



EDITORIAL COMMENT

Assessment of diastolic function: How much more evidence do we need?



Avaliação da função diastólica – de que mais provas necessitamos?

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Diastolic dysfunction (DD) usually reflects impaired left ventricular (LV) relaxation and increased LV chamber stiffness, leading to increased filling pressures.¹

It may relate to altered LV geometry, myocardial stiffness and fibrosis, molecular mechanisms underlying delayed myocardial relaxation and tone, and disturbed ventricular-arterial coupling.²

DD may manifest as altered diastolic suction and filling, mitral annular movements, myocardial strain patterns, torsional movements, LV synchrony, and left atrial (LA) size and function.²

There is increasing evidence documenting the association of DD with aging,³ cardiovascular risk factors (diabetes and pre-diabetes, hypertension and pre-hypertension, and obesity),^{4,5} and various comorbidities, including coronary artery disease and end-stage kidney disease.^{6,7} DD is also a known contributor to clinical heart failure in patients with reduced LV ejection fraction (LVEF), and plays a central role in heart failure with preserved LVEF.^{2,8}

The association of DD with prognosis is the subject of increasing interest, with a large body of accumulating evidence.

In the current issue of the *Journal*, Ladeiras-Lopes et al.⁹ present a systematic review and meta-analysis assessing the prevalence of DD and quantifying its association with the risk of cardiovascular events and death.

Their paper includes 19 community-based studies for general analysis, of which nine were suitable for quantitative estimation of the magnitude of the association. More than 63 000 participants were included, with mean ages ranging from 50 to 82 years. Diabetes, LV systolic dysfunction and coronary heart disease were among the comorbidities in these populations, while significant chronic kidney failure was an exclusion criterion. DD was mostly defined according to echocardiographic criteria, which varied widely among the studies included (of note, none of them included the 2016 recommendations for DD classification¹). One study defined DD according to hemodynamic criteria. The range of follow-up periods was also quite wide, from one to 11 years.

The mean prevalence of DD was 35.1%, ranging from 5.3% to 65.2%. Overall, DD was associated with adverse cardiac events, with 17 of the included studies showing that it was a significant predictor of events and/or mortality. Interestingly, one of the two studies that did not find this association was the one that defined DD according to hemodynamic criteria. In this study, DD in the absence of coronary artery disease and systolic dysfunction was not associated with a higher rate of events.¹⁰ In the nine studies included in the

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meta-analysis, DD was associated with a 3.53-fold higher risk of combined events and/or death.

The considerable heterogeneity in study populations (due to the different subgroups included in each paper or to the lack of consistency in the criteria used for the diagnosis of DD) is evident and is clearly pointed out by the authors. This major limitation, common to most systematic reviews, means a degree of caution is required when interpreting the results. Even so, the magnitude of the association found should be cause for reflection and for acceptance, once and for all, that assessment and interpretation of diastolic function should be mandatory in every echocardiographic report. This vulnerable population clearly needs to be identified to better manage and control their risk.

Naturally, a clearer and simpler definition of DD would be welcome. However, DD is a complex entity and it is unrealistic to expect a perfect classification of all patients.

The first clinical guidelines on the assessment of diastolic function in clinical practice were published in 2009.¹¹ Although comprehensive, they recommended the assessment of various two-dimensional and Doppler parameters to grade DD and to estimate LV filling pressures, including mitral inflow, pulmonary venous flow, LA maximum volume index, tissue Doppler velocities, pulmonary artery systolic and diastolic pressures, and flow propagation velocity. The assessment was based on LVEF and relied on several different algorithms. This multiparametric and multistep approach was considered complex and challenging to integrate into daily practice by many clinicians.

The primary goal of the 2016 consensus document¹ was to simplify the assessment of diastolic function. It focuses mainly on four variables: mitral inflow velocities, tissue Doppler early diastolic velocity, LA maximum volume index and peak tricuspid regurgitation velocity. There are two general algorithms for patients in sinus rhythm, with the addition of specific recommendations for patients with relevant clinical conditions such as atrial fibrillation, mitral valve disease, and pulmonary hypertension. Of note, in the presence of evidence of heart disease (such as LV hypertrophy and/or LA enlargement in patients with hypertension or reduced LVEF), instead of assessing the four variables, it is recommended to go directly to estimation of mean pulmonary capillary wedge pressure.

The accuracy of the 2016 algorithm has been compared to the invasive gold-standard measurement of LV filling pressures in several studies that together represent validation in a large number of patients. In the EACVI Euro-Filling study it was a good predictor of increased invasive LV end-diastolic pressure (area under the curve of 0.78),¹² and in Andersen et al.'s study¹³ it had an overall accuracy of 87% in estimating LV filling pressure.

Moreover, the impact of the 2016 guidelines on the diagnosis of DD has been compared with the 2009 recommendations, the former producing a much lower prevalence of DD, with poor agreement between the classifications.¹⁴ The newer guidelines appear to diagnose only the most advanced cases of DD, classifying many patients as having indeterminate diastolic function. This higher specificity seems to translate into better prediction of cardiovascular events: using the 2016 classification, DD diagnosis was associated with worse outcomes than normal diastolic function (unlike the 2009 classification, in which similar event-free survival

was predicted in patients with normal and abnormal diastolic function) and was a major predictor of adverse cardiac events following myocardial infarction (whereas a diagnosis of DD by the 2009 classification was not).¹⁵

Of course the assessment of diastolic function is still limited and results in a proportion of indeterminate cases, estimated to be 10-15% in experienced laboratories, which is considered to be acceptable.¹⁶

In these cases, additional parameters or testing conditions should be used. Since diastolic function is dynamic, one solution is to reassess under exercise and other hemodynamic maneuvers that can unmask the presence of DD, such as the Valsalva maneuver. Assessment of E/e' at peak exercise is feasible, and correlates with invasive measurements of LV filling pressures and with prognosis.²

Other solutions have been proposed to better assess diastolic function, including deriving new, age-specific reference ranges for old parameters,¹⁷ using new markers of diastolic function such as ventricular and atrial strain/strain rate, LV untwisting or E/e'sr, or using new computational analyses for automated classification of repetitive patterns.¹⁸⁻²⁰

All these new approaches appear promising but at the present time, most new parameters derived from deformation analysis lack clinical validation, while artificial intelligence-based algorithms are difficult to integrate into routine workflow, and are still beyond the reach of clinicians.²¹

In conclusion, the findings of Ladeiras-Lopes et al. are important: they are a reminder that assessment of diastolic function is mandatory as an important non-invasive risk-stratifying tool. In this context, even though not perfect, the current guidelines are easy to apply and will at least identify patients with more advanced diastolic dysfunction, and therefore higher risk of worse cardiovascular outcomes. Hopefully future evidence will lead to more effective approaches to earlier identify these vulnerable patients, in whom preventive measures will improve outcomes, and save costs.

Conflicts of interest

The author has no conflicts of interest to declare.

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