Prognostical relevance of diastolic dysfunction in HfpEF

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The prognostic relevance of diastolic dysfunction has to be evaluated in a more general prognostic framework, including epidemiological, clinical, laboratory and echocardiographic indicators of prognosis and outcome. The relevant question for the clinician is to know if he can improve his prognostic assessment with adding echocardiographic parameters, in particular diastolic parameters, i.e. does diastolic dysfunction have an independent prognostic value over and above available prognostic indicators and does adding diastolic dysfunction provide a significant net re-classification of patients?

General approaches for evaluating prognosis in HFpEF

In the I-PRESERVE population (mean age 72), the most powerful prognostic parameters were N-terminal pro-B-type natriuretic peptide, age, diabetes mellitus and previous hospitalization for heart failure. Other independent factors associated with poor outcome included quality of life, chronic obstructive lung disease, inflammation (neutrophile count), heart rate and estimated GFR. These simple and widely available parameters were associated with outcome and identified subgroups at very high and very low risk of events. [1]

A randomized clinical trial (RCT) population may be different from the population at large suffering from HFpEF. Inclusion in trials may have been more focused on echocardiography criteria. RCT investigators might have been more restrictive toward elderly, female, and/or co-morbid patients. Retrospective population studies could be biased as well and may have captured more strongly confirmed primary heart failure diagnoses. In the KArolinska-RENnes (KAREN) study HFpEF was prospectively searched for in the population. The independent predictors of prognosis were age, history of non-cardiovascular syncope (a proxy for frailty), valvular heart disease, anemia, lower sodium, and higher potassium levels (impaired renal function) but not the remaining co-morbidities. Of note and in contrast with RCT findings, the use of renin–angiotensin system antagonist and mineralocorticoid receptor antagonist independently predicted improved prognosis.[2]

Other studies looked at the value of specific parameters such as worsening of renal function (I-PRESERVE data),[3] albuminuria independently from renal function,[4] and anemia.[5]

Echocardiographic approaches for improving prognosis in HFpEF

In the prospectively identified HFpEF (Framingham HF criteria, ejection fraction ≥ 50%) patients from Olmsted County, right ventricular pressures and function were assessed. Function was evaluated with TAPSE (tricuspid annulus peak systolic excursion) or with a semi-quantitative assessment. Evidence of right ventricular dysfunction was present in a significant subset of patients and was associated with more advanced clinical and echocardiographic characteristics and poorer outcomes. Right ventricular dysfunction provided

important prognostic information, which was independent from the prognostic information of systolic pulmonary artery pressure.[6]

In the I-PRESERVE echo sub-study, about two thirds of the participants had left ventricular hypertrophy or remodeling, about two thirds had increased left atrial size and about two thirds had some degree of diastolic dysfunction. A multivariable analysis controlled for 7 key clinical variables (including the most powerful log NT-pro-BNP). The classification of diastolic dysfunction and the lateral E/e' ratio didn't survive multivariate analysis. LV mass and LA size remained independently associated with an increased risk of morbidity and mortality.[7]

A similar analysis was performed in the TOPCAT echo sub-study. Neither LV volumes nor LVEF was predictive of worse outcomes in this population with an LVEF ≥45%, consistent with prior studies and possibly related to the narrow spectrum of mostly normal values represented in this population. LV hypertrophy, elevated LV filling pressure (evaluated with septal E/e'), and higher tricuspid regurgitation velocity (rather than estimated pulmonary pressure) were predictive of prognosis and outcome beyond clinical and laboratory characteristics. LV hypertrophy, elevated filling pressure, and elevated pulmonary artery pressure frequently coexist, and greater number of these abnormalities is associated with higher risk for the primary composite end point and incident HF hospitalization. Finally, the presence these abnormalities significantly improved risk prediction based on the c statistic, net reclassification improvement, and integrated discrimination improvement.[8]

Arterial function and wave reflection

Arterial function with its resistive and pulsatile aspects may contribute to improve prognostic evaluation of HFpEF subjects. In general, the best-validated parameter is pulse wave velocity.[9] An emerging parameter is pathological wave reflection in the arterial tree, which elevates time-varying pressure in late-systole and hence late-systolic wall stress.[10] The magnitude of wave reflection appears to be independently associated with diastolic dysfunction[11-14] and elevated left ventricular mass.[15] It is an independent predictor of cardiovascular events, specifically incident heart failure,[16] and mortality.[17] The prognostic value of wave reflection is independent of and as potent as e.g. systolic blood pressure.

The most important prognostic parameters are listed in the appended table. They are subdivided in clinical data, laboratory data and imaging data.

Table

Prognostic stratification of HFpEF patients

Clinical data

- Age, diabetes, previous hospitalisation for heart failure, non-cardiac syncope (frailty)
- COPD, heart rate

Laboratory data

- BNP, NT-pro-BNP
- Estimated GFR, worsening GFR, sodium, potassium
- Micro-albuminuria
- Anaemia, inflammation (neutrophile count),

Cardiovascular imaging

- Left ventricular mass
- Left atrium volume
- Left ventricular filling pressures (septal E/e')
- Pulmonary venous S/D ratio
- Tricuspid regurgitation velocities
- Right ventricular function (TAPSE)
- Presence of valvular heart disease
- Arterial function (wave reflection)

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