infiltrative cardiomyopathy (Amyloidosis, Sarcoidosis, hemochromatosis), endomyocardial fibrosis (EMF), idiopathic.

II. Other causes of HFNEF:
1. Prior valvular Heart Diseases: Aortic Stenosis & regurgitation, mitral stenosis & regurgitation, LA myxoma etc.
2. Pericardial Diseases: Constrictive pericarditis, cardiac tamponade.

For practical purposes & clinical evaluation at bed side, the true cases of HFNEF come into the category 1 i.e., HFNEF with abnormal diastolic function. The other causes listed under category 2 are excluded when we want to study HFNEF patients.
DIAGNOSTIC CRITERIA FOR HFNEF

In 2000 Vasan & Levy 1 suggested following criteria for the diagnosis of HFNEF or “Diastolic HF” based on Framingham Heart Study 6:

1. Clinical criteria for HF
   I. Major Criteria: Paroxysmal nocturnal dyspnea
      → Jvp↑
      Pulmonary rales
      Radiographic cardiomegaly & pulmonary edema
      S3
      Hepatojugular reflux
      CVP >16 cms H2O.
   II. Minor Criteria: Bilateral ankle edema
      Nocturnal cough
      Dyspnea on exertion
      Tender hepatomegaly
      Pleural effusion, often bilateral
      Heart rate >120pm
      Decrease in vital capacity by 1/3.

Two major or one major plus two minor criteria required for diagnosis of HF.

2. Evidence of normal LVEF ≥ 50% within 72 hours of onset of HF in a non-dilated LV i.e. LV end-diastolic volume (LVEDV) of < 97 ml/m2. This could be estimated by echocardiography. LV size & volume, ejection phase indexes like EF, % fractional shortening, septal thickness, posterior wall thickness, RV size etc. can be precisely measured. This gives us the status of LV systolic function.

3. Objective evidence of LV Diastolic Dysfunction
   This is based on abnormal LV relaxation / filling / distensibility indexes on cardiac catheterization as originally proposed by Vasan & Levy 1. Based on this, European Working Group on HFNEF 7 proposed a new diagnostic algorithm (Fig.2) utilizing the non-invasive tools to estimate the LV filling pressures particularly echocardiographic techniques using conventional Doppler, Tissue Doppler Imaging (TDI) as well as color M-mode. Echo-Doppler criteria for the assessment of the LV diastolic dysfunction have been standardized and the grading assigned (Fig.3, 4, 5, 6, & 7) 6, 9, 10:
   - Step 1: Mitral inflow velocities by PW Doppler; Early (E) and late (A) velocities and E/A ratio. E Deceleration time (DCT) & isovolumic relaxation time (IVRT) measured.
   - Step 2: Pulmonary venous flow pattern at the right pulmonary vein opening into the LA.
   - Step 3: TDI at medial mitral annulus (E', A', & E/E' ratio).
   - Step 4: Color M-Mode Doppler echocardiography showing the velocity of flow propagation into the LV can be determined

Fig. 2: Principles of the Algorithm Proposed for the Diagnosis of HFNEF by the Working Group of the European Society of Cardiology

Fig. 3: Echo Doppler criteria for grading of LV diastolic dysfunction.

Fig. 5: LV Diastolic Dysfunction: Mitral Inflow Velocities

Fig. 6: Mitral Doppler & pulmonary venous Doppler in normal & abnormal relaxation

Fig. 4: LVH: 2D & M-Mode Echo

Fig. 7: Patterns of mitral inflow and mitral annulus velocity by TDI
by slope of color wave front. Rapid flow propagation indicates normal LV relaxation whereas slow propagation indicates slowly relaxing LV.

The currently used cut off values are given in the algorithm (Fig.2; 5). It is obvious that assessment of extent of LV diastolic dysfunction can be exactly done by the above echo - Doppler criteria of the algorithm(Fig.2 & Fig.3). Echocardiography is of immense help in excluding valvular heart disease, constrictive pericarditis or pericardial effusion, hypertrophic obstructive cardiomyopathy & infiltrative cardiomyopathies like amyloidosis and EMF where the definitive treatment modalities can be undertaken. Practically speaking, the combination of conventional mitral Doppler velocities (E/A ratio) & the TDI at the medial mitral annulus (E/E' ratio) can give plenty of information about the LV diastolic dysfunction.

LV Diastolic Dysfunction & DHF

Diagnosis of HF in the presence of LV diastolic dysfunction is based on clinical & echo Doppler criteria & the biomarkers like BNP & NT Pro BNP(Fig.1; 5). BNP level of > 200 pg/ml or NT ProBNP level of >220pg/ml confirms the diagnosis of HFNEF in patients with symptoms of HF, LVEF ≥ 50% and E/E' ratio clearly > 15 or 8-15. If BNP or NT pro - BNP are below 100 & 120 pg/ml respectively, HF is excluded.

Other techniques to diagnose HFNEF

1. Cardiac MRI: This is likely to play an important role in future for the assessment of HFNEF. Currently the cardiac MRI is very good to estimate the LV volume, LA volume & LV mass. Besides, cardiac MRI can evaluate focal areas of fibrosis (Hyper - enhancement), aortic enlargement, aortic dissection & pericardial thickness.

2. Cardiac catheterization: Simultaneous right & left heart catheterization can be useful in total hemodynamic assessment including elevated LV pressures & CO. Coronary angiography will help us to diagnose significant CAD. In some instances Endomyocardial biopsy may have to be done to evaluate potentially treatable cause. In one study 11, the endomyocardial biopsies done in patients with HFNEF showed higher cardio - myocyte diameter & higher myofibrillar density compared to those with HF with impaired LVEF whereas collagen volume was similar.

TREATMENT OF HFNEF

As the mechanisms underlying HFNEF are still under debate, there is no evidence - based treatment for patients with HFNEF. However, LVH is an important target for prevention of HF. LVH is a predictor for the development of HF independent of age, sex, obesity, diabetes & hypertension. Aggressive treatment of hypertension &/or diabetes is recommended to prevent HF.

For the treatment of HFNEF, ACC/AHA guidelines2 recommend blood pressure control at the evidence level A, class I. All other recommendations are at the level C. Hypertension is present in about 88% of individuals with HFNEF & in these patients reduction of BP reduces pulmonary congestion, relieves cardiac ischemia & in the long run leads to regression of LVH. Since the prevalence of diabetes (DM) and LVH is quite high among these patients, there is a compelling indication for ACE Inhibitors or ARBs to treat these patients. However trials evaluating the ARBs and ACEIs did not reveal a survival benefit with that seen in placebo as shown in the 3 importanttrials 12,13,14. In the Hong Kong Diastolic Heart Failure study, Diuretics, Diuretics + Irbesartan, or Diuretics + Ramipril were used. Investigators found at the end of one year Irbesartan & Ramipril groups were better than diuretics alone in reducing BNP & improving LV systolic & diastolic function. Although quality of life & SBP & DBP were similar in all 3 groups 17. Of note is, in most of these trials the blood pressure control appeared to be a key factor in determining the response to treatment. The possible therapeutic strategies for the treatment of patients of HFNEF are being determined for the future guidance. Assuming that impaired relaxation and increased stiffness are major mechanisms underlying HFNEF, it is appropriate that the therapy should be addressed to these abnormalities. The substances that have been evaluated for the treatment of patients with HFNEF in completed or ongoing clinical studies are given in the table (Fig.4), as per the NIH clinical trial registry 15. In the presence of atrial fibrillation or fast heart rate, B-Blockers & negatively chronotropic calcium-channel blockers are advised for the treatment of HFNEF based on the assumption that rate-lowering and prolongation of diastole results in better LV filling and output. A study evaluating the purely heart rate lowering agent Ivabradine in HFNEF is currently ongoing (15). In patients with myocardial ischemia (silent ischemia or unstable angina) who are admitted as patients of HFNEF, ischemia has to be ruled out by sensitive methods & treated with coronary revascularization.

Summarily speaking the role of B-Blocker therapy and similar heart rate lowering in HFNEF is still not well established. Even the optimal management of AF in HFNEF is not clear.
either.
Less recognized factors like obesity, obstructive sleep
apnea & anemia may have to be identified and treated.

DM both Type 2 and long standing Type 1 causes LVH & diastolic
abnormalities because of the accumulation of advanced
glycation end-products (AGEs), intra-cardiomyocyte
abnormalities and collagen deposition ultimately resulting in
myocardial stiffness. So there is a close relationship between
DM & diastole. Hence optimal control of DM is an integral
part of such patients with HFNEF. In addition, algebrium an
AGEs crosslinks breaker has been used in diabetic diastolic
heart disease to improve the LV relaxation in a pilot study16.

PROGNOSIS
Once hospitalized for HF, patients with HFNEF have a high
mortality. 5 year mortality is high and a similar to HF with
reduced EF. Cause of death in HFNEF is multifactorial
including LV pump failure, pulmonary edema & fatal
arrhythmias which may result in sudden cardiac death.

CONCLUSIONS
HFNEF, a condition associated with HF symptoms and normal
LVEF & without obvious explanation for the symptoms
(e.g., CAD, Valvular Heart Disease) is typically associated
with concentric LVH or remodeling, increased LA size & LV
diastolic dysfunction. Unrecognized ischemia, paroxysmal
AF altered LA function, chronotropic incompetence and
vascular stiffness may add to the problem. Further research
to unravel the pathophysiology of HFNEF is clearly needed.
Since hypertension is commonly associated with HFNEF,
blood pressure lowering by appropriate drugs particularly
RAS inhibitors is extremely useful. Similarly control of DM
& AF are needed.

Substances Evaluated for the Treatment of Patients With HFNEF in Completed but Unpublished or Ongoing
Clinical Studies (According to NIH Clinical Trials Registry*)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Drug Class</th>
<th>Postulated Targets</th>
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<tbody>
<tr>
<td>Valsartan</td>
<td>Angiotensin-receptor blocker</td>
<td>RAAS, blood pressure, LVH, LV relaxation</td>
</tr>
<tr>
<td>Aliskiren</td>
<td>Selective renin inhibitor</td>
<td>RAAS, blood pressure, LVH, LV relaxation</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Aldosterone antagonist</td>
<td>Collagen turnover, LV relaxation and stiffness</td>
</tr>
</tbody>
</table>
| Eplerenone    | Aldosterone antagonist                   | Collagen turnover, LV relaxation and stiffness, endothelial
dysfunction                                             |
| Sitaxsentan   | Endothelin receptor A antagonist         | Blood pressure, LVH                                     |
| Alagebrium    | Advanced glycation end products cross-links breaker | Advanced glycation end products, LV relaxation and stiffness |
| Atorvastatin  | Phosphodiesterase-5 inhibitor           | Collagen turnover, LV relaxation and stiffness, vascular function |
| Sildenafil     | Glucagon-like peptide-1 receptor antagonist | LVH, LV stiffness, vascular stiffness                  |
| Exenatide     | Inhibitor of the slowly inactivating component of the cardiac Sodium current (late INa channel) | Aortic stiffness, LV stiffness                          |
| Ranolazine    | Inhibitor of the “funny” channel (If channel) | Intracellular calcium, LV relaxation                     |
| Ivabradine    |                                        | Heart rate, duration of diastole                        |

REFERENCES
2. AHA / ACC Task Force on practical guidelines - 2005 on Diagnosis and management of chronic heart failure in adult. JACC; 2005, 46;e1-82.
5. Maedar M T, Kaye D M; Heart Failure with normal LV fraction. JACC; 2009, 53; 905-918. (Updated to September 26th 2010).


