Diastolic heart failure currently accounts for more than 50% of all heart failure cases in Western societies.1 Because of normal left ventricular (LV) systolic function, diastolic heart failure is mainly attributed to diastolic LV dysfunction evident from slow LV relaxation and high diastolic LV stiffness.2,3 High diastolic LV stiffness is the most important cause of the repetitive heart failure episodes occurring in these patients,4 while high arterial elastance,5 atrial remodelling,6 and impaired chronotropic7 or vasomotor8 responses are additional contributors. Because of the pathophysiological importance of diastolic LV dysfunction, all previous diagnostic guidelines for diastolic heart failure considered evidence of diastolic LV dysfunction to be essential for the diagnosis.9–11 The recently updated diagnostic guidelines for diastolic heart failure provided by the Echocardiography and Heart Failure Associations of the European Society of Cardiology12 continued to adhere to this principle and required three conditions to be simultaneously satisfied for the diagnosis of diastolic heart failure: (i) signs or symptoms of fluid congestion; (ii) a normal systolic LV function evident from a LV ejection fraction (EF) >50% and a LV end-diastolic volume index <97 mL/m²; and (iii) evidence of diastolic LV dysfunction. The latter can be acquired by cardiac catheterization, by Doppler echocardiography, and by biomarkers such as brain natriuretic peptide (BNP) and NT-proBNP. A pulmonary capillary wedge pressure larger than 12 mmHg, an LV end-diastolic pressure (LVEDP) larger than 16 mmHg, and a ratio of mitral early diastolic flow velocity over tissue Doppler mitral annular lengthening velocity (E/E’) in excess of 15 provide stand-alone evidence of diastolic LV dysfunction. An E/E’ ratio ranging from 8 to 15 (E/E’ 8–15), BNP larger than 200 pg/mL, and NT-proBNP larger than 220 pg/mL require additional investigations to establish presence of diastolic LV dysfunction. For E/E’ 8–15, the second line of additional investigations consists of mitral flow velocity Doppler, pulmonary venous flow velocity Doppler, echocardiographic measures of left atrial volume index (LAVI) or of LV mass index (LVMI), and electrocardiographic evidence of atrial fibrillation. E/E’ 8–15 provides diagnostic evidence of diastolic LV dysfunction, when the ratio of early (E) to late (A) mitral flow velocity (E/A) is less than 0.5 and the E-wave deceleration time larger than 280 ms or when the duration of the pulmonary venous retrograde A-wave exceeds the duration of the mitral A-wave by more than 30 ms (Ard-Ad > 30 ms) or when LAVI exceeds 40 mL/m² or when LVMI exceeds 122 g/m² in females and 149 g/m² in males or when the ECG shows atrial fibrillation. The study by Emery et al.13 reported in this issue of the journal explores the validity of the cutoff criteria for LAVI, LVMI, and flow velocity Doppler measurements, which were used as additional, second line evidence for diastolic LV dysfunction in the presence of an equivocal E/E’ 8–15. Such a validation of the recently proposed diagnostic flowchart for diastolic heart failure is important as it could lead to adjustment by daily clinical practice of cutoff criteria, which were derived from the statistical analysis of published data. Adjustments are indeed proposed in the study by Emery et al., which demonstrates the used cutoff of LAVI (>40 mL/m²) to provide optimal sensitivity and specificity, the used cutoffs of LVMI (122 g/m²; 149 g/m²) to provide only optimal specificity, and the flow velocity Doppler measurements not to contribute to the diagnosis of diastolic heart failure. Straightforward implementation of these findings into the recently proposed diagnostic flowchart for diastolic heart failure12 seems however premature.

Emery et al. based their conclusions on a retrospective analysis of consecutive echocardiograms excluding severe valvular heart disease, transplant recipients, and presence of atrial fibrillation. Extrapolation of findings derived from such a poorly identified study population to patients suspected of diastolic heart failure is questionable. Although the study population was split up in subgroups with normal (>50%) or reduced (<50%) LVEF, the subgroup with normal LVEF still missed essential evidence for the diagnosis of diastolic heart failure because of lack of signs or symptoms of fluid congestion and lack of a normal LV end-diastolic volume index (< 97 mL/m³). Failure to assess LV end-diastolic volumes is especially worrisome because concentric LV remodelling is typical for diastolic heart failure, whereas eccentric LV remodelling is characteristic for heart failure...
with reduced LV systolic function, usually labelled systolic heart failure.13,14 Furthermore, exclusion of atrial fibrillation, which is a comorbidity of diastolic heart failure in 25% of patients,15 eliminated portion of the diastolic heart failure target population from the study cohort.

The analysis used by Emery et al. to determine optimal cutoff criteria of LAVI, LVMI, and flow velocity Doppler measurements raises concerns. Sensitivity and specificity of cutoff values of LAVI, LVMI, and flow velocity Doppler measurements were derived from patients with E/E' < 8, considering not to have diastolic LV dysfunction, and from patients with E/E' > 15, considering to have diastolic LV dysfunction. Such an analysis evaluates the use of LAVI, LVMI, and flow velocity Doppler measurements as stand-alone evidence of diastolic LV dysfunction against E/E' < 8 and E/E' > 15, the gold standards for absence or presence of diastolic LV dysfunction. The recently proposed diagnostic flowchart for diastolic heart failure, however, positions LAVI, LVMI, and flow velocity Doppler measurements as a second line of evidence in the presence of an equivocal E/E' 8–15. Serial positioning of different investigations was introduced in the recently proposed diagnostic flowchart because of concerns of an E/E' cutoff value between 8 and 15 having too low a specificity for the stand-alone diagnosis of diastolic LV dysfunction. Serial positioning of tests increases diagnostic specificity and could therefore overcome this concern. This serial positioning was overlooked in the analysis by Emery et al., which performed a head-to-head comparison between E/E' and LAVI, LVMI, or flow velocity Doppler measurements. A more meaningful but unfortunately also more difficult analysis would have been to validate in patients with E/E' 8–15 the outcome of serial testing with LAVI, LVMI, or flow velocity Doppler measurements against other stand-alone evidence of diastolic LV dysfunction, such as pulmonary capillary wedge pressure, LVVEDP, or LV diastolic stiffness modulus. A validation of tissue Doppler E/E' against LV diastolic stiffness modulus has recently been reported.16 Surprisingly, this study observed a high specificity (92%) of E/E' = 8 as cutoff value for diastolic LV dysfunction and therefore suggested a second line of tests to be superfluous in patients with E/E' 8–15. Hence, the necessity of serial testing in patients with an equivocal E/E' 8–15, as proposed in the recent diagnostic flowchart for diastolic heart failure, needs to be urgently reassessed.

Exclusion of LAVI, LVMI, and flow velocity Doppler measurements of patients with E/E' 8–15 also creates a statistical problem for the analysis performed by Emery et al. The cohort of patients with E/E' 8–15 represents the middle portion of a diastolic function distribution, whereas patients with E/E' < 8 and E/E' > 15 occupy the two outer extremities with either clearly normal or prominently abnormal diastolic LV function. Optimization of cutoff values of LAVI and LVMI against E/E' data derived from these outer extremities erroneously increased sensitivity and specificity of these cutoff values because patients representing a diagnostic challenge were more likely to be in the E/E' 8–15 range, which was removed from the analysis. Removal of the E/E' 8–15 patients could also explain why mitral flow velocity Doppler measurements did not contribute to the diagnosis of diastolic LV dysfunction in the study by Emery et al. Continued use of mitral flow velocity Doppler measurements for the assessment of diastolic LV function was recently advocated by eminent investigators,17,18 who felt that it allowed for a comprehensive assessment of diastolic LV function, which did not only address LV filling pressures but also LV relaxation kinetics. To include selective LV relaxation disturbances, the proposed diagnostic flowchart for diastolic heart failure used cutoff values of mitral valve flow velocity Doppler corresponding to a ‘slow relaxation type’ of diastolic LV dysfunction (E/A<0.5 and DT−0.5<280 ms). Patients with this type of diastolic LV dysfunction were again most likely to be found in the E/E' 8–15 patient cohort, as they had no important elevation of LV filling pressures. Hence, exclusion of the E/E' 8–15 patient cohort precisely removed these patients, in whom mitral flow velocity Doppler measurements could have been a valuable adjunct to the diagnosis of diastolic LV dysfunction.

Validation of the recently proposed diagnostic flowchart for DHF is important as the proposed cutoff values of the different investigations were derived from the published research and not from routine clinical practice. Such a validation effort should, however, be carried out in patients suspected of having diastolic heart failure, respect the serial position of different investigations, preferably refer to invasively acquired stand-alone evidence of diastolic LV dysfunction, and cover the entire spectrum of diastolic LV dysfunction from slow LV relaxation to high diastolic LV stiffness. When the measurement stick needs polishing, use good wax and a clean cloth.

References

12. Paulus WJ, Tschöpe C, Sanderson JE, Ruscini C, Flachskampf FA, Rademakers FE et al. How to diagnose diastolic heart failure? A consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction (HFNEF) by the Heart Failure and Echocardiography...


