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An Overview on H2FPEF Score

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Abstract:

Heart failure with preserved ejection fraction (HFpEF) is a common and complex clinical syndrome characterized by signs and symptoms of heart failure despite a normal or near-normal left ventricular ejection fraction (LVEF ≥50%). Diagnosing HFpEF can be particularly challenging, as patients often present with non-specific symptoms such as exertional dyspnea, and traditional heart failure diagnostics may not definitively confirm the condition. To address this diagnostic uncertainty, the H2FPEF Score was developed by Dr. Barry A. Borlaug and colleagues at the Mayo Clinic and published in *Circulation* in 2018. The score provides a simple, evidence-based tool to estimate the likelihood that a patient's symptoms are due to HFpEF rather than non-cardiac or alternative cardiovascular causes.

Keywords: HFpEF, H2FPEF Score, of heart failure

Introduction:

Over the past 3 decades, the prevalence of heart failure with preserved ejection fraction (HFpEF) relative to total heart failure prevalence rose from 41% to 56%. Simultaneously, the prevalence of heart failure with reduced ejection fraction and heart failure with midrange ejection fraction fell from 44% to 31% and from 15% to 13%, respectively. Despite this alarming increase in HFpEF prevalence, a reference strategy to establish the diagnosis of HFpEF is still lacking **(1)**.

As a consequence, trials continue to recruit patients with HFpEF by using a wide array of criteria and cutoff values. To remediate the confusion, professional societies such as the European Society of Cardiology and the American Society of Echocardiography issued several consensus statements providing diagnostic guidelines or recommendations for HFpEF. These statements were frequently met by skepticism qualifying them as overcomplicated and even triggered disbelief in the existence of HFpEF: “If HFpEF is that difficult to diagnose, it does not exist!”

On top of symptoms and signs of volume overload and a preserved ejection fraction, the diagnostic strategies recommended by the professional societies all consisted of similar elements: evidence of structural left ventricular (LV) remodeling based on left atrial (LA) volume index or LV mass; diastolic LV dysfunction based on early diastolic mitral inflow velocity (E), early diastolic mitral annular tissue velocity (e′), and the ratio thereof (E/e′); pulmonary hypertension based on peak tricuspid regurgitation velocity; and increased myocardial wall stress based on plasma levels of natriuretic peptides. Over the past decade, these elements have been repeatedly reshuffled like a deck of cards to yield yet another algorithm **(2)**.

Major issues involving the diagnosis of HFpEF remained unaddressed, however. These consisted of distinct clinical phenotypes predisposing to HFpEF, such as obesity, diabetes mellitus, and chronic kidney disease; existence of an early stage of HFpEF whereby patients present with normal LV filling pressures at rest but a brisk rise of filling pressures during exercise; and a specific plasma biomarker profile that differs from heart failure with reduced ejection fraction and frequently features normal or minimally raised levels of natriuretic peptides **(3)**.

The study by **Reddy et al. (4)** addressed these issues and proposed to diagnose HFpEF in symptomatic euvolemic patients by using a H2FPEF score derived from dichotomized variables, or a HFpEF nomogram derived from continuous variables.

The H2FPEF score and HFpEF nomogram were based on simple clinical and echocardiographic characteristics that served as variables in a logistic regression analysis. This analysis evaluated their ability to discriminate noncardiac dyspnea from HFpEF, both rigorously established using invasive hemodynamic exercise testing. The H2FPEF score and the HFpEF nomogram were subsequently validated in a separate cohort and performed robustly with areas under the curve of 0.886 and 0.910, respectively. Finally, sensitivity analyses confirmed that the H2FPEF score performed equally well in local and referral populations **(3)**.

Selected variables:

An extensive panel of clinical and echocardiographic variables was first evaluated in univariable analysis. Variables that were associated with HFpEF in isolation were subsequently entered in combination into a multivariable model. For the H2FPEF score, 6 dichotomized variables remained associated with HFpEF and received a score proportional to the strength of their respective association. These scores were added and yielded the global H2FPEF score ranging from 0 to 9. At a score of ≥6, HFpEF was diagnosed with a probability ≥90%.

For the HFpEF nomogram, 5 combined variables were associated with HFpEF, whereby atrial fibrillation was treated as a dichotomous variable and all others were treated as continuous variables, yielding a value range of 0 to 260. At a nomogram value ≥136, HFpEF was again diagnosed with a probability ≥90% **(2)**.

The 6 variables that constituted the H2FPEF score were a body mass index (BMI) >30 kg/m2 (H); use of ≥2 antihypertensive medications (H); the presence of atrial fibrillation (F); pulmonary hypertension defined as pulmonary artery systolic pressure >35 mm Hg (P); (5) elderly with an age >60 years (E); and elevated filling pressures evident from E/e′ >9 (F). The presence of persistent or paroxysmal atrial fibrillation yields 3 points, a BMI >30 kg/m2 yields 2 points, and all other variables yield 1 point. The relative weights and cutoff values of these variables deserve closer attention.

Metabolic risk factors scrutinized in univariable analysis were BMI >30 kg/m2, BMI >35 kg/m2, prediabetes or diabetes mellitus combined, and diabetes mellitus. BMI >30 kg/m2 was strongly associated with HFpEF in multivariable analysis and received a score of 2 points, whereas prediabetes and diabetes mellitus combined just failed to reach statistical significance. An additional classification and regression tree analysis also demonstrated that the largest portion of patients with HFpEF (27%) was identified by an age of >60 years, the absence of atrial fibrillation, and BMI >29 kg/m2. All these findings support the importance of metabolic risk for development of HFpEF and are in line with earlier results of epidemiological registries **(4)**.

In a large community-based sample of elderly persons (64±8 years) recruited by the Framingham Heart Study, progression of echocardiographic diastolic LV dysfunction over a 5-year period was closely related to evolving metabolic risk expressed as body weight gain or worse diabetes status **(5)**. A similar outcome was observed in a

community-based cohort from Olmsted County in which diastolic LV stiffness tracked body weight gain and not arterial hypertension **(6)**.

In comparison with metabolic risk, arterial hypertension was less strongly associated with HFpEF because, in the dichotomized point score model, treatment with ≥2 antihypertensive medications yielded only a single point for the H2FPEF score. Moreover, in the HFpEF nomogram, which used continuous variables for the prediction of HFpEF, the number of antihypertensive medications was no longer associated with HFpEF and therefore excluded from the nomogram. These findings again suggested that HFpEF appears to be driven more by metabolic comorbidities than by myocardial overload **(7)**.

The latter was also evident from an analysis of the TOPCAT trial (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) that observed no relation between systolic blood pressure quartiles and outcome, or between blood pressure–lowering and treatment effect. Atrial fibrillation stood out as the most important predictor of HFpEF in the logistic regression analysis of the H2FPEF score and concordantly received a 3-point score when positive **(8)**.

This high relative weight mirrors an electrophysiological study describing a high prevalence of HFpEF in patients with atrial fibrillation and dyspnea with an odds ratio favoring HFpEF equal to 39 in permanent atrial fibrillation and 8 in paroxysmal atrial fibrillation. HFpEF and atrial fibrillation have indeed correctly been labeled as vicious twins **(4)**.

In the presence of sinus rhythm, all remaining variables have to be positive to attain a H2FPEF score of 6 and to diagnose HFpEF with 90% probability. This specifically implies that pulmonary hypertension defined by a pulmonary artery systolic pressure >35 mm Hg becomes an obligatory condition and that evidence of raised LV filling pressures is therefore not solely inferred from E/e′ >9 **(2)**.

Rejected variables:

Some characteristics, which are usually considered typical for HFpEF, surprisingly failed to reach statistical significance either in univariable analysis or in the multivariable model. The former applies to sex and the latter to LA volume index and levels of circulating N-terminal probrain natriuretic peptide. Although women accounted for 61% of the HFpEF population, female sex was excluded from the H2FPEF score, probably because of the control noncardiac dyspnea group that had a similar sex ratio with 59% women.

The LA volume index also failed to be maintained in the multivariable model, despite the LA volume being considered reflective of LV diastolic dysfunction, much like glycohemoglobin is used in diabetes mellitus, because of its ability to integrate filling pressures over time **(2)**.

In the study by **Reddy et al. (4)**, 45% of patients had early HFpEF with diastolic pressure overload absent at rest and evident only during invasive hemodynamic exercise testing. Because of this intermittent diastolic pressure overload in early HFpEF, LA expansion will be less, especially when LA compliance is reduced as previously reported in HFpEF. In early HFpEF, functional indices such as global LA strain or LA conduit strain might be more appropriate than maximal LA volume index.

Finally, circulating levels of N-terminal probrain natriuretic peptide also failed to significantly contribute to the multivariable model and were not maintained in the H2FPEF score or in the HFpEF nomogram. Although N-terminal probrain natriuretic peptide is prognostic in HFpEF, it can be notoriously low, especially in obesity-related

HFpEF where epicardial fat raises diastolic LV cavity pressures without elevating LV transmural pressures because of the induction of constrictive physiology **(3)**.

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