Utility and limitations of ejection fraction and of diastolic dysfunction in heart failure patients

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Abstract

The echocardiographic evaluation of left ventricular (LV) systolic function, and especially of ejection fraction (EF) plays a central role in the diagnosis of heart failure (HF) due to its undisputed prognostic value. Limitations of EF are substantially: i) the variability and reproducibility of measurements, and ii) the load-dependence. Measurement of stroke volume, longitudinal function and myocardial strain can overcome the limitations of EF in assessing the contractile reserve of patients with HF and may help to define both the phenotype and prognosis of the disease. The recognition of diastolic dysfunction (mainly by echocardiography) is the pathophysiological basis to make diagnosis of HF with preserved ejection fraction (HFpEF). The limitations are essentially related to its feasibility, since performing a multi-parametric quantitative echocardiographic evaluation, as indicated by the guidelines, may be difficult in clinical practice. Difficulties in method standardization, the poor attitude of cardiologists to test their reproducibility (test-retest, variability) favor the evaluation “at-a-glance” of LV structural and functional LV abnormalities.

Left ventricular systolic function

The echocardiographic assessment of left ventricular (LV) systolic function, especially of ejection fraction (EF) plays a central role in the diagnostic and prognostic assessment of patients with either suspected or ascertained heart failure (HF). This role, always accepted by clinicians, has been strongly strengthened by the guidelines of the European Society of Cardiology [1]. In fact, after the initial history and clinical evaluation and the electrocardiogram, which are used to select the patient, and after a possible evaluation with biomarkers (natriuretic peptides), mainly used as an exclusion test, echocardiography serves to confirm the diagnosis and to define the phenotype. If HF is confirmed, the next step is to determine the etiology and choose the appropriate therapy. EF also plays a central role in the therapeutic choice. As the 2016 European guidelines report, the main terminology used to describe HF is historical and is based on measurement of the EF.

The EF values are typically considered normal when ≥50%. Therefore, in the presence of HF with normal EF the patient is classified as having HF with preserved EF (HFpEF), while patients with depressed EF (considered for EF <40%) are classified as HF with reduced EF (HFrEF). Those patients who present with an EF between 40-49% represent a “new” category, considered as a grey area now defined as HF with mid-range EF (HFmrEF). The distinction of patients on the EF basis is important because the different phenotypes identified by the EF underlie various etiologies, demographic characteristics, comorbidities and response to therapies [2]. Actually, a similar classification was already proposed previously by the Echocardiographic Heart of England Screening Study (ECHOES) [3], a population screening conducted on 6162 random selected patients, showing that borderline systolic dysfunction (EF: 40-50%) was associated with an adverse prognosis. However, the 40% cut-off used for the diagnosis of HFpEF form is arbitrary and many patients with mid-range EF have been classified as patients with HFpEF in clinical trials [1,4].

Usefulness and limitations

The usefulness of EF in HF patients is undisputed as it is one of the most important predictors of mortality in HF of any etiology [1,5-7], mainly of ischemic origin, as an expression of post-infarct ventricular remodeling [8-10]. Moreover, EF has a pivotal role in the indication of drug therapy, which in turn affects the long-term prognosis in both symptomatic and asymptomatic patients [11-13]. The predictive prognostic power of EF has also been demonstrated in studies of asymptomatic population [14] and, recently,
was also confirmed in patients with acute ST elevation myocardial infarction (STEMI) treated with primary angioplasty.

In fact, in a cohort of 2086 consecutive STEMI patients, enrolled between 2007 and 2016, patients presenting with mid-range EF (858, 41%) had a worse long-term prognosis (8 years) than those who had a normal FE (1013, 48%) (9.8% vs 7.2%, p<0.01) but showing a lower mortality rate compared to those with reduced EF (9.8% vs 29.2%, p<0.001) [15]. It has also been shown that serial evaluation of EF changes over time is a powerful predictor of survival and hospitalization in HF, thus representing a simple but feasible measure of prognosis in heart failure with HFrEF [16]. This result is in line with the results of a meta-analysis that included 30 mortality trials, 25 therapeutic interventions for a total of 69,766 patients and 88 studies that had LV remodeling in same therapies as End-points (19,921 patients). The risk of death (odds ratio) in mortality trials was correlated with the pharmacological effect on both EF (r = 0.51, p<0.001) and LV remodeling [17].

The main limitations of LV function evaluation by EF are substantially of two types i) the variability and reproducibility of the data, and ii) the load dependence of EF. Previous studies have reported a high intra-observer variability of both end-diastolic volume (EDV) and end-systolic volume (ESV) (11-15% and 15-25% respectively), and of EF (7-10%), regardless of the methods used (Area-length, Simpson). This variability increases in dilated ventricles and for the lowest EF values (<20%), markedly limiting the measurements reproducibility, at least in laboratories that have not performed intra and inter-observer variability tests. The second important limit lies the fact that the EF is a parameter of chamber function (expressing the emptying of the left ventricle) rather than a real index of LV contractile function. Thus, it is strongly affected by LV geometry and load. The relationship between EDV (ml/m²) and the EF is inverse and is regulated by LV geometry. In the initial phase of heart failure, LV pre-load and after-load tend to increase, acting in opposite directions on the EF which therefore remains normal despite the development of eccentric hypertrophy and dilatation, tending to stay stable for progressive volume increases as expressed by Starling principle [18]. For this reason, in advanced HF, EF can remain constant even in the presence of significant pre-load and after-load changes. On the contrary, in the presence of concentric geometry, EF can vary considerably with the loading conditions and may overestimate the real contractile ventricular performance. In fact, the contractile amplification towards the endocardium determined by the interaction that the myocardial fibers, structurally oriented in different ways (opposed helical, radial and longitudinal fibers), exercise during contraction can result in an amplification of the shortening measured at the endocardium and in an overestimation of EF. This phenomenon is particularly evident in concentric hypertrophy. In experimental models, a 15% shortening of the single isolated myocardial fiber correspond to a thickening of about 40% of the endocardium [19]. This explains why a measure of the contractile function taken at the center of the LV wall (midwall shortening) may reveal a sub-clinical latent contractile dysfunction earlier than those taken at endocardium (such as fractional shortening or EF). The relationship of midwall fractional shortening to circumferential end-systolic stress [20-22] (that physiologically oppose to the contraction) showed a significant prognostic value in different clinical settings. Measurement of stroke volume, longitudinal function and measurements of myocardial strain may exceed the limitations of EF in assessing the contractile reserve of heart failure patients and may define the phenotype and prognosis [23] when considered together with morphologic LV data (chamber dilation, wall thickness, relative wall thickness) [24].

Left ventricular diastolic function

The diagnosis of heart failure with preserved systolic function (HFrEF) can be difficult because it requires multi-parametric evaluation and can coexist with a number of comorbidities that makes that phenotype peculiar and complex. The physio-pathological basis needed for diagnosis of HFrEF is the recognition of diastolic dysfunction, which can also be associated with a preclinical systolic dysfunction, the latter being detectable through the assessment of myocardial deformation parameters or, as previously mentioned, the LV end-systolic stress/LV function relationships [21]. The diastolic dysfunction diagnosis should include at least the evaluation of the transmitral flow velocities (peak E velocity, E deceleration time, EA velocity ratio) and the tissue Doppler velocity (TDI) at the level of the lateral and medial mitral annulus (E/e ≥13 cm / sec and mean e’ septal and lateral wall ≥9) [25]. An important finding of confirmation, necessary in case of initial suspicion/evidence of HFrEF / HFrEF, consists in the co-existence of structural cardiac changes demonstration in addition to the functional ones, able to explain the clinical presentation of heart failure (HF). Among these, the ESC guidelines underline the importance of detecting LV hypertrophy (left ventricular mass index ≥115 g/m² for males and ≥95 g/m² for females) left atrial dilatation (left atrial volume index> 34 ml/m ²) which both identify HF stage B and are obviously present in the more advanced stages (C and D). Diastolic dysfunction, including preclinical, asymptomatic or symptomatic forms, has a high negative prognostic value confirmed by population and clinical studies [26,27]. Clinical conditions associated with HFrEF [25] are advanced age, female gender, arterial hypertension, atrial fibrillation (AF), renal dysfunction, obesity, metabolic syndrome, obstructive pulmonary disease (COPD) and/or pulmonary hypertension (PH), sleep apnoea syndrome and physical deconditioning. Many of these conditions are included in a more extensive definition of HF stage B [28,29]. The diagnosis of HFrEF in patients with AF can be difficult. AF may be a consequence of HFrEF or simply a determinant of a transient decompensation condition, which however may underline a predisposition to HF development (stage B). Therefore, the echocardiographic recognition of diastolic dysfunction is central in confirming diagnostic hypothesis of HFrEF/preclinical diastolic cardiac dysfunction (stage B of the HF). It is useful in subjects exposed to risk, mainly with advancing age because it is a condition with a high prevalence in the elderly [30,31].

The limitations are essentially linked to the feasibility of performing a multi-parametric quantitative echocardiographic evaluation (to recognize structural and functional myocardial abnormalities during hospital admission or in the outpatient setting. The data from the VASTISSIMO study (EValuation of the AppropriateneSs of the preclInical phase (Stage A and Stage B) of Heart Health Management in Outpatient Clinics in Italy) indicate that this quantification, performed in the hospital and / or community practice, is still not optimal. The EF and the diastolic dysfunction are important predictors of clinical events and mortality in HF.

The limitations are essentially related to its feasibility, since performing a multi-parametric quantitative echocardiographic evaluation, as indicated by the guidelines, may be difficult in clinical practice. Difficulties in method standardization, the poor attitude of cardiologists to test their reproducibility (test-retest, variability) favor the evaluation “at-a-glance” of LV structural and functional LV abnormalities. In conclusion, although obtaining a complete LV systolic and diastolic function assessment may be considered to be difficult and time consuming, only maintaining an elevated skill in diagnostic techniques can guarantee to cardiolo-
gists a progression in the knowledge and in the comprehension of such a complex clinical picture.

References

