Minireview Article

EFFORT ECHOCARDIOGRAPHY IN EVALUATION OF DIASTOLIC FUNCTION AND HFpEF

Abstract

The diastolic function is defined as the filling of the heart during diastole. Diastolic dysfunction in patients with normal fraction ejection (FE) or HFpFE is defined by echocardiographic criteria according to the European Society of Cardiology guidelines. Elderly patients, with multiple comorbidities, make the diagnosis difficult and involve the exclusion of other causes that may explain the symptoms of the patients, in particular anemia, sleep apnea, coronary artery disease, dynamic MI, metabolic syndrome and obesity. The prevalence of HFpEF is increasing, leading to the performance of stress diastolic function to detect asymptomatic patients at rest.

We summarize in this mini review the important ESC guidelines and criteria for the echocardiographic evaluation of the diastolic dysfunction in patients with HFpFE.

Keywords: diastolic function, comorbidities, metabolic syndrome, asymptomatic patients

INTRODUCTION

Diastolic dysfunction is the most frequent cause for heart failure (HF) representing more than 40%. Patients with heart failure with preserved LVEF or HFpEF (heart failure with preserved ejection fraction) are symptomatic only during exercise and their echocardiography at rest may be strictly normal, hence the interest of an evaluation of diastolic function during exercise. These are most often elderly patients with multiple comorbidities, making the

diagnosis difficult and involving the exclusion of other causes that may explain the symptoms of the patients, in particular anemia, sleep apnea, coronary artery disease, dynamic MI, metabolic syndrome and obesity. **(14)**

DEFINITIONS

The diastolic function is defined as the filling of the heart during diastole. It requires two components:

• Relaxation: with an active phase by "ventricular suction" mechanism, corresponding to filling and a passive phase thanks to the elastic capacity of the left ventricle (LV).
• LV compliance and its degree of rigidity.

Diastolic dysfunction in patients with normal fraction ejection (FE) or HFpFEis was defined by echocardiographic criteria according to the European Society of Cardiology guidelines (ESC) **(1)**. Four main criteria must be evaluated:

• E/E' ratio > 14
• Septal E ' <7 cm/s and/or lateral E'<10 cm/s
• TR peak velocity > 2.8 m / s
• Left atrial volume index(LAVI) > 34 ml / m²

The presence of at least three from four criteria expresses a diastolic dysfunction. If only two criteria are present, the diastolic function is indeterminate, and below two, it is normal **(1)**.

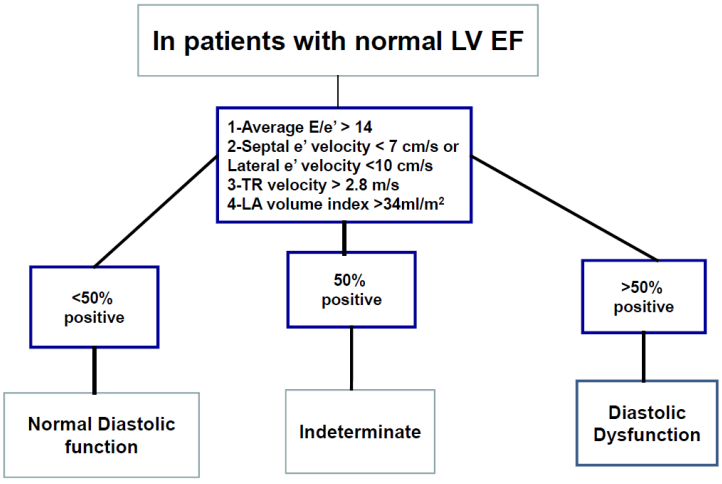


Fig. 1: Flow chart

HFpEF, or heart failure with preserved ejection fraction, is defined by the combination of clinical, biological and echocardiographic criteria (ESC Guidelines 2016 on the diagnosis and treatment of acute and chronic heart failure):

• Symptoms and clinical signs of heart failure
• LVEF> 50%
• High levels of BNP (> 35 pg / ml) or NT pro-BNP (> 125 pg / ml)
• With at least one additional criterion:

o A structural abnormality (Left ventricular mass index > 95 g / m² in women and> 115 g / m² in men) or left atrium (LA) dilation (LAVI> 34 ml / m²),

o Or echocardiographic criteria for diastolic dysfunction: average E/E'> 13; average E'<9cm/s; TR peak velocity> 2.8 cm / s

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

Graph: New HFpEF diagnostic probability score:

A new score was proposed in 2018 to establish the probability of HFpFE, taking into account several items:

BMI> 30 kg / m² (2 points),

Hypertension with 2 or more antihypertensive treatments (1 point),

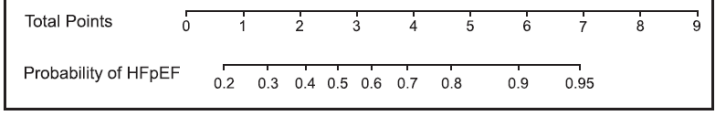
Age> 60 (1 point),

Pulmonary artery systolic pression (PASP)> 35 mmHg (1 point),

E/E '> 9 (1 point).

The probability of HFpEF depends on the total score (example 4 points = 70% risk of HFpEF) **(2)**

	Clinical Variable	Values	Points
H_2	Heavy	Body mass index > 30 kg/m²	2
	Hypertensive	2 or more antihypertensive medicines	1
F	Atrial Fibrillation	Paroxysmal or Persistent	3
P	Pulmonary Hypertension	Doppler Echocardiographic estimated Pulmonary Artery Systolic Pressure > 35 mmHg	1
E	Elder	Age > 60 years	1
F	Filling Pressure	Doppler Echocardiographic E/e' > 9	1
H_2FPEF score			Sum (0-9)



Reddy et al. Circulation. 2018;138:861–870.

Fig. 2: Clinical variables

PHYSIOPATHOLOGY:

HFpEF is the result of different hemodynamic, cellular and metabolic mechanisms:

• Hemodynamic mechanisms: LV congestion / diastolic dysfunction / LA hypertension, pulmonary hypertension / right ventricle (RV) dysfunction, volume overload.
• Cellular and metabolic mechanisms: Microvascular inflammation, cardio-metabolic abnormalities, structural, cellular and extracellular modifications.

Several hypotheses have been discussed to explain why symptoms of HF can occur despite apparently normal LV systolic function.

• Ventricular hypothesis: double component of diastolic dysfunction and longitudinal systolic dysfunction. The overall function of the LV is preserved by an increase in the function of the radial component of the LV, which compensates the reduction in longitudinal function. Longitudinal systolic function is still impaired (S'LV <6.5 cm / s)

• Atrial hypothesis like remodeling and mechanical dysfunction of the LA:

- o Reduced LA strain and the stiffness index of the LA.
- o Presence of inter-atrial block (IAB)

• Arterial hypothesis: arterial rigidity which increases the LV afterload. Consequently, the LV increases it filling pressures to compensate. Over time, this leads to concentric remodeling and left ventricular hypertrophy.

Physiopathology of diastolic function during exercise:

We need to understand what happens at rest, before studying what happens during the exercice. **(15)**

The E wave corresponds to the passive filling of LV, it reflects the LA-LV pressure gradient. It is therefore dependent of the load conditions and gradually increases over the grades of diastolic dysfunction. While the A wave, which corresponds to the atrial contraction, it is frequently degraded.

The E' wave corresponds to the mitral annular peak diastolic velocity, and provides information on ventricular relaxation. It is independent of the load conditions and is getting reduced from grade I of diastolic dysfunction without modifications.

As a result, the E/E'ratio increases progressively with the grades of diastolic dysfunction, indicating the elevation of ventricular filling pressures.

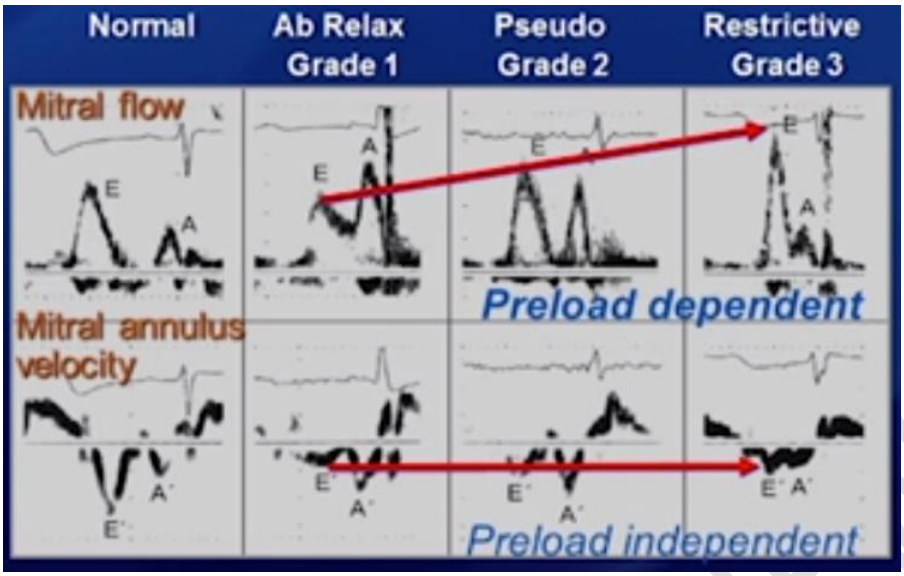


Fig. 3: Physiopathology of diastolic function during exercise (13)

During exercise, in a normal patient **(3, 4)**: there is an increase in heart rate and cardiac output. Thanks to a diastolic reserve (ability of the LV to increase its myocardial relaxation during exercise by a powerful protodiastolic suction mechanism), there is a concomitant increase in E and E' waves, the E/E' ratio remains constant and therefore no increase in filling pressures.

When there is a diastolic dysfunction: the filling time and the LV compliance are reduced, which implies an increase in the filling pressures since there is no adaptation of the LV. The echocardiography shows an increase of only the E wave without elevation of E', implying an elevation of the E/E' ratio **(5)**.

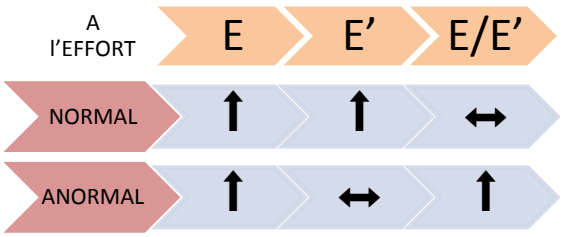


Fig. 4. Normal and abnormal functions

DIASTOLIC FUNCTION ON EFFORT ECHOCARDIOGRAPHY (DIASTOLIC STRESS):

I. INDICATIONS

Diastolic stress is indicated:
- In symptomatic patients, mainly during exercice: Dyspnea, asthenia
- With a non-symptomatic resting echocardiogram and non-elevated LVFP.
- Or patients with diastolic dysfunction at an infra-clinical stage (hypertensive heart disease, diabetes, elderly patients ...)

Note that dyspnea on exertion is an equivalent of angina and represents a frequent indication for stress echocardiography to research ischemia, and to detect diastolic dysfunction. Giving that ischemia is the primary cause of HFpEF **(6, 16, 17)**.

Diastolic stress is not indicated in:
- Patients with normal diastolic function and relaxation at rest with septal E'>7 and lateral E'> 10 cm/s. There is indeed a low probability of developing an elevation of LVFP during exercise in this situation.
- Patients with already elevated LVFP at rest: the cardiac aetiology is already established.

II. PROTOCOLS:

According to the latest ESC 2017 guidelines for indication of stress echocardiography in non-ischemic pathologies **(7)**:

- Physical stress must always be preferred to the pharmacological stress. Physical stress is physiological and it reflects the lived reality of the patient. In addition to that, pharmacological stress improves diastolic function which can affect the results.

- Always prefer stress echocardiography on a bicycle rather than the protocol with a treadmill: it gives more time to get the images with high quality.

- 25W protocol every 2 or 3 min (Bruce protocol)
- ECG and blood pressure monitoring.
- Image acquisition at different phases: at the rest - during effort at low load - at the peak - and in early and late recuperation.

Data to be acquired:

- Mitral flow (E, A, E / A, pulsed Doppler at the leaflets, sample volume at 1-2 mm)
- Septal E '+++, and lateral E', E / E '(DTI, sampling volume at 5-10mm, Nyquist limit at 15-20 cm/s, adjustment of gains and filters)
- TR (on different incidences +++)
- Recording 5-10 cycles

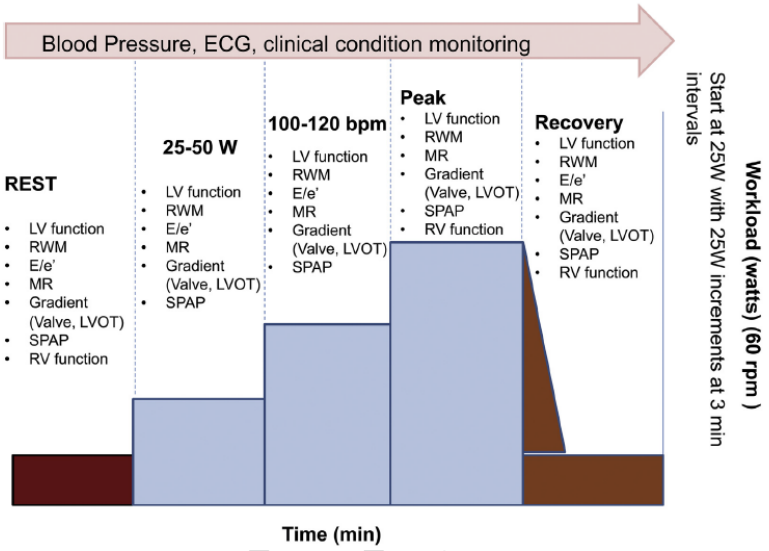


Fig. 5. Clinical conditions monitoring

	Functional	Morphological	Biomarker (SR)	Biomarker (AF)
Major	septal e' < 7 cm/s or lateral e' < 10 cm/s or Average E/e' ≥ 15 or TR velocity > 2.8 m/s (PASP > 35 mmHg)	LAVI > 34 ml/m² or LVMI ≥ 149/122 g/m² (m/w) and RWT > 0,42 #	NT-proBNP > 220 pg/ml or BNP > 80 pg/ml	NT-proBNP > 660 pg/ml or BNP > 240 pg/ml
Minor	Average E/e' 9 -14 or GLS < 16 %	LAVI 29-34 ml/m² or LVMI > 115/95 g/m² (m/w) or RWT > 0,42 or LV wall thickness ≥ 12 mm	NT-proBNP 125-220 pg/ml or BNP 35-80 pg/ml	NT-proBNP 365-660 pg/ml or BNP 105-240 pg/ml

Major Criteria: 2 points	≥ 5 points: HFpEF
Minor Criteria: 1 point	2-4 points: Diastolic Stress Test or Invasive Haemodynamic Measurements

Fig. 6: Calculation and interpretation of the HFA – PEFF score

Echocardiographic and natriuretic peptid heart failure with preserved ejection fraction workup and scoring system (diagnostic workup).

- If an ischemia cause is suspected, the acquisition echocardiography images should be preferred first. And the acquisition must be done in less than 60 seconds when the stress test is performed by treadmill **(7)**.
- When using a contrast product, tissue Doppler measurements are no longer reliable, only the collection of TR is possible under these conditions.

NB: If early fusion of E and A waves; It is recommended to leave the acquisition of the mitral flux to late recovery as soon as the waves begin to separate, and begin with the acquisition of the TR.

Sub-maximal stress protocol: the MEDIA study (8):

It has the following advantages:

- Suitable for elderly patients
- More corresponding to the physiological activity of the patients
- Dyspnea is less important, then the images are of a better quality
- The HR is lower, which avoids the fusion of E and A waves

Process of the protocol:
- Start with a load of 15 W which progressively increases by 5 W / min until a target HR under maximum of 100-110 bpm or until symptoms appear
- Once the target is reached, maintain the charge for 3 minutes to acquire the images.

III. RESULTS AND INTERPRETATION:

Three main criteria must be studied: the E/E' ratio, the E' (especially septal; the lateral being less reliable during effort) and the TR peak velocity. **(7)**

The test is considered POSITIVE when:

- Average E/E'> 14 or E/E' sep > 15
- Septal E' <7 cm/s (or lateral E' <10 if only the lateral E' has been acquired)
- TR peak velocity > 2.8 m / s

The test is considered NEGATIVE when:

- Average E/E' <10
- TR peak velocity <2.8 m / s

The diastolic function is undetermined when only one from two criteria is positive.

NB: take into account the age and the load reached by the patient when interpreting the PASP that says a TR peak velocity > 3m/s generally signs an abnormal response (except for trained athletes).

NB: Currently, there are no studies that demonstrate the indication of strain during exercise to evaluateHFpEF **(9).**

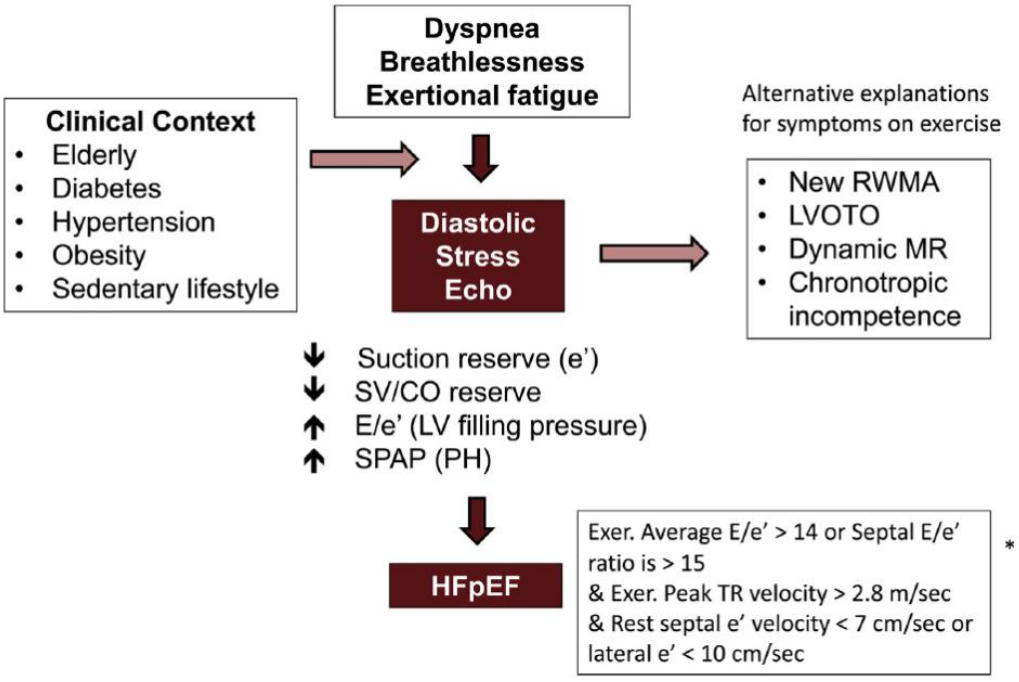


Fig. 7. Interpretation of results

IV. THERAPEUTIC AND PROGNOSTIC INVOLVEMENT :

When HFpEF is confirmed, we must:

- Treat congestion:

o Diuretics +++

o New therapies: sodium glucose co-transporter-2 inhibitors (SGLT2i) (eg: empagliflozin), act as osmotic diuretics by reducing renal reabsorption of glucose and increasing its urinary excretion, with a concomitant natriuretic and diuretic effect, and are being studied in HFpEF (EMPEROR-preserved essay, phase III) .

- Treat co-morbidities (Atrial fibrillation, ischemia, diabetes, etc.)

- New percutaneous interatrial shunt device (IASD) is still into study. It could improve exercise capacity (Essay REDUCE LAP-HF II).

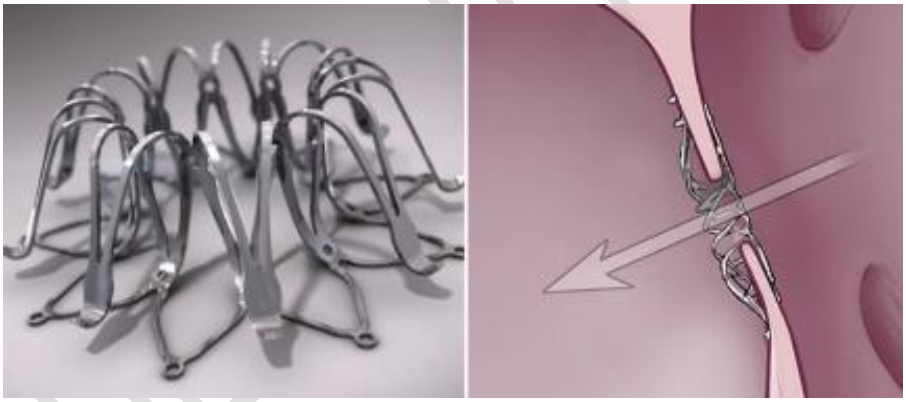


Fig. 8. Therapeutic and prognostic involvement

- Act on metabolic changes and micro-vascular inflammation (research area).

o Intravenous iron (FAIR-HFpEF essay, phase III)

o Molecular targeting Titin (or connectin): involved in the assembly of sarcomere proteins, rigidity / elastance

o Inhibitor of growth factor TGF-β (targets the extracellular matrix) involved in the genesis of fibrosis => PIROUETTE test

o Trimetazidine: anti-oxidant effect

o Carnitine palmitoyltransferase-1 inhibitor (CPT1): blocks the mitochondrial oxidation of

glucose
o Partial agonists of adenosine A1: improves myocardial metabolic energy and its utilization

Other molecules:

- Beta-blockers (11): Several studies are in progress.
The strain could identify patients with HFpEF earlier, which indicates a positive response to beta blockers => reduction in mortality from any cause if GLS <14%.

- Salcubitril / valsartan: (10)

o PARAGON HF study; no significant reduction in hospitalizations for heart failure and cardiovascular death (with a possible benefit in women and in patients with moderately altered LVEF (45-57%)), but significant improvement in NYHA stage.
o Significant decrease in NT-pro BNP levels (regardless of gender, or LVEF), ACC 2020 (PARAGON HF investigators)

Prognosis involvement: **(12)**

A E/E'sept during exercise> 13, a slight change in the amplitude of the E' waves, as well as PASP> 50 mmHg during exercise indicates a poor prognosis. (KAREN study)

CONCLUSION:

The prevalence of HFpEF is increasing, leading to the performance of stress diastolic function to detect asymptomatic patients at rest.

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