Heart Failure With Normal Ejection Fraction (HFNEF)

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In heart failure with normal ejection fraction (HFNEF), although the left ventricle contracts normally, relaxation is impaired and cardiac output, especially during exercise is limited by abnormal filling characteristic of the ventricle. For a given ventricular volume, ventricular pressure are elevated leading to breathlessness on exertion and edema. The patients with HFNEF are typically elderly, female and often obese with hypertension and diabetes (1).

THE PATHOPHYSIOLOGY OF HEART FAILURE WITH NORMAL EJECTION FRACTION :

About one-half of the patients presenting with symptoms and signs of heart failure will have a normal left ventricular ejection fraction (LVEF) (2,3,4). This form of heart failure has been variously labeled as diastolic heart failure, heart failure with preserved systolic function, or more simply heart failure with a normal ejection fraction (HFNEF). The pathophysiology of HFNEF and the generation of symptoms remain controversial (5). Zile etal. (6) showed on the basis of invasive hemodynamic studies that patients with HFNEF have significant abnormalities in active relaxation and passive stiffness, and concluded that the pathophysiological cause of elevated diastolic pressures and symptoms is abnormal diastolic function studies used invasive techniques with the subjects at rest. However the primary symptoms of HFNEF patients is breathlessness on exercise. Futhermore, the orthodox view that systolic function is entirely normal has been challenged in studies using newer echocardiographic techniques, which have shown that systolic function does not seem to be entirely normal in all subjects with HFNEF (7-9) or those with LV hypertrophy (10) and diabetes (11), both etiologic factors for HFNEF (12). New advances in echocardiography enable a better assessment of LV systolic and diastolic function, including measurement of myocardial deformation or strain in 3 planes, ventricular twist and untwist annular motion (longitudinal function), and LV suction, which is a vital mechanism in early diastolic ventricular filling (13-15).

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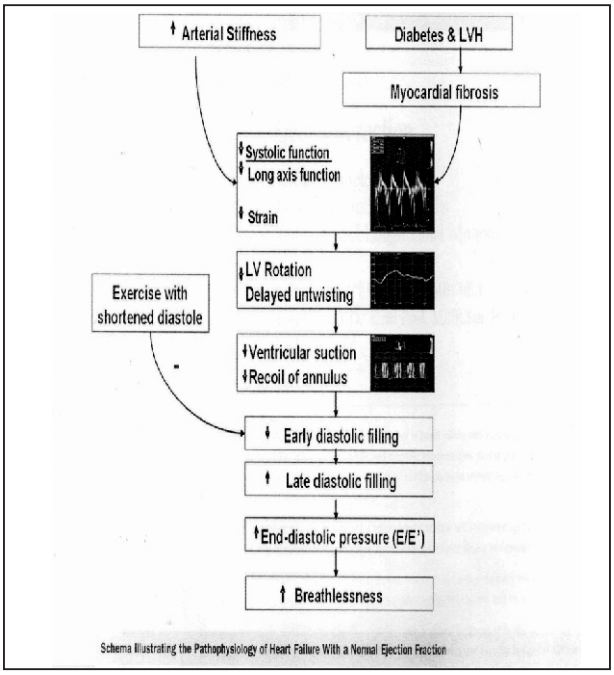
CLINICAL FEATURES AND DIAGNOSIS :

Although there are clinical differences between the typical patient presenting with HFNEF and with SHF these relate more to aetiology and whether remodelling has taken place (5). The typical patient with HFNEF is an elderly women with history of hypertension often with diabetes whose heart failure is episodic, often precipitated by an episode of AF, ischaemia or infection (16). In fact these simple criteria based on aetiology and the presence or absence of ventricular remodelling point to a more useful classification. Patients with HFNEF usually have hypertensive heart failure with LV hypertrophy, whereas the typical SHF patient has usually had a previous myocardial infarction with significant LV remodelling, myocarditis or idiopathic dilated cardiomyopathy. Approaching the diagnosis of all types of heart failure along the following lines appears more useful. Firstly, establish the presence of heart failure by symptoms and concentrations of brain natriuretic peptide (and exercise testing if unsure). Secondly, determine the main aetiology and mechanisms : hypertension or ischaemia, infarction, etc. Thirdly, determine whether remodelling has taken place (are LV volumes increased) ? Lastly, look for the presence of

additional deleterious factors: dyssynchrony, arrhythmias, metabolic/electrolyte abnormalities, etc.



(Tan et al, JACC 2009; 54:44)

This process focuses on the two major stages of the clinical process : firstly, deciding whether this is heart failure and , secondly, identifying treatable factors such as ischaemia, remodelling, dyssynchrony, etc. Echocardiography has a vital role in all these processes. Measurement of the LVEF is not relevant. Systolic heart failure and HFNEF have a mixture of systolic and diastolic abnormalities and it appears more useful to classify according to the aetiology and the mechanisms involved in the individual patient, which may be different. Measurements of long axis function are sensitive and can be used to confirm the presence of impaired systolic and diastolic dysfunction, and peak early diastolic velocity is a powerful predictor of future prognosis. However, all measurements of long axis function and mitral inflow velocities need to be corrected for age. Ageing has powerful deleterious effect on ventricular function and on these diastolic indices. Criteria for diagnosis of HFNEF based on diastolic measurements of mitral inflow velocites are not usually corrected for age. Indeed the whole definition of diastolic dysfunction, based on echocardiography, is difficult and there is no ideal method. Extreme mitral filling patterns such as the restrictive filling pattern are obvious indicators of severe diastolic dysfunction but usually occur only in the presence of severe systolic dysfunction as well. Indeed, Sim etal (17) found no difference in the LV filling patterns seen on echocardiography between an appropriate reference population and patients with breathlessness. The previous guidelines on diagnosis of " diastolic heart failure" are now less relevant in view of these recent findings and new guidelines are clearly required.

TREATMENT

Until results of further sound RCTs are available appropriate therapy is a follows: (18)

1) Diuretics used judiciously in smaller doses than used for systolic HF. Preferably chlorthalidone 25 mg/day. The drug, however, causes hypokalemia and an aldosterone antagonist may be added.

2) Level ACE inhibitors and ARBs, are not effective (see I-PRESERVE: Irbesartan failure).

3) Aldosterone antagonists have a role; spironolactone 25mg/day; or eplerenone 25mg/day; or amiloride 5 mg/day. These agents must be used with frequent monitoring of serum potassium if the serum creatinine is above normal 1.2 mg/dl e GFR<65 ml/min; use with caution for creatinine 1.5-1.9 mg/dl and should be avoided if > 1.9 mg/dl (170 mol/L), so as to avoid hyperkalemia. With HFNEF, ACE inhibitors and ARBs are not recommended; thus less occurrence of hyperkalemia is expected with use of aldosterone inhibitors.

4) Beta-blocker: Based on the results of the SENIORS study (Flather et al. 2005; van Veldhuisen et al. 2009), nebivolol is recommended; if not available, choose carvedilol.

5) Treat the underlying cause of the heart disease.

6) Atrial fibrillation should be managed with a combination of digoxin and a small dose beta-blocker (nebivolol, carvedilol, or bisoprolol) to maintain a ventricular response of 55-70 at rest.

CONCLUSION

There may be significant left ventricular systolic dysfunction in patients with HFNEF. The preserved LVEF gives the illusion of normal systolic function and masquerades as poor ventricular performance. For that reason the terms left ventricular function and ejection fraction are not interchangeable and the expression systolic function should be avoided when referring to LVEF. The predicted reduction in stroke volume in the precompensated state rather than ejection fraction may explain the symptoms of heart failure in these patients.

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