Left Ventricular Strain in Heart Failure with Preserved Ejection Fraction: A Fast Dive into Diagnosis, Response to Exercise and Afterload Challenge

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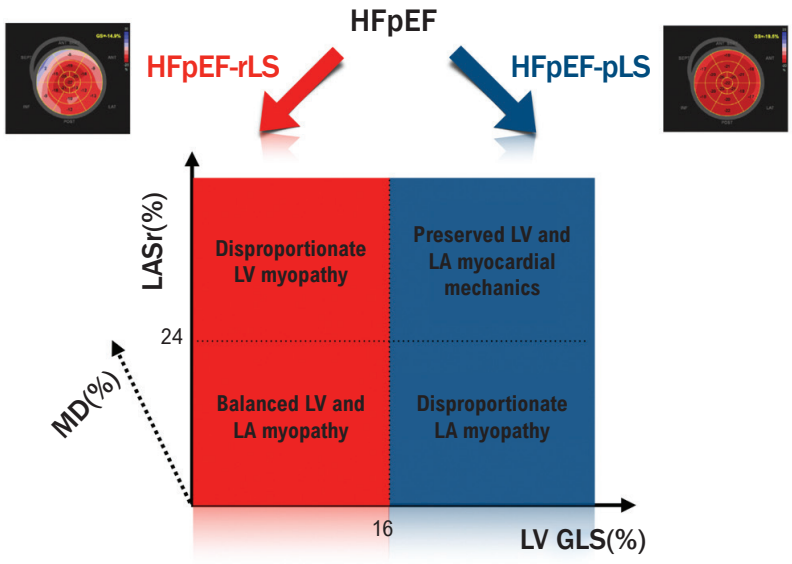
Central Illustration: Left Ventricular Strain in Heart Failure with Preserved Ejection Fraction: A Fast Dive into Diagnosis, Response to Exercise and Afterload Challenge



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Phenotyping Strategy for HFpEF. Based on the left ventricular strain, there are two distinct HFpEF phenotypes: HFpEF with reduced longitudinal systolic function (HFpEF-rLS) and HFpEF with preserved longitudinal systolic function (HFpEF-pLS). Integrating the LA strain reservoir (LASr) is suggested to introduce a comprehensive dimension that addresses impairments in both the LV and LA. Additionally, the potential inclusion of MD could further refine stratification.

Keywords

Heart Failure; Echocardiography; Exercise

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Abstract

Heart Failure with Preserved Ejection Fraction (HFpEF) is an increasing challenge in cardiology, marked by impairments in systolic and/or diastolic function. HFpEF patients often present with exercise intolerance, yet diagnosis is complicated by overlapping comorbidities, such as obesity and hypertension. Left ventricular Global Longitudinal Strain (GLS) enables the detection of subtle systolic dysfunction, with studies indicating a stronger correlation between GLS and exercise capacity than ejection fraction (EF). In exercise echocardiography, GLS displays a characteristic bimodal pattern due to hemodynamic adaptations, with deviations

suggesting HFpEF. When exercise testing is unfeasible or when a specific evaluation of ventricular-arterial coupling is desired, an afterload challenge offers a controlled alternative by increasing systemic resistance. Beyond GLS, mechanical dispersion (MD) measures contractile heterogeneity, while left atrial strain (LAS) has shown promise in identifying atrial dysfunction linked to HFpEF. These parameters, evaluated alongside E/e' ratios and pulmonary systolic pressure during exercise, enhance HFpEF diagnosis, provide a more comprehensive view of the syndrome's pathophysiology, and offer insights to support treatment.

Introduction

Heart Failure with Preserved Ejection Fraction (HFpEF) is a major public health disorder, accounting for at least 50% of all heart failure patients, with an increasing prevalence.[1] It represents a significant unmet need in cardiology, with considerable knowledge gaps regarding its pathophysiology, natural history, diagnosis, and treatment.[1]

The primary complaint of HFpEF patients is exercise intolerance. However, accurately assessing this symptom solely based on patient-reported outcomes can be challenging. The typical HFpEF phenotype, often referred to as "Garden Variety HFpEF" (an English term describing something ordinary or standard, lacking exceptional characteristics), typically includes at least four comorbidities, such as obesity, hypertension, atrial fibrillation, and kidney disease. These comorbidities complicate the differential diagnosis, making it difficult to distinguish between reduced exercise capacity caused by the comorbid conditions and the heart failure syndrome itself.[2,3] Additionally, many patients exhibit clinical presentations without signs of fluid overload on physical examination, making the classical Framingham criteria less sensitive for recognizing these patients.[2-4]

In this context, echocardiography plays a crucial role in evaluating patients with suspected HFpEF, and strain imaging can indeed provide critical information to improve diagnostic performance.[5,6] HFpEF has traditionally been associated with severe diastolic dysfunction leading to "backward failure" and pulmonary congestion, which limits exercise capacity.[7] While diastolic dysfunction is undeniably key in HFpEF pathophysiology, other abnormalities, including subtle systolic dysfunction despite preserved ejection fraction (EF), also play an important role.[1,8,9] Using left ventricular Global Longitudinal Strain (GLS) allows us to assess these subtle systolic impairments.[2]

Left Ventricular GLS as a Diagnostic Criterion for HFpEF

The technical requirements for obtaining high-quality GLS have been detailed in the guidelines.[5,10] The normal range of GLS is between 18% to 22% (modular values), with values between 16% to 18% considered borderline. GLS values below 16% are indicative of systolic dysfunction.[11]

The score proposed by the European Society of Cardiology (HFA-PEFF)[12] includes GLS as one feature in the functional domain, along with measurements from the structural (morphological domain) and biomarkers (natriuretic peptides) domains (Figure 1). This approach is important as it guides the physician to interpret GLS in the context of these other features for the diagnosis of HFpEF.

Evaluating GLS in conjunction with other features is crucial, as an abnormal GLS has been associated with various clinical conditions known to impair the myocardium, such as hypertension, diabetes mellitus, aortic stenosis, and amyloidosis. These conditions may act as risk factors or HFpEF mimics.[1,13]

Abnormalities in GLS without other pathophysiological impairments may not fulfill all conditions to increase filling pressures and cause HFpEF syndrome. Indeed, other studies have shown that GLS only moderately correlates with filling pressures.[14] Conversely, previous studies indicate that overt HFpEF can occur without impaired resting GLS, suggesting that using GLS in isolation may have sub-optimal sensitivity.[11]

Nonetheless, there is evidence that GLS may have a significant role in the physiological cardiocirculatory adaptations that determine exercise capacity. A recent meta-analysis of 25 studies, comprising 2136 patients with preserved and reduced EF, demonstrated that both GLS and EF have a linear relationship with peak oxygen uptake (VO2). However, the correlation between VO2 and GLS was twice as strong as the correlation between VO2 and EF.[9] These findings highlight the relevance of strain imaging features in assessing the cardiocirculatory components of exercise intolerance.

Left Ventricular GLS in Exercise Echocardiography

Patients with HFpEF may exhibit functional abnormalities primarily during hemodynamic overload, with the exercise test using a cycle ergometer being the preferred modality for inducing such stress.[12,15-17] Assessing GLS during exercise is, therefore, logical and has significant potential to enhance the diagnostic accuracy for HFpEF.

It is crucial to recognize that GLS is a load-sensitive parameter,[4,5,10] and its behavior during exercise must be interpreted in the context of the physiological adaptations occurring at different exercise phases. During the initial phases of exercise, cardiac output increases due to elevated preload and cardiac contraction, leading to a rise in stroke volume. At this stage, GLS typically improves compared to resting conditions. In the subsequent phase, around the ventilatory anaerobic threshold, stroke volume tends to plateau, and further increases in cardiac output are achieved through an elevated heart rate, which reduces preload and consequently lowers GLS.[18,19] Thus, GLS demonstrates a characteristic bimodal pattern during exercise (Figure 2).

Despite that, there is a notable gap in research concerning how pathological deviations in HFpEF might affect or alter GLS patterns during exercise.

Trade-Off Between Frame Rate and Heart Rate During Exercise

One of the key technical considerations when assessing GLS during exercise echocardiography is the trade-off between frame rate and heart rate. As the heart rate increases during exercise, the cardiac cycle shortens, necessitating a higher frame rate to capture sufficient detail of myocardial motion throughout the cycle. High frame rates are crucial for accurately tracking myocardial deformation, especially at higher heart rates.[20]

HFA-PEFF score			
Functional Domain	**Morphological Domain**	**NP Domain (SR)**	**NP Domain (AF)**
Major:	**Major:**	**Major:**	**Major:**
e'septal < 7 or e'lateral < 10cm/s*	LAVI > 34mL/m²	NT-Pro-BNP > 220pg/mL	NT-Pro-BNP > 660pg/mL
E/e' ≥ 15	LVMI ≥ 149 or and RWT > 0.42	BNP > 80pg/mL	BNP > 240pg/mL
TR velocity > 2.8m/s			
Minor:	**Minor:**	**Minor:**	**Minor:**
E/e': 9-14	LAVI: 29-34mL/m²	NT-Pro-BNP: 125-220pg/mL	NT-Pro-BNP: 365-660pg/mL
GLS < 16%	LVMI ≥ 115 or 95g/m²	BNP: 35-80pg/mL	BNP: 105-240pg/mL
	RWT > 0.42		
	LV wall thickness ≥ 12 mm		
Major: 2 points ; Minor: 1 point			
HFA-PEFF score ≥ 5 ⇨ HFpEF			
HFA-PEFF score: 2-4 ⇨ Diastolic Stress Test or Invasive Hemodinamics Measurement			

Figure 1 – *The HFA-PEFF score for the diagnosis of HFpEF. HFA-PEFF score to evaluate the diagnosis of HFpEF. HFA-PEFF: Heart Failure Association-PEFF; NP: natriuretic peptide; e': early diastolic mitral annular velocity; E: early transmitral flow velocity; TRV: tricuspid regurgitation velocity; GLS: left ventricular global longitudinal strain; LAVI: left atrial volume index; LVMI: left ventricular mass index; RWT: relative wall thickness; LV: left ventricle; SR: sinus rhythm; NT-pro-BNP: N-terminal pro-B-type natriuretic peptide; BNP: B-type natriuretic peptide; AF: atrial fibrillation. *Values should adjust to e'<5cm/s and e' lateral<7cm/s if patients has age>75years/old.*

However, achieving higher frame rates often involves compromising spatial resolution, which can impact the accuracy of strain measurements.[20,21] Additionally, maintaining high frame rates can be technically challenging due to the need for high temporal resolution while ensuring image quality remains adequate for precise tracking.

Optimizing frame rate during exercise echocardiography is essential to balance the need for detailed temporal resolution and the limitations of spatial resolution. An inadequate frame rate can lead to under-sampling of myocardial motion, resulting in inaccurate GLS measurements and potential misinterpretation of myocardial function.[20]

In clinical practice, it's essential to adjust ultrasound settings dynamically during exercise to maintain optimal frame rates as heart rates increase. This dynamic adjustment helps ensure that GLS measurements remain reliable and reflective of true myocardial performance under exercise conditions. For an accurate evaluation of peak longitudinal and peak circumferential strain, a proportion of 30 frames per cardiac cycle is recommended. This means that the minimum frame rate must be adjusted to ensure that at least 30 frames are captured during each cardiac cycle to provide reliable strain measurements. For instance, for a heart rate of 80 bpm, the minimum frame rate would be > 40 fps, while for a heart rate of 160 bpm, the minimum frame rate would be > 85 fps. From a practical point of view, it is recommended to aim to maintain a frame rate above 70% of the heart rate. Of note, this does not apply to the evaluation of the isovolumic phases, where frame rates as high as 500 fps would be required, which is an area to be explored with the new algorithms of high-frame-rate speckle tracking imaging.

Left Ventricular GLS in Afterload Challenge

In certain clinical settings or due to technical limitations, patients may be unable to undergo standard exercise tests. In such cases, alternative stress modalities, such as preload or afterload challenge, can provide valuable insights into myocardial function.[2] An afterload challenge involves inducing pressure overload to assess myocardial performance under conditions of increased systemic resistance. This can be achieved through various methods, including:

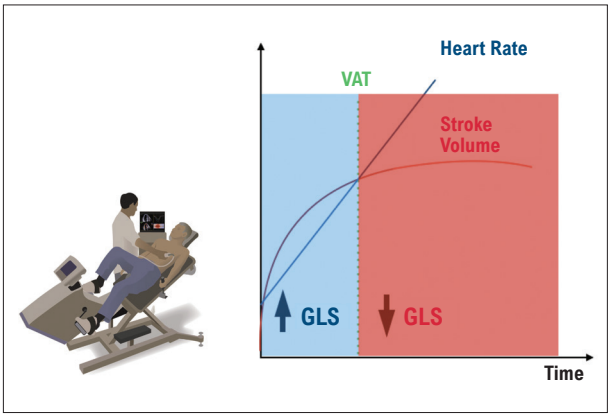

Figure 2 – *Bimodal Behavior of GLS during exercise. GLS: Global Longitudinal Strain; VAT: Ventilatory Anaerobic Threshold.*

- **Handgrip Exercise:** The patient squeezes a handgrip dynamometer, which generates sustained isometric muscle contractions. This method induces an increase in systemic vascular resistance.
- **Limbs Constriction:** This involves applying external pressure to the limbs using cuffs or bands to create a controlled resistance against blood flow. The resulting increase in systemic resistance provides a measurable afterload challenge.

These methods can be used either individually or in combination. Afterload challenges may offer distinct advantages over standard dynamic exercise, as they induce a controlled hemodynamic overload without significantly raising heart and respiratory rates. This leads to less noise in echocardiographic signals, thereby enhancing the accuracy of advanced deformation imaging.

Nonetheless, it is important to recognize the fundamental differences between standard dynamic exercise and afterload challenge. Standard dynamic exercise primarily induces a "forward perturbation," which sequentially increases central venous pressure, pulmonary artery wedge pressure, left atrial preload, and the left atrium-left ventricle (LA-LV) gradient, raising the mitral E wave. This type of stress challenges the left ventricle (LV) to enhance the velocity of relaxation (e'), thereby assessing diastolic reserve.

In contrast, an afterload challenge creates a "backward perturbation" by increasing systemic resistance, which reduces the velocity of LV relaxation. This results in lower e' velocities and a diminished LA-LV gradient (lower mitral E wave). Consequently, echocardiographic features such as the E/e' ratio exhibit different behavior under this type of stress, often without a significant increase. The normal ventricular response to increased afterload typically involves a reduction in the velocity and extent of ventricular contraction, leading to a compensatory increase in preload and activation of the Frank-Starling mechanism for heart contraction. Notably, LV longitudinal function assessed through strain imaging appears particularly sensitive to these contraction changes.[4]

Studies investigating GLS during hemodynamic stress induced by afterload challenge can provide significant insights.[4,22-24] Recent data has highlighted myocardial dysfunction related to increased afterload in patients with HFpEF, who initially exhibit preserved resting GLS (Figure 3).[1,4]

Therefore, the afterload challenge presents characteristics that make it the modality of choice to study changes in myocardial deformation and ventricular-arterial coupling during stress.

Left Ventricular Strain Beyond GLS: The Role of Mechanical Dispersion

The GLS measures the average amount of longitudinal contraction performed by the LV from the onset of isovolumetric contraction to the end of ventricular ejection. Consequently, valuable information about other phases of the cardiac cycle, such as isovolumetric relaxation, is not captured by GLS.[20,21] While GLS provides an accurate quantification of ventricular contraction, it does not qualitatively explain how the contraction is performed.

Mechanical dispersion (MD) is a strain feature that expresses the degree of temporal heterogeneity of contraction, serving as an indicator of mechanical dyssynchrony (Figure 4).[25] Dyssynchrony has been established as an important characteristic of abnormal myocardial contraction in the

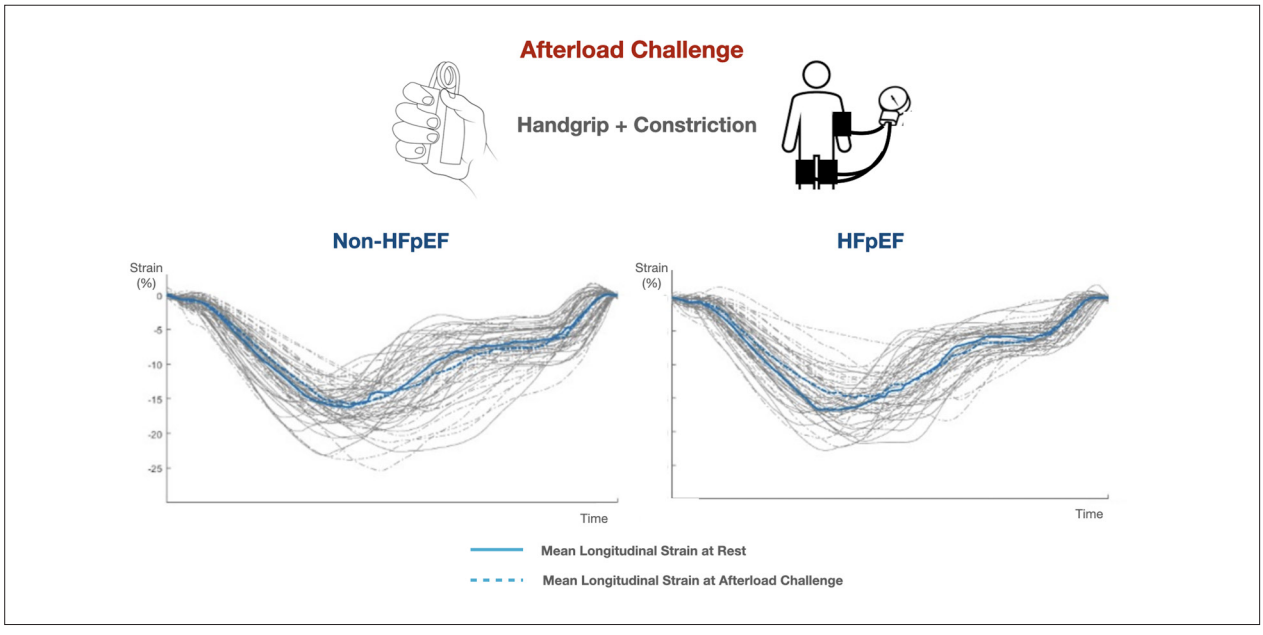

Figure 3 – *The Behavior of GLS during the Afterload Challenge and the increased afterload mediated systolic dysfunction. HFpEF: Heart Failure with Preserved Ejection Fraction.*

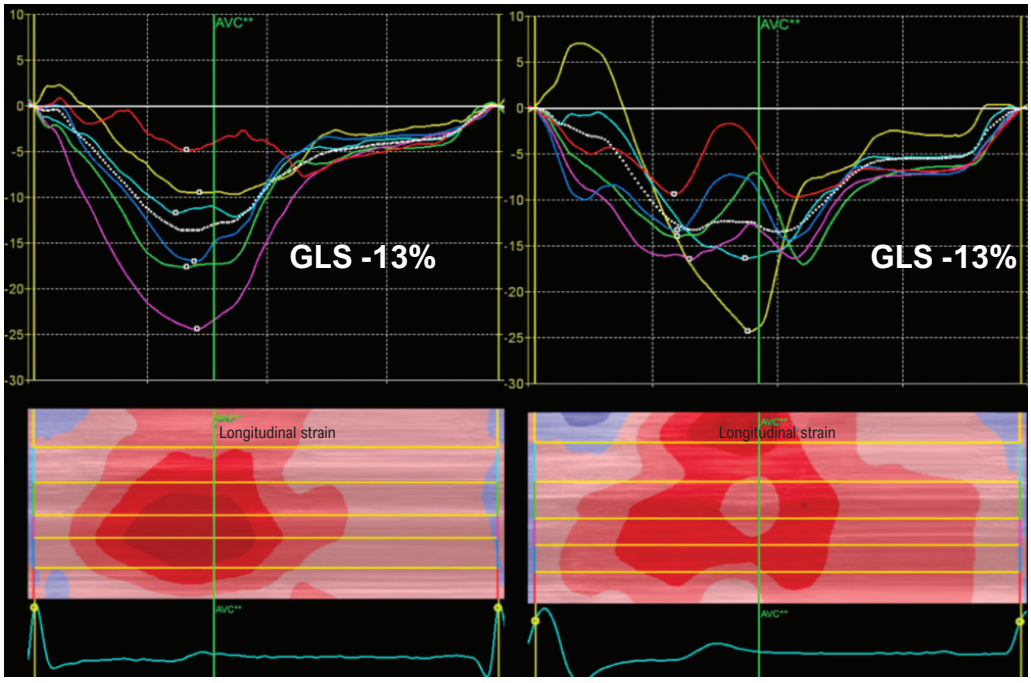

Figure 4 – *The Role of MD. On the left, the patient has an abnormal GLS and low MD. At right, a patient with the same value of GLS but displaying a high MD. GLS: Global Longitudinal Strain.*

context of conditions such as heart failure with reduced EF,[26] coronary artery disease,[27] hypertrophy, and HFpEF.[28,29]

The rationale for using this index in HFpEF is that, theoretically, a heterogeneous cardiac contraction, as stated by a high MD, leads to regional contractions that do not reach the reciprocal force from the opposite cardiac walls. Therefore, part of cardiac deformation will not be translated into an effective force to expel blood towards the aorta. Furthermore, dyssynchrony will affect both AV and VA coupling. This double hit in LV performance makes the heart more prone to higher increases in left atrium (LA) pressure during exercise adaptations such as increased preload and tachycardia. Thus, in the context of relatively preserved GLS, information on the synchronicity of contraction may help explain the subtle impairments observed in a subset of patients with HFpEF.

Recent data suggest that MD is more associated with exercise capacity in patients with pre-HFpEF and HFpEF when compared to GLS and other components of HFA-PEFF score, and it may provide new insights into how the heart could be more prone to the steep increase in filling pressures during exercise that characterizes this syndrome.[25]

Currently, there is no precise cutoff for MD, but recent data indicate that values greater than 65 ms have high specificity for identifying subjects with a high probability of HFpEF.[25]

Strain Imaging for Phenotyping HFpEF Syndrome

The patterns of different indices of strain imaging can help identify specific phenogroups within HFpEF.[11,30] Patients with HFpEF and reduced GLS (HFpEF-rLS) display contractile dysfunction, as well as myocardial abnormalities.

Conversely, 18-48% of HFpEF patients retain preserved GLS (HFpEF-pLS), yet they may still have other pathophysiological issues such as atrial dysfunction and pulmonary vascular disease.[30] In this group, Left atrial strain (LAS) is a promising biomarker for HFpEF and LA myopathy, enhancing diagnostic and prognostic insights.[31] Reduced LAS in HFpEF-pLS patients indicates significant LA impairment due to atrial cardiomyopathy, challenging the traditional notion that links LA disease solely to LV diastolic dysfunction. Combining GLS and LAS for HFpEF phenotyping provides a comprehensive understanding of cardiac impairments in these patients[11] (Central Illustration).

Final Messages

Despite the preserved EF, the compromise of systolic function, observed by the abnormalities in GLS and MD, and the impairment of atrial reservoir function demonstrated by a reduction in LAS, whether isolated or in association, support the diagnosis of HFpEF. Likewise, the lack of increasing GLS during physical exertion could be a sign of HFpEF. Besides, it is important to interpret these measures in conjunction with other echocardiographic data. An increase in E/e' above 15, either alone or in combination with a rise in pulmonary artery systolic pressure above 60 mmHg during cicloergometer exercise, is a strong indicator of increased left ventricular filling pressures with exertion.[12] Despite this, there is still a lack

of knowledge on how the hemodynamic information provided by Doppler should be interpreted alongside strain measurements. Finally, we still need to understand better how to interpret these findings in conjunction with the many clinical and laboratory variables that can be modified in HFpEF patients. Developing scores that integrate all these variables in different HFpEF phenotypes would be clinically relevant.

Author Contributions

Conception and design of the research: Hortegal RA, Le Bihan D, Mathias Jr W; acquisition of data: Hortegal RA, Le Bihan D; writing of the manuscript: Hortegal RA, Le Bihan D, Mathias MM; critical revision of the manuscript for intellectual content: Le Bihan D, Barretto R, Mathias Jr W.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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