



Diagnostic algorithm for HFpEF: how much is the recent consensus applicable in clinical practice?

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Abstract

Heart failure with preserved ejection fraction (HFpEF) represents an important cardiovascular entity with increasing prevalence and relatively high mortality. The agreement about diagnostic algorithm for HFpEF is still missing. Echocardiographic approach remains the cornerstone in HFpEF diagnosis. Echocardiographic diastolic stress test provides numerous useful parameters that correlated well with indexes obtained by cardiac catheterization. Recently published consensus recommended new scoring system that included functional and structural echocardiographic parameters, as well as biomarkers. The new score for evaluation of HFpEF introduces a new set of parameters and proposed novel cutoff values for some of them. There are several important points that need to be resolved before full acceptance and clinical usage. First, some cutoff values are new and represent the result of expert consensus, without previous validation. Second, many patients with hypertension, obesity, and diabetes would be referred for further investigations as the result of this scoring, which is difficult to achieve in clinical circumstances. Third, the consensus equalized non-invasive and invasive diastolic stress tests in diagnosing of HFpEF, which is not a small issue. Namely, even though cardiac catheterization provides the final confirmation of elevated left ventricular filling pressures, it is still an invasive method, associated with procedural risk and other limitations. The aim of this review was to summarize the current knowledge diagnosis of HFpEF, as well as the recent consensus about diagnostic algorithm in patients with suspected HFpEF with its advantages and disadvantages.

Keywords Heart failure with preserved ejection fraction · Diastolic stress test · Cardiac catheterization

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a well-recognized entity in the last two decades [1]. However, there are still many controversies regarding the mechanisms, diagnosis, treatment, and outcome of patients with HFpEF. Diagnosis of HFpEF is relatively straightforward when patients are decompensated. The diagnostic algorithm is more

complicated when patients are chronically dyspnoic, without typical signs of HF. Left ventricular ejection fraction (LVEF) cutoff value for diagnosis of HFpEF significantly varied, which is why recently third entity was introduced—HF with mid-range LVEF (HFmrEF) defined by LVEF between 40 and 49% [1].

Detection of HFpEF and HFmrEF in stable and compensated patients represents the priority and greatest challenge of modern diagnostics. Echocardiography is a cornerstone for detection of cardiac changes. Determination of LVEF represents the first step in evaluation of HF patients. Reduced LVEF together with symptoms and elevated biomarkers indicates HF with reduced LVEF (HFrEF) or HFmrEF. However, diagnosis of HFpEF requires additional measurements. Pulsed and tissue Doppler have been considered the main techniques for evaluation of functional parameters that indicate HF [2]. Nevertheless, Doppler-derived LV filling parameters remain normal at rest and display abnormalities only during exercise [3]. Assessment of left atrial enlargement is the next step that can help in determination of LV diastolic dysfunction [4], and evaluation of LV longitudinal strain is the next stage that

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enabled detection of high-risk patients beyond LVEF [5]. Invasive hemodynamic exercise testing represents the reference method for HFpEF diagnosis in patients with exertional dyspnea of unclear etiology [3, 6]. However, the main limitations of this diagnostic approach are elevated risk, relatively high costs, and necessity of specialized training and equipment. Diastolic stress echocardiographic test emerged as non-invasive equivalence of invasive testing that has high sensitivity and specificity for diagnosis of HFpEF [6].

The most important risk factors for development of HFpEF are age, female sex, hypertension, obesity/overweight, diabetes, and renal disease [7–11]. These comorbidities are associated with similar cardiac structural and functional changes as HFpEF, and therefore, it is a challenging task to determine difference between HFpEF and cardiac remodeling induced by these risk factors. The latest consensus of the European Society of Cardiology proposed new criteria for diagnosis of HFpEF [12]. The appropriate validation of these new criteria is lacking, and therefore, they deserve discussion that would help clinicians in making decision if these guidelines are acceptable for everyday clinical practice and justified by currently available data.

The aim of this review was to summarize the current knowledge on diagnostic algorithm in patients with suspected HFpEF and discuss the proposed criteria in recently published consensus of the European Society of Cardiology on diagnosis of HFpEF. We particularly wanted to investigate the applicability of the proposed criteria in the patients with arterial hypertension.

Classification

Approximately 50% of all HF patients have preserved LVEF [2]. On the other hand, one must emphasize different definitions of preserved LVEF that varied from 40 to 55% [1]. This was the main reason for introduction of third group of HF patients, besides existing HFrfEF and HFpEF. This third group is called HFmrEF, which was defined by LVEF between 40 and 49% [1]. Previous studies that were comparing prevalence and mortality in HFrfEF and HFpEF patients showed no difference in any of these findings between these groups [3, 4]. Meta-analysis revealed that mortality in HFpEF patients was lower than in HFrfEF patients (25% vs. 32%) [5]. The investigators reported significant difference in clinical characteristics between these two groups. Namely, women were significantly more prevalent among HFpEF patients, who were also more obese with higher prevalence of arterial hypertension and significantly lower prevalence of coronary artery disease than HFrfEF patients [2–5]. Nevertheless, the effect of LVEF should not be neglected. Park et al. reported significantly worse outcome in patients with HFpEF (LVEF > 50%) with declining LVEF during the first year of 4-year follow-up [13].

The investigators found almost two times higher mortality in patients with HFpEF and declining LVEF than in patients with HFpEF and stable LVEF [13]. These differences encouraged investigations in patients with HFmrEF, which showed that mortality in these subjects was similar to those with HFpEF and significantly lower than in HFrfEF [7]. Composite outcome that included mortality and hospitalization in HFmrEF patients was between HFpEF and HFrfEF [7]. Plasma (NT-proBNP) was similarly related to mortality in all HF patients (HFpEF, HFmrEF, and HFrfEF) independent of other clinical parameters and LVEF [7].

Hypertension in HFpEF

Arterial hypertension represents one of the most important risk factors in development of HFpEF [14]. The most important mechanism that connects arterial hypertension and HFpEF is left ventricular hypertrophy (LVH) associated with myocardial fibrosis and consequent LV diastolic dysfunction (LVDD). The role of sympathetic nervous system, renin-angiotensin-aldosterone system, and oxidative stress in the HFpEF development is still controversial, which is why hypertension-induced hemodynamic changes are probably the most responsible for HFpEF development in hypertensive patients.

Considering the fact that percentage of hypertensive patients among HFpEF individuals usually exceeds 70% in large studies [14], and large overlapping between hypertensive-induced cardiac remodeling and cardiac changes seen in HFpEF patients, it is a challenging task to differentiate hypertensive heart disease from HFpEF.

HFpEF and hypertensive heart disease have two major overlapping areas: LVH and LV diastolic dysfunction. LVH is prevalent among hypertensive patients and our group showed that its prevalence ranged between 36 and 41% depending on echocardiographic criteria that were used in meta-analysis of 36,000 hypertensive patients [15]. Eccentric LVH was more prevalent than concentric LVH in hypertensive patients (range 20.3–23.0% vs. 14.8–15.8%, respectively, $p < 0.05$) [15]. Similar prevalence of LVH was reported in HFpEF patients. Shah et al. found LVH in 43% HFpEF patients [16].

LVH significantly increased the risk of HF development [17]. This is reported for both, HFpEF and HFrfEF, even after adjustment for known risk factors, such as age, gender, blood pressure, myocardial infarction, and diabetes [17]. This relationship appears to be linear. de Simone et al. demonstrated that each 1% increase in LV mass above the normal range was related with a 1% increased incidence of HF after controlling for risk factors [17].

LVDD is another important common issue in hypertensive heart disease and HFpEF. Our recent study showed that 29%

of untreated hypertensive patients had LVDD [18]. In hypertensive patients with long-lasting hypertension, the prevalence of LVDD is significantly higher and exceeds 50% [19]. In patients with HFpEF, investigators reported LVDD in 66% and 69% HFpEF patients, respectively [16, 20]. The majority of patients had first or second degree of LVDD [16, 18, 20]. However, one must emphasize that almost all these studies used old guidelines for assessment of LV diastolic function that did not include left atrial enlargement, which means that prevalence of LVDD was most likely underestimated.

Stress diastolic test

Parameters that describe LV filling could be normal or only mildly impaired in both, hypertensive and HFpEF patients. Therefore, exercise is the only method that can unmask diastolic abnormalities which cannot be seen under rest conditions. In patients with exertional dyspnea, exercise hemodynamic response is crucial and provides more physiological and diagnostic information than assessment of LV diastolic function at rest. Therefore, in these patients, it may be appropriate to assess the hemodynamic response to exercise to confirm that dyspnea is a consequence of LVDD. There are two types of diastolic stress test—invasive and echocardiographic.

Invasive diastolic stress test is performed while patient is doing exercise on a bicycle, which is fixed at the catheterization table in a supine position [6]. Changes of pulmonary capillary wedge pressure, an indirect parameter of LV filling pressure, during exercise can be evaluated by right heart catheterization through the right internal jugular vein or by introducing a pigtail catheter into the LV from a radial arterial access site [6]. LV systolic pressure, minimal LV pressure, LV end-diastolic pressure, and mean LV diastolic pressures can be measured in this way. However, this invasive method is impractical and related with some risk due to cardiac catheterization, and therefore, non-invasive techniques had to be introduced.

The combination of pulsed and tissue Doppler parameters (E/e') seemed to be the best non-invasive surrogate for evaluation of LV filling pressures [21, 22]. Validation studies showed high sensitivity and specificity of E/e' to discover elevated LV filling pressure measured during cardiac catheterization [21, 22]. Talreja et al. performed simultaneous echocardiographic examination and catheterization at rest and during exercise in patients with exertional dyspnea and found that E/e' provided a reliable estimation of pulmonary capillary wedge pressure at rest and during exercise [21]. Obokata et al. reported similar results from the cohort of patients with HFpEF without identifiable cardiac pathology [23]. The authors demonstrated that exercise E/e' data improved sensitivity and negative predictive value of this non-invasive test in comparison with cardiac catheterization that remains the gold

standard technique for hemodynamic assessment in HFpEF patients [23].

It has been proposed that diastolic stress test should be considered abnormal in presence of all these three parameters: (i) septal e' velocity < 7 cm/s or lateral e' velocity < 10 cm/s at rest; (ii) average $E/e' > 14$ or septal E/e' ratio > 15 with exercise; (iii) peak tricuspid regurgitation (TR) velocity > 2.8 m/s with exercise [24]. Belyavskiy et al. demonstrated that $E/e' > 15$ during diastolic stress test was the most accurate parameter to detect HFpEF (accuracy 86%) with a low sensitivity (45.5%) [25]. The combination of E/e' and TR > 2.8 m/s during exercise had significantly higher sensitivity for detection of HFpEF (sensitivity 72.7%, specificity 79.5%, and accuracy 78%). [25]. Furthermore, elevation of E/e' was related with reduced oxygen consumption, whereas the combination of increased E/e' and TR velocity was associated with elevated NT-proBNP values during exercise [25]. The authors did not investigate all three parameters (e' , E/e' , and TR) simultaneously due to small sample size, and therefore, the predictive value of this combination was not determined.

Systematic review that included 9 studies with 451 HFpEF patients showed that E/e' cannot be used for reliable assessment LV filling pressure changes in response to exercise [24]. Only 2 small studies (cumulative $n = 22$) support use of E/e' for assessment of LV filling pressure changes in HFpEF patients, whereas 7 other studies (cumulative $n = 429$) reported that E/e' was not useful for evaluation of LV filling pressure in HFpEF patients [24].

On the other hand, large studies showed significant predictive value of abnormal exercise E/e' . Holland et al. followed 522 patients for more than 1 year and found that exercise E/e' had the highest predictive value in patients who had normal rest E/e' [26]. The prognostic value was particularly high for cardiovascular hospitalization. Large study included 14,446 patients who underwent treadmill stress echocardiography due to suspected coronary artery disease and revealed that post exercise $E/e' > 15$ was a strong predictor of all-cause mortality independently of age, ischemia, and exertional dyspnea [27]. Patients with post exercise $E/e' > 15$ had a double higher risk of death than patients with $E/e' < 15$, even in the absence of ischemia [27].

These contradictory results regarding the importance of stress E/e' , its correlation with LV filling pressures, and predictive value only emphasize the importance of further prospective studies that would validate the use of this algorithm.

European consensus on diagnostic approach in HFpEF

The lack of algorithm for diagnosis of HFpEF in patients with exertional dyspnea is evident. In order to provide flow chart

Table 1 Criteria proposed in the consensus about diagnostic algorithm for HFpEF*

Criteria	Functional	Morphological	Biomarkers	
			Sinus rhythm	Atrial fibrillation
Major criteria (each criterion 2 points)	Septal e' velocity < 7 cm/s	LAVI > 34 ml/m ²	NT-proBNP > 220 pg/ml or BNP > 80 pg/ml	NT-proBNP > 660 pg/ml or BNP > 240 pg/ml
	Lateral e' velocity < 10 cm/s at rest	LVMi \geq 149 g/m ² for men and \geq 122 g/m ² for women and RWT > 0.42		
Minor criteria (each criterion 1 point)	Average $E/e' >$ 14 or septal E/e' ratio > 15 with exercise			
	TR velocity > 2.8 m/s with exercise			
	Average $E/e' >$ 9–14	LAVI 29–34 ml/m ²	5-NT-proBNP 125–220 pg/ml or BNP 35–80 pg/ml	NT-proBNP 365–660 pg/ml or BNP 105–240 pg/ml
	GLS < 16%	LVMi > 115 g/m ² for men and 95 g/m ² for women RWT > 0.42 LV wall thickness \geq 12 mm		

*Only one criterion from each group can be included in the score (\geq 5 points: HFpEF; 2–4 points: diastolic stress test or invasive hemodynamic measurements)

BNP brain natriuretic peptide, HFpEF heart failure with preserved ejection fraction, E and e' early diastolic mitral flow velocity measured by pulsed and tissue Doppler, GLS left ventricular global longitudinal strain, LAVI left atrial volume index, LVMi left ventricular mass index, RWT relative wall thickness

that could help in identification of patients with HFpEF, the European Heart Failure Association recently published consensus and proposed criteria for diagnosis of HFpEF [12]. This consensus was aimed to provide stepwise diagnostic approach—from clinical assessment to more specific tests. However, it is debatable how much the introduction of minor and major criteria with new cutoff values could help clinicians. Scoring system is useful in clinical practice because it simplifies diagnosis and management of different diseases. However, this considers that all criteria and their thresholds are validated. It is questionable whether new cutoff values should be used in algorithm that could indicate invasive hemodynamic test.

Minor and major criteria

The recent suggested usage of major and minor criteria for diagnosis of HFpEF (Table 1) [12]. The criteria were separated into 3 groups: functional, morphological, and biomarker. Major functional criteria included echocardiographic parameters that were proposed in the guidelines for assessment of LV diastolic dysfunction (reduced septal e' , increased E/e' , and increased TR) [12]. Minor functional criteria included intermediate values of E/e' (9–14) and reduced LV global longitudinal strain ($< -16\%$) [12]. Major morphological criteria include dilated left atrial volume index (LAVI ≥ 34 ml/m² in sinus rhythm and ≥ 40 ml/m² in atrial fibrillation) or LVH defined as LV mass index (LVMI) ≥ 149 g/m² in men or ≥ 122 g/m² in women together with increased relative wall thickness ≥ 0.42 [12]. Interestingly, minor morphological criteria were high normal values of LA volume index (29–34 ml/m² in sinus rhythm and ≥ 34 –40 ml/m² in atrial fibrillation), increased LV mass index defined by current echocardiographic guidelines (≥ 115 g/m² in men or ≥ 95 g/m² in women), or relative wall thickness ≥ 0.42 or LV wall thickness ≥ 12 mm [12]. Major and minor biomarker criteria refer to different levels of BNP and pro-BNP with various cutoff values for patients with sinus rhythm and atrial fibrillation (values are 3 times higher in the atrial fibrillation group) [12].

Criteria that are included in this algorithm are acceptable, but the major problem with these criteria is the cutoff value for each of them. Namely, patients with risk factors such as arterial hypertension, diabetes, and obesity very often satisfy these functional and morphological echocardiographic criteria, even the major criteria. Ballo et al. included 532 asymptomatic hypertensive patients and found that 72% of patients had LVDD and average value of e' , E/e' , and particularly LAVI indicated that large percentage of these patients would satisfy recommended echocardiographic criteria for HFpEF [28]. Considering the fact that LAVI in the whole population of hypertensive patients was 38.3 ± 12.4 ml/m²; it means that the majority of hypertensive patients would

have 2–4 points according to the newly proposed scoring system, and these patients would be recommended for echocardiographic diastolic stress test or invasive hemodynamic test. Additionally, recently published study indicated that threshold for LA enlargement should be increased or at least adjusted for age [29]. The upper normal limits were 39.4 ml/m² for healthy men and 36.5 ml/m² for healthy women, which further means that 13.0% of all men and 5.4% of all women had LAVI above the current upper normal limit of 34 ml/m² [29]. The same study showed that 40% of hypertensive patients and 11% of diabetic patients had LAVI > 34 ml/m², whereas majority of patients with atrial fibrillation had LAVI > 40 ml/m² [29]. These findings indicate that LAVI > 34 ml/m² is too low threshold for major criterion for diagnosis of HFpEF and it definitely should be adjusted for sex.

The threshold for LV structural criteria deserves discussion because the justification for LVMI ≥ 149 g/m² in men or ≥ 122 g/m² in women is not clear. LV mass is associated with increased cardiovascular and overall mortality independently of other cardiovascular risk factors [30]. However, increased LVMI and LVH are the main echocardiographic features in hypertensive, obese, and diabetic individuals [30–32]. There is a linear association between blood pressure, body mass index, and level of glucose and/or glycated hemoglobin and LVMI [30–32]. Additionally, each of these parameters independently of other risk factors was associated with LVH. The presence of 2 or more concomitant risk factors has cumulative rather than additive effect on LVMI. Furthermore, LVH is often related with LVDD and reduced LV longitudinal strain, which increases the score according to the proposed algorithm and puts the patients in the group which should be at least tested for HFpEF with non-invasive or invasive methods. The next question that rises from newly proposed criteria is the threshold values for LVMI. It is clear that threshold for minor criteria for LVH was taken from the current guidelines (≥ 115 g/m² in men or ≥ 95 g/m² in women) [33]. However, it is not clear how was the cutoff value for major criterion determined.

LV mechanics represent important set of functional parameters that are significantly impaired in HFpEF patients [5], but also in subjects with hypertension, diabetes, and obesity [34–36]. The effect of these risk factors on LV mechanics is again cumulative negative, and therefore, it is very difficult to determine threshold for LV longitudinal strain that would distinguish HFpEF from hypertension-, diabetes-, or obesity-induced LV mechanical changes. On the other hand, LV longitudinal strain is less load-dependent than echocardiographic parameters of LV diastolic function, more reproducible than LVEF and better predictor of outcome than LVEF [37–39], which indicate that reduced LV longitudinal strain could be appreciated as a major criterion for diagnosis of HFpEF.

Biomarkers in HFpEF diagnosis

The prognostic value of B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) has been recognized for HFpEF patients [40, 41]. However, natriuretic peptide levels should always be interpreted in context of clinical situation and individual patients, as stated in the consensus. Thresholds for diagnosis of HFpEF are not well established, and various trials used different cutoff values, which can make confusion in interpretation of their results. NT-proBNP is a less useful biomarker in HFpEF than it is in HFrEF because many clinical features of HFpEF (obesity, hypertension, atrial fibrillation, renal impairment) are independently associated with increased NT-proBNP. Furthermore, the range of NT-proBNP in HFpEF expands into the normal range in some patients, which is why one needs to speculate about the risk in these patients. There is no doubt that NT-proBNP cutoff in patients with atrial fibrillation should be higher than in patients with sinus rhythm, but it is not clear if > 220 pg/ml and > 660 pg/ml, as it was suggested in this consensus [12].

It is commendable that the threshold for NT-proBNP in the current consensus is higher than it was previously (> 125 pg/ml) and that cutoff is different between patients with sinus rhythm and atrial fibrillation. Complete adjustment for all confounders is practically impossible, and therefore, one has to determine some cutoff. However, validation studies are necessary to evaluate whether these cutoff values are correct or should be revised.

It is also questionable if such variable parameter as NT-proBNP should be a major criterion or perhaps degraded to minor criterion. There are many promising biomarkers on the horizon (urinary albumin to creatinine ratio, plasminogen activator inhibitor 1, galectin-3, cystatin C, and interleukin 6) that might be used together with or even replace NT-proBNP in the future [42]. Naturally, large validation studies are missing, which is why new biomarkers could not be incorporated in this consensus, but hopefully will be included in the next recommendations.

Echocardiography vs. invasive testing

The consensus recommends that patients with 2–4 points for diagnosis of HFpEF should undergo diastolic stress test or cardiac catheterization in order to diagnose or exclude HFpEF [12]. Suggested tests are equalized, without giving advantage to any of them. This is potentially a large problem for clinical practice, and there are several important reasons why not all patients with suspicious on HFpEF could be referred for cardiac catheterization: (i) many centers that are responsible for heart failure patients do not have possibility to perform invasive hemodynamic measurements; (ii) procedure-related complications and risks

are not negligible; (iii) cost-effectiveness of this approach is questionable. Therefore, it is of a great importance to define patients who are indicated for invasive tests and not to send all patients with suspected HFpEF for cardiac catheterization. Cardiac catheterization should be the last step in diagnosis and the number of referred patients has to be limited.

According to the proposed scoring system, many symptomatic hypertensive patients and particularly those with concomitant obesity and diabetes would be sent to echocardiographic or invasive diastolic stress test. Putting all patients into the group with potentially high risk of HFpEF (score between 2 and 4), this score is losing its importance and purpose.

Remarkable number of patients is not able to perform physical stress echocardiographic examination. Kosmala et al. reported that the implementation of a 2-step algorithm (resting E/e' and assessment of galectin-3) improved diagnosis and prognostic value of HFpEF in patients who are not able to exercise [43]. Nedeljkovic et al. found that parameters obtained by cardiopulmonary exercise test can accurately identify masked HFpEF in population of hypertensive patients with sensitivity of 100% and specificity of 90% [44]. These studies showed that some new diagnostic techniques (cardiopulmonary exercise testing) and novel biomarkers (galectin-3) could be promising future direction in resolving challenges in diagnosing of HFpEF.

Future directions

Scoring system in cardiology is a well-established approach in diagnosis and therapy in the large range of cardiovascular conditions, and therefore, the initiative coming from these recommendations is commendable. However, it is doubtful if minor criteria are necessary and particularly in this form, with non-validated cutoff values for LAVI, E/e' , and NT-proBNP. LV global longitudinal strain perhaps should be included as major functional criterion, and threshold for LVMI, as major criterion, should be returned to cutoff value for LV hypertrophy, which clinicians already use in clinical practice. Furthermore, the scoring system should be more flexible than in the current form, and risk of HFpEF should be stratified for example into 3 levels (1–2 points—mild risk; 3–4 points—moderate risk; 5 point—HFpEF diagnosis).

The most important point is that echocardiographic diastolic stress test could not be equated with invasive diastolic test in diagnostic algorithm. Non-invasive stress tests should definitely have advantage over invasive tests in diagnostic process. This includes not only echocardiographic diastolic stress test but also cardiopulmonary exercise test, which can provide many important parameters of cardiorespiratory fitness

besides oxygen consumption and ventilatory inefficiency. Hemodynamic measurements should be evaluated only when other tests are inconclusive. We believe that these modifications and simplifications would increase application of this score in clinical practice.

Conclusion

HFpEF is a heterogeneous entity with unresolved pathophysiology which is largely overlapping with arterial hypertension, obesity, and diabetes. Mortality of HFpEF is lower than in HFrEF, but still very high. Therefore, timely diagnosis of HFpEF remains the cornerstone of adequate management in these patients. Even though invasive hemodynamic measurements represent the gold standard for HFpEF diagnosis, echocardiographic diastolic stress test has been more often used for detection of HFpEF. Recently proposed scoring system for evaluation of HFpEF introduced a new set of parameters and novel thresholds for these parameters. The authors of guidelines stated that new cutoff values were based on the expert consensus and require the validation in prospective studies. Different scores are very useful in modern clinical medicine because they significantly facilitate diagnosis and management of various diseases. However, one should be cautious regarding the criteria included in each score because our aim is to avoid false positive and false negative patients. Large prospective studies are necessary for validation of this score and its modification(s).

Compliance with ethical standards

Conflict of interests The authors declare that they have no conflict of interest.

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