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Research Article

Does global longitudinal strain improve stratification risk in heart failure with preserved ejection fraction?

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Abstract

Background: Heart Failure with Preserved Ejection Fraction (HFPEF) accounts for more than half of the cases of heart failure.

Long regarded as an abnormality of left ventricular diastolic function, recent studies using longitudinal strain (two-dimensional speckle tracking mode) have suggested that left ventricular longitudinal systolic function is altered in HFPEF.

Despite these interesting pathophysiological perspectives, the data in the literature on the prognostic value of the alteration of longitudinal strain are controversial. Given these conflicting results, it is difficult to confirm the magnitude and prevalence of impaired LV longitudinal systolic function in patients with HFPEF and its prognostic relevance.

Purposes: This work aims to study the prognostic value of Global the left ventricle's Global Longitudinal Strain (GLS) Algerian cohort of patients with HFPEF.

Patients and methods: We conducted a monocentric prospective observational study from April 2018 to April 2020, with a minimum follow-up of 1 year for each recruited patient. We included patients over the age of 18 referred to the echocardiography laboratory for chronic or acute HFpEF, defined according to the criteria of ESC 2016. 153 consecutive patients underwent clinical examination, biological tests, and echocardiography with measurement of GLS at rest, in addition to routine management by the attending physicians.

Results: 153 patients were collected. The average age of our patients is 73 +/- 11 years ranging from 42 to 91 years old. The female population is predominant with a rate of 67%. Comorbidities are predominant mainly by arterial hypertension (86%) and diabetes (64%), with a history of atrial fibrillation (46%).

63% of patients have impaired GLS (< 16%). Contrary to our hypothesis, GLS was not shown to be a powerful predictor of cardiovascular events in HFPEF patients either in dichotomous analysis (OR = 0.79; p = 0.64) or in continuous analysis (OR = 0.97; p = 0.69).We were able to identify that congestive venous signs, anemia, and pulmonary hypertension, are the main independent prognostic factors in our Algerian population study.

Conclusion: We were unable to demonstrate the prognostic role of mpaired GLS in our population of patients with HFPEF.

More Information

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Keywords: Heart failure; Preserved ejection fraction; Global longitudinal strain; Prognosis

Abbreviations: ACE: Angiotensin Conversion Enzym; AF: Atrial Fibrillation; ARAII: Angiotensin Receptors Antagonists; BMI: Body Mass Index; BNP: Brain Natriuretic Peptide; CI: Confidence Interval; CRI: Chronic Renal Insuffisency; COPD: Chronic Obstructive Pulmonary Disease; CV: Cardiovascular; CVE: Cardiovascular Events; EF: Ejection Fraction; ESC: European Society of Cardiology; GDF: Growth Differentiation Factor; GLS: Global Longitudinal Strain; HF: Heart Failure; HFpEF: Heart Failure with a preserved Ejection Fraction; HFrEF: Heart Failure with a reduced Ejection Fraction; LA: Left Atrium; LAV: Left Atrial Volume; LV: Left Ventricle; LVEF: Left Ventricular Ejection Fraction; LVH: Left Ventricular Hypertrophy; LVM: Left Ventricular Mass; MACE: Main Acute Cardiovascular Events; 6M-WT: 6 Minutes - Walk Test; NT-proBNP: N Terminal pro Brain Natriuretic Peptide; OR: Odds Ratio; PAH: Pulmonary Arterial Hypertension; Pg: Picograms; SD: Standard deviation; WHO: Word Heart Organization

Introduction

Heart Failure (HF) is a major public health problem with an alarming rate of progression. HF with Preserved ejection fraction heart failure (HFPEF) accounts for 40% - 70% of heart failure cases [1,2]. HFPEF will increase with the aging of the population, with a simultaneous increasing prevalence of comorbidities including hypertension, obesity and diabetes [Error! Bookmark not defined.].

It is one of the leading causes of morbidity and mortality with a considerable impact on quality of life, comparable to that of reduced ejection fraction heart failure (HFREF) [3-5].

Labeled an "orphan disease," many uncertainties persist about it, as evidenced by the failures of therapeutic trials in this patient population. Long considered an isolated diastolic dysfunction, it is now clearly established that it is a heterogeneous entity with complex pathophysiology, with the coexistence of systolic cardiac dysfunction [6], which could be identified in many patients at rest, and more markedly with effort [7]. The etiology of this subclinical systolic dysfunction as well as its significance in terms of disease progression are still unknown [8,9].

Although it's prognostic value is clearly established in patients with heart failure with reduced ejection fraction, the prognostic relevance of the global longitudinal strain of VG or global longitudinal strain "GLS" in patients with ICFEP remains controversial. Therefore, it seemed interesting to us to try, through this work, to determine the prognostic importance of GLS in patients with HFPEF.

Population and methods

We conducted a prospective monocentric study including adult patients, aged 18 years and over, with Informed consent from each patient recruited, and a minimum follow-up of one year. Consecutive patients are referred to the echocardiography laboratory of the A2 cardiology department of the University Hospital of Mustapha Bacha, between April 2018 and April 2020 and the diagnosis of HFPEF is retained according to the criteria of the last ESC guidelines of 2016 at the time of the realization of our study., namely, the presence of signs and/or symptoms of HF, LVEF ≥ 50%, a terminal fraction level of natriuretic peptides type B (NT-ProBNP) > 125 pg/ml or Brain natriuretic peptides (BNP) > 35 pg/ml with at least one ultrasound criterion for structural heart disease (Indexed left ventricular mass (LVM ≥ 115 g/m^2 in men and ≥ 95 g/m^2 in women, or an indexed left atrial volume (LAV) > 34 ml/m^2), or functional abnormality (E/E ≥ 13 and e' septal and lateral medium < 9 cm/s).

Are excluded from the study, patients who present with signs of HF with preserved ejection fraction but which present a more than moderate valvular heart disease, Pulmonary Arterial Hypertension class 1, 3, 4, or 5 of the WHO, arrhythmogenic dysplasia of the right ventricle, congenital heart disease, infarction of the right ventricle, pericardial disease (Tamponnade, constrictive pericarditis), specific cardiomyopathy (viral infections, inflammatory (Sarcoidosis), genetic (Hypertrophic cardiomyopathy) and restrictive cardiomyopathy). An abnormal GLS of LV is defined as ≤ 16% in its absolute value.

Statistical analysis

Basic characteristics, echocardiography, and biological data are expressed on average ± standard deviation Proportions are indicated as a percentage and continuous parameters are reported as mean standard deviation (MD). Dichotomous parameters were analyzed by the chi-two test and continuous variables by a bilateral "t" student test. Survival curves using Kaplan Meier's method were used to determine survival at 12 months. Cox proportional risk analysis was used to determine the independent prognostic power of each variable to predict prognosis. All statistical analyses were performed using R. 4.0 software. For all tests, a p - value ≤ 0.05 is considered statistically significant.

Results

The average age of our patients is 73 years ± 11 ranging from 42 to 91 years, with 67% of female. Our population is predominantly hypertensive (86%) and diabetic (65%) with a history of atrial fibrillation in nearly half of the cases. The majority of our patients had signs of isolated left HF (71%), varying from exercise dyspnea to orthopnea. Signs of peripheral venous congestion are noted in 29% of patients. 19% of patients were hospitalized for primary decompensation or worsening of signs of congestion despite a therapeutic readjustment on an outpatient basis.

Echographic characteristics

The mean left ventricular ejection fraction is 59% ± 6.65, ranging from 50% to 77%. The average indexed LV mass is 121.4 ± 37.65 g/m^2 ranging from 55 to 331 g/m^2. The prevalence of Left Ventricular Hypertrophy (LVH) in HFPEF patients is 74%, 51% of which is eccentric. Isolate remodeling without hypertrophy is present in 11% of cases, while normal left ventricular geometry is present in 15% of cases. The mean indexed volume of the left atrium is 48.35 ml/m^2 ± 18.53 ranging from 18 to 150 ml/m^2. 81% of patients have an enlargement of the left atrium (indexed left atrial volume > 34 ml/m^2). The average value of the mitral E/e ratio (Septal and lateral) is 15.8 ± 5.36 ranging from 6 to 37. Sixty-one percent of patients have an E/E ratio > 14 while 94% of patients have an E/E ratio > 9.

The mean peak velocity of tricuspid regurgitation is 2.86 m/s ± 0.43 ranging from 1.94 to 4.18 m/s. Just over half of patients (53%) have a V max IT > 2.8 m/s. The average Pulmonary Arterial Systolic Pressure (PASP) is 43mmHg ranging from 20 to 84 mm Hg. More than two-thirds of patients (68%) have a PASP > 35 mmHg. The average GLS value is

14.29% ± 6.1 ranging from 3.2% to 24%, with an impaired GLS (≤ 16%) in 63% of cases. When the 95 patients with low GLS are compared to the 58 patients with normal GLS, there is no significant difference between the 2 groups regarding sex, age, type of HF, comorbidities and risk factors.

Among the classic echocardiographic variables, the E/E ratio is the only parameter significantly associated with the decrease in GLS with a moderate correlation. It is significantly higher in the group of patients with GLS ≤ 16% with an average of 16.92 ± 5.8 vs 14 ± 4; $p = 0.00039$, respectively (Table 1).

Biochemical markers: The average value of NT-pro BNP is 2995 ± 5148 pg/ml, ranging from 133 to 35000 pg/ml. We have measured plasmatic concentrations of growth differentiation factor (GDF 15) in only 111 patients Table 2. The average value is 4102 pg/ml ± 4,274 ranging from 400 to 25632 pg/ml. In 70% of cases, levels of GDF 15 exceeds 1800 pg/ml, while 17% of patients had values < 1200 pg/ml and 13% had values between 1200 and 1800 pg/ml.

Functional ability: Functional ability was assessed using the 6-minute walking test (6M-WT). Due to inappropriate physical conditions, physical deconditioning, or osteoarticular pathology, this test could only be performed in 42.5% of our patients. The average value of the walking perimeter is 265 meters ± 146, ranging from 100 to 512 meters. 53% of patients have a walking perimeter of < 300 meters.

Treatments Nearly 90% of our patients were on renin-angiotensin system inhibitors, Angiotensin II receptor antagonists (ARAII), or Angiotensin Conversion Enzym

Table 2: Baseline Characteristics of population study.

Clinical Characteristics	(*n* = 153)
Age (year)	72.76 +/- 11.19
Female (n, %)	101 (67)
Hypertension (n, %)	133 (86.93)
Diabetes (% prevalence)	100 (65.36)
Obesity (% prevalence)	54 (35.76)
Chronic renal insufficiency* (prevalence in %)	59 (38.56)
Anemia (% prevalence)	65 (42.48)
Chronic obstructive pulmonary disease (prevalence in %)	31 (20.39)
Smoking (% prevalence)	6 (3.92)
Coronary artery disease (% prevalence)	39 (25.66)
Atrial fibrillation (% prevalence)	70 (45.76)
Ultrasound characteristics	59.08 ±6.663
Left ventricular ejection fraction (%)	121.4 ± 37.65
Indexed left ventricular mass (g/m²)	48.35 ±18.53
Indexed volume of left atrium (ml/m²)	15.79 ± 5.358
Average E/E' (ratio)	42.74 ± 12.93
Systolic pulmonary arterial pressure (mm Hg)	2.863± 0.4345
Maximum velocity of tricuspid regurgitation (m/s)	14.29 ± 3.974
Global longitudinal strain (%)	2995 ±5148
Biochemical characteristics	3978 ±4346
NT- Pro BNP (pg/ml)	265 +/- 149.3
GDF 15 (Pg/ml)	125 (82)
Functional Capacity	102 (67)
6-minute walking test (meters)	35 (23)
Treatments	137 (90)
Diuretics (n, %)	97 (63)
Angiotensin II Receptor Antagonists (ARA II) (n, %)	47 (31)
Converting enzyme inhibitors (ACE inhibitors) (n, %)	59 (39)
AIIB or ACE inhibitors (n, %)	71 (46)
Beta-blockers (n, %)	36 (24)
Calcium inhibitors (n, %)	9 (6)

NT-proBNP: N Terminal pron Brain Natriuretic Peptide; GDF-15: Growth Differentiation Factor. *: Glomerular Filtration Rate < 60 ml/min/1.73 m²SC. ARA II: Angiotensin II Receptor Antagonists; ACE: Antagonists of Converting Enzyme.

Table 1: Characteristics of population study by GLS and their association with impaired GLS in HFPEF.

Effectif	GLS ≤ 16% *n* = 95	GLS > 16% *n* = 58	CI 95%	OR	P
Age Mean (sd)	72.06 (11.14)	73.9 (11.27)	0.9849, 1.046	1.015	0.3254
Men, n (%)	29 (55.77)	23 (44.23)	0.7507, 2.979	1.496	0.2486
Congestive HF n (%)	3 (30)	7 (70)	0.8879, 15.14	3.667	0.0702
Hypertension n (%)	81 (60.9)	52 (39.1)	0.5369, 4.179	1.498	0.4365
Diabetes n (%)	62 (62)	38 (38)	0.5061, 2.021	1.011	0.9744
Coronary artery disease n (%)	26 (66.67)	13 (33.33)	0.3548, 1.657	0.766	0.4957
COPD n (%)	18 (58.06)	13 (41.94)	0.5503, 2.775	1.236	0.6050
Obesity n (%)	38 (70.37)	16 (29.63)	0.2801, 1.166	0.571	0.1209
Anemia n (%)	43 (66.15)	22 (33.85)	0.3774, 1.447	0.739	0.3740
Atrial fibrillation n (%)	48 (68.57)	22 (31.43)	0.3059, 1.171	0.598	0.1305
CRI, n (%)	38 (64.41)	21 (35.59)	0.4312, 1.681	0.851	0.6402
Ratio E/E' Mean (sd)	16.71 (5.776)	13.98 (3.975)	0.8205, 0.961	0.888	0.0030
LVEF mean (%) (sd)	58.34 (6.881)	60.29 (6.156)	0.9943, 1.099	1.045	0.0798
LVM (g/m²) Mean (sd)	119.9 (34.45)	123.3 (42.39)	0.9937, 1.011	1.002	0.5857
Indexed LAV Mean (sd) (ml/m²)	46.85 (18.53)	50.28 (18.38)	0.9922, 1.028	1.01	0.2703
Left atrial dilatation n (%)	72 (58.54)	51 (41.46)	0.9216, 5.877	2.327	0.0715
peak velocity of TR (m/s) Mean (sd)	2.83 (0.37)	2.868 (0.5112)	0.5747, 2.657	1.236	0.5847
PASP (mmHg) mean (sd)	41.56 (10.42)	42.94 (16.13)	0.9830, 1.001	1.008	0.5172
NT-Pro BNP (pg/ml) Mean (sd)	3144 (5618)	2569 (392	0.9086, 1.048	0.975	0.4960
GDF 15 (pg/ml) Mean (sd)	3870 (3837)	4285 (5035)	0.9369, 1.115	1.022	0.6205
6M-WT (meters) Mean (sd)	243.6 (146.3)	291.1 (151.3)	0.9987, 1.006	1.002	0.2108
MACE at one year	34 (35.79)	16 (27.59)	0.3333, 1.402	0.683	0.2951

GLS: Global Longitudinal Strain, CI: Confidence Interval; Sd: Déviation Standard; HF: Heart Failure; COPD: Chronic Obstructive Pulmonary Disease; CRI: Chronic Renal Insufficiency (Débit de filtration glomérulaire < 60 ml/min/1.73m²), LVEF: Left Ventricular Ejection Fraction; LVM: Left Ventricular Mass; LAV: Left Atrial Volume; TR: Tricuspid Regurgitation; PASP: Pulmonary Artery Systolic Pressure; NT-pro BNP: N-Terminal pro Brain Natriuretic Peptide; GDF15: Growth Differentiation Factor 15; 6M-WT: 6 Minutes Walk Test; MACE: Main Acute Cardiovascular Events.

(ACE) inhibitors, 67% and 22% respectively. 81% of patients received diuretics, 63% were on beta-blockers, and 25% were on Spironolactone.

Prognosis: A total of 58 (38%) cardiovascular events were recorded (all-cause mortality, hospitalization for heart failure, stroke, acute rhythm disorders, and acute coronary syndrome). The hospitalization rate for HF is 5.9%. There were 21 deaths from any cause during the one year of follow-up, representing a rate of 13.73%. Cardiovascular origin of deaths accounts for 55% of cases while non-cardiovascular origin represents 45% of cases. There was no statistically significant association between GLS and the outcome at one year, either in continuous analysis (p = 0.117), or dichotomic analysis (p = 0.295). After multivariate adjustment, independent prognostic factors are signs of peripheral venous congestion (p = 0.003), anemia (p = 0.026) and PASP (0.024). The findings of growth differentiation factor are useless regarding this article and the objective since they were measured in a small proportion of patients and did not show prognostic significance.

Discussion

The prevalence of longitudinal systolic dysfunction of LV (GLS ≤ 16%) reported in 10 studies including 1810 patients with HFPEF and 462 asymptomatic controls, was significantly higher in patients with HFPEF with an average of 65.4% ranging from 37% to 95%, while it is only 13% (0% - 29.6%) in asymptomatic subjects [10]. Our results closely match these data with a prevalence of 62%. The average value of the GLS in absolute value is 14.29+/- 3.97% ranging from 3.2% to 24%.

Prognostic relevance of impaired GLS in HFPEF

Although the prognostic relevance of impaired GLS has been demonstrated in HFREF [11], the literature data on HFPEF are contradictory. Several studies highlight its prognostic value in these patients [10-13], while others found no correlation between low GLS and cardiovascular events. The results of the recent metanalysis published in 2017 by Morris, et al. who was interested in all the studies that evaluated the prevalence and the prognostic value of impaired GLS in patients with HFPEF [10] Table 3, were divergent. Out of nine studies, two multicentre studies and three single-center studies found no significant association between GLS and prognosis [10].

The prognostic value of GLS in HFPEF has been reported in other studies in patients with acute heart failure independently of LVEF [14], after discharge from hospitalization for HF [15] and in patients with stable chronic HF [16].

However, no prognostic value was found in an analysis of the RELAX trial, conducted on 187 patients. With chronic HFPEF. Impaired GLS was also not correlated with quality of life and functional capacity [17]. Even more surprisingly, this same negative correlation was observed in patients with HFPEF after discharge from hospitalization for acute HF [18] and in patients with acute HF [19].

Contrary to our hypothesis, GLS was not found to be a powerful predictor of cardiovascular events in HFPEF patients. The heterogeneous population of the study could lead to such conflicting data. However, several considerations need to be emphasized when interpreting studIes' data to explain, even partially, these disparate results. On the one hand, the monocentric character and the small sample size of our series, and the low rate of events, do not allow us to draw conclusions on the prognostic relevance of GLS. On the other hand, we have evaluated the prognostic value of GLS at rest, which does not allow to unmask a decrease in GLS at exercise, an important feature of HFPEF syndrome [20,21]. This was well demonstrated by Wang, et al. who found a significant association between the GLS of effort, and not of rest, with CV events [22] and by Gozdzik, et al. in a recent Australian study [23] Table 4.

Our negative results could also be explained by the fact that we only evaluated the value of the baseline GLS at the time of inclusion in the study without taking into account its evolution during follow-up or the possible effect of certain therapies dedicated to reducing parietal stress and fibrosis, such as antialdosterones. This was also observed in the TOPCAT trial in LVEF patients > 45%, treatment with spironolactone compared with placebo in a small subgroup of 131 patients with low GLS, was associated with a trend to improve GLS over 12 to 18 months in Americans [24].

This could correspond to one aspect of reverse remodeling, where the GLS could predict changes in LVEF, as demonstrated by a recent Koréenne study [25].

Table 3: Association between impaired GLS and outcome in HFPEF population studies [10].

Studies	N° patients	CVE	Region	Statut	Statistic Methodology	Delay	Correlation
Donal, et al. (KaRen) [29]	413	177	Suède-France	After AHF	Dichotomic	18 mois	S
Burke, et al.	419	175	USA	After AHF	Continue	18 mois	NS
Freed, et al.	308	115	USA	CHF	Continue	13 mois	NS
Stampehl, et al.	100	17	USA	Mixt	Dichotomic	12 mois	S
Wang, et al.	80	43	Asie	After AHF	Continue	36 mois	NS
Shah, et al. (TOPCAT)	447	115	USA	CHF	Dichotomic	18 mois	S
Buggey, et al.	463	97	USA	AHF	Dichotomic	12 mois	NS
Our study	153	58	Algérie	Mixt	Douicho-contin	12 mois	NS

GLS: Global Longitudinal Strain; HFPEF: Herat Failure with Preserved Ejection Fraction; CVE: Cardiovascular Events; AHF: Acute Heart Failure; CHF: Chronic Heart Failure.

Table 4: Prevalence of longitudinal systolic dysfunction in HFPEF population studies [10].

Study	HFPEF abnormal GLS(%)	Sujet contrôle Normal GLS (%)	Cut-off abnormal GLS	Software package
Wang, et al.	95%	5%	-16%	EchoPac
Liu, et al.	85%	15%	-17.5%	EchoPac
Morris, et al.	81.5%	15.5%	-16%	EchoPac
Yip, et al.	37%	0%	-16%	EchoPac
Kraigher-krainer, et al.	54.3%	29.6%	-15.8%	TomTec
Donal, et al. [29]	39%	Pas de groupe contrôle	-16%	EchoPac
Shah, et al.	52%	Non rapporté	-15.8%	TomTec
Freed, et al.	75%	Pas de groupe contrôle	-20%	TomTec
Devore, et al.	65%	Pas de groupe contrôle	-16%	TomTec
Huang, et al.	75.9%	Pas de groupe contrôle	-15.8%	EchoPac
Our study	62%	Pas de groupe contrôle	-16%	EchoPac

On the other hand, the heterogeneity of the HFPEF definitions underlines once again the complexity of this heroic entity where no optimal definition exists, which makes it difficult to compare the different results. This was demonstrated by a recent study comparing the different definitions of invasive hemodynamic data as well as their prognostic implication [26]. Thus, some definitions lacked specificity while others lacked sensitivity. But what is even more interesting, is that this heterogeneity is reflected by the heterogeneity of the prognosis that was up to 4 times more risk [26].

The absence of pathognomonic diagnostic criteria, and criteria for the exclusion of other pathologies, makes the diagnosis of HFPEF in the elderly, with multiple comorbidities, sometimes nuanced, not allowing to distinguish dyspnea related to HFPEF from dyspnea of non-cardiac cause related to pulmonary pathology or physical deconditioning. This was observed in an ancillary study of the RELAX trial, where age, sex, body mass index, hemoglobin, and chronotropic reserve accounted for 64% of the variability observed in the VO2 peak [17]. Thus, a cardiopulmonary stress test could help differentiate "HFPEF" from non-cardiovascular dyspnea, although its feasibility may be limited in some elderly or frail people. Similar to the data from the RELAX trial, GLS was not correlated with NT-proBNP values, the 6-minute walk test, or prognosis in our study. In addition, it is not yet clear whether patients with symptoms of HF preserved ejection fraction and more than benign epicardial coronary artery disease can be considered to have HFPEF, since the symptoms of HF are disproportionate to the severity of coronary artery disease and sometimes persist after revascularization [27], hence the interest in carrying out comparative studies excluding patients with HFPEF and coronary artery disease. It is difficult to extrapolate the data related to the GLS, when it is measurable, on all patients in HFPEF in whom the GLS is not measurable. This was highlighted in the TOPCAT trial where GLS was only measurable in 14% of cases with notable differences from the overall trial cohort and patients in whom GLS was not measurable [28].

The heterogeneity of the statistical methodology of the different studies was also raised by Morris, et al. in their latest meta-analysis [10]. However, in our study, the link between GLS and prognosis remains insignificant using continuous analysis and dichotomous analysis. It should also be remembered that few international studies exist in Africa. The ownership of the African population is 9% in total and 23% in the United States in the TOPCAT trial, 2% in I-PRESERVE, and 4% in CHARM-Preserved. Recruitment of patients of African descent is particularly important in clinical trials of mineralocorticoid receptor antagonists, given data showing higher aldosterone levels in hypertensive individuals from Africa [28].

Limits of our study

Our study is monocentric with a small sample which requires caution in interpreting the results. All echocardiography was performed at rest, which does not allow to unmask a decrease in GLS during exercise, an important characteristic of ICFEP syndrome. The effect of the evolution of GLS over time (Effects of treatments and reverse remodeling) has not been studied. GLS was measured only at rest, which does not unmask a decrease in GLS during exercise and limits the ability to assess the relationship between GLS and impaired functional capacity, an important feature of HFPEF syndrome.

Conclusion

In conclusion, these conflicting results regarding the prognostic value of longitudinal systolic dysfunction as assessed by the GLS could be explained in part by the heterogeneity of populations according to the study design, the inpatient or outpatient status of patients, the threshold used to define a preserved LVEF and exclusion criteria inducing selection bias. To this would probably be added the impact of regional variations in comorbidities, living standards, nutritional mode, physical activity, and genetic predisposition around the world. Despite this significant prevalence, these results underscore the fact that while these pathophysiological mechanisms may play a role in the development of HFPEF, they do not necessarily announce a poor prognosis, suggesting that other processes may be more responsible for these aspects of HFPEF syndrome. These data should not discredit the prognostic role of GLS, but rather encourage other large, selective, and comparative multicentre studies in subgroups of patients with HFPEF. Thus a new therapeutic target could emerge for this complex disease, for which few treatments exist.

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