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The prognostic role of galectin-3 and endothelial function in patients with heart failure

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Abstract

Background: *Heart failure (HF) is nowadays classified as HF with reduced ejection fraction (HFrEF), HF with mildly reduced EF (HFmrEF), and HF with preserved EF (HFpEF). Endothelial dysfunction (assessed by flow-mediated dilatation [FMD]), increased arterial stiffness (assessed by carotid-femoral pulse-wave velocity [PWV]), and galectin-3, a biomarker of myocardial fibrosis, have been linked to major adverse cardiovascular events (MACE) in patients with ischemic HF.*

Methods: *In this study we prospectively enrolled 340 patients with stable ischemic HF. We assessed the brachial artery FMD, carotid-femoral PWV, and galectin-3 levels, and patients were followed up for MACE according to HF group.*

Results: *Interestingly, the FMD values exhibited a stepwise improvement according to left ventricular ejection fraction (LVEF) (HFrEF: 4.74 ± 2.35% vs. HFmrEF: 4.97 ± 2.81% vs. HFpEF: 5.94 ± ± 3.46%, p = 0.01), which remained significant after the evaluation of possible confounders including age, sex, cardiovascular risk factors, and number of significantly stenosed epicardial coronary arteries (b coefficient: 0.990, 95% confidence interval: 0.166–1.814, p = 0.019). Single-vessel coronary artery disease was more frequent in the group of HFpEF (HFrEF: 56% vs. HFmrEF: 64% vs. HFpEF: 73%, p = 0.049). PWV did not display any association with LVEF. Patients who presented MACE exhibited worse FMD values (4.51 ± 2.35% vs. 5.32 ± 2.67%, p = 0.02), and the highest tertile of galectin-3 was linked to more MACEs (36% vs. 5.9%, p = 0.01).*

Conclusions: *Flow-mediated dilatation displayed a linear improvement with LVEF in patients with ischemic HF. Deteriorated values are associated with MACE. Higher levels of galectin-3 might be used for risk stratification of patients with ischemic HF.* (Cardiol J 2023; 30, 5: 725–733)

Key words: heart failure, galectin-3, endothelial function, prognosis, ejection fraction

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Introduction

Heart failure (HF) is a complex clinical syndrome that is the result of numerous structural and functional alterations of the heart [1]. The prevalence of HF is about 1–2% in adults, although it might be much higher due to underdiagnosis, and it increases with age and the presence of comorbidities [2]. Ischemic HF is attributed to coronary artery disease (CAD) and is one of the most common etiologies of HF, especially in western countries [3]. Understanding the specific cause of HF and its pathophysiologic background may facilitate treatment of the patients [1]. HF is currently classified into three categories: HF with reduced ejection fraction (EF) (HFrEF, when EF ≤ 40%, which depicts an important deterioration of left ventricular [LV] systolic function), HF with mildly reduced EF (HFmrEF, when 40% < EF ≤ 49%), and HF with preserved EF (HFpEF, when EF ≥ 50% along with the presence of structural or functional dysfunction and/or elevated natriuretic peptides) [1, 4].

Endothelial dysfunction has been associated with the initiation and development of cardiovascular disease [5]. Endothelial function is impaired in patients with ischemic HF contrary to patients without ischemic HF [6]. Flow-mediated dilatation (FMD) of the brachial artery is a non-invasive method for the assessment of endothelial function, which evaluates the endothelium-dependent vasomotor properties of the vascular wall due to nitric oxide (NO) production [7]. Arterial stiffness and markers of wave reflection, such as pulse wave velocity (PWV), have been associated with poorer cardiovascular prognosis, especially when measured together with classic risk factors [8]. Moreover, biomarkers of fibrosis and cardiovascular remodeling have demonstrated a prognostic capability in patients with HF along with natriuretic peptides [9]. Indeed, galectin-3, a well-known biomarker of fibrosis and myocardial remodeling, has exhibited a correlation with clinical status in patients with chronic HF [10].

The aim of this prospective follow-up study was to investigate the association of endothelial dysfunction, arterial stiffness, and galectin-3 with left ventricular ejection fraction (LVEF) categorization in ischemic HF and their prognostic value.

Methods

Study design

In this single-center, prospective cohort study we enrolled 340 patients (age 62 ± 11 years) with ischemic heart disease and HF according to European Society of Cardiology (ESC) guidelines of HF (2016) [11]. All patients were recruited from the HF outpatient clinic of Hippokration University Hospital, Athens, were in stable clinical condition for at least 6 months and under optimal medical treatment, and were classified as HFrEF, HFmrEF, or HFpEF [11].

Coronary artery disease was defined by history of myocardial infarction (MI) or stenosis of at least one epicardial vessel with ≥ 50% narrowing of the artery lumen based on invasive coronary angiography and evidence of myocardial ischemia [12, 13]. All patients underwent coronary angiography according to indications (i.e., positive stress test, angina, post-acute coronary syndrome [ACS]); coronary angiography was assessed by at least two experienced cardiologists, and the degree of vessel stenosis was evaluated with the quantitative coronary angiography system.

We excluded patients with significant valvular or congenital heart disease, uncontrollable hypertension, persistent or permanent atrial fibrillation, severely impaired functional capacity (New York Heart Association [NYHA] class IV), advanced renal disease (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2), advanced liver disease, chronic lung disease, severe systematic or inflammatory disease and active malignancy, morbid obesity, thyroid disease, and transplantation.

Informed consent form was obtained from each of the subjects before enrollment in the study.

Several demographic and clinical parameters were recorded such as age, sex, body mass index (BMI), the presence of arterial hypertension, diabetes mellitus, dyslipidemia, and smoking. Smokers of at least one cigarette per day or those who quitted smoking less than a year before enrollment in the study were defined as current smokers; patients who smoked before this time were classified as ex-smokers; and patients who had never smoked were classified as never-smokers.

Patients were followed-up for major adverse cardiovascular events (MACE) including cardiovascular death, MI, coronary revascularization, stroke, and hospitalization due to HF. Deterioration of HF clinical status was defined as a secondary endpoint.

Assessment of endothelial function

Flow-mediated dilatation measured at the right brachial artery was used as a marker of endothelial dysfunction [7]. All patients were in a fasting state for at least 12 h before their participation in the study and withdrew any vasoactive medications for that period. The measurement took place in

a quiet and temperature-controlled room after a 10-min rest period. Then, the examiner assessed the right brachial artery in a longitudinal section using a Vivid e-ultrasound system (General Electric, Milwaukee, Wisconsin, USA) equipped with a 5.0–13.0-MHz (harmonics) linear array ultrasound transducer positioned 5 cm above the antecubital fossa. A pneumatic cuff was placed on the forearm distally to the ultrasound probe and was inflated to suprasystolic pressure for 5 min to induce reactive hyperemia. After the release of the cuff, the brachial artery diameter was assessed manually with electronic calipers (as the average value of several measurements of the arterial diameter at the border of the media adventitia). Measurements were repeated every 15 s for a period of 2 min. FMD was defined as the percentage change of the brachial artery diameter from the baseline measurement to the maximum artery diameter post cuff release. All the measurements were performed by the same examiner throughout the study, whereas another blinded observer evaluated the FMD values to avoid systemic bias [14].

Assessment of arterial stiffness

Arterial stiffness was evaluated by carotid-femoral pulse wave velocity (PWV) [15]. The pulse transit time and the distance traveled between the 2 recording sites was recorded to calculate the carotid-femoral PWV (PWV = distance in meters divided by the transit time in seconds). All measurements were performed by a well-validated non-invasive device (SphygmoCor; AtCor Medical). Pulse waves were recorded with the transducer at the base of the neck for the common carotid and over the right femoral artery. Distance was defined as the distance from the suprasternal notch to the femoral artery minus the distance from the carotid artery to the suprasternal notch.

Echocardiographic evaluation

All patients underwent echocardiographic assessment with a vivid e-cardiovascular ultrasound system (General Electric, Milwaukee, WI, USA) equipped with a 2.0–3.6 MHz (harmonics) phased array transducer. According to the guidelines of the European Association of Cardiovascular Imaging and American Society of Echocardiography, LVEF was evaluated according to the Simpson biplane method [16].

Biochemical measurements

Blood samples were collected with venipuncture after a fasting of 12 h and were centrifuged at 3000 rpm. Serum/plasma samples were stored at –80°C until their analysis. Galectin-3 levels were assessed by the biochemistry laboratory of the 1st Cardiology Clinic, Hippokration University Hospital, Athens, Greece with commercial enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions (R&D Systems Inc., Minneapolis, MN, USA).

Bioethics

All participants were informed for the purposes and the aims of the research, and a written consent form was obtained before the initiation of the study. The study was performed according to the Declaration of Helsinki (1989) and was accepted by the Scientific Institute for Research of Hippokration University Hospital.

Statistical analysis

All variables were tested for normal distribution with the use of P-P plots. Variables with normal distribution were expressed as means ± standard deviation, and otherwise as median with interquartile range. Categorical variables were expressed as valid percentages of the specific subpopulation. The t-test was applied to test for intergroup differences between two categories of normally distributed variables. One-way analysis of variance (ANOVA) or Kruskal-Wallis test was applied to test for intergroup differences of continuous variables according to LVEF classification. Bonferroni correction for multiple comparisons was applied to test for intergroup differences among the three studied groups. The χ^2 test was performed to evaluate differences between categorical variables. To examine the interrelationship of FMD with LVEF independently of confounders known to affect FMD, we applied a linear regression analysis. To examine the prognostic significance of variables for MACE, we performed a receiver operating characteristics (ROC) analysis. All the reported p-values corresponded to two-sided tests. P-values were considered statistically significant at the level of < 0.05. Data were analyzed using SPSS version 26.0 (IBM, SPSS Statistics, Version 25.0. Armonk, NY, USA).

Results

Baseline characteristics of the study population

The basic demographic and clinical characteristics of the study population are demonstrated in Table 1. The mean age of the patients was

Table 1. Basic demographic and clinical characteristics of the study population.

Characteristics of the study population	Data
Age [years]	62 ± 11
Male sex	63%
Body mass index [kg/m^2]	28.11 ± 3.95
Hypertension	73%
Diabetes mellitus	28%
Dyslipidemia	76%
Smoking:	
Current smokers	25%
Ex-smokers	57%
Never-smokers	18%
eGFR [mL/min/1.73 m^2]	96 ± 32
Heart failure category:	
HFpEF (EF ≥ 50%)	46%
HFmrEF (EF: 41–49%)	28%
HFrEF (EF ≤ 40%)	26%
Single vessel disease	60%
Flow mediated dilatation [%]	5.05 ± 2.78
Pulse wave velocity [m/s]	8.91 ± 2.49
Galectin-3 [ng/mL]	9.58 (8.32, 15.88)

Data are presented as mean ± standard deviation for normally or as median with interquartile range for parametric and non-parametric data, respectively. Categorical variables are presented as valid percentages; eGFR — estimated glomerular filtration rate; EF — ejection fraction; HFrEF — heart failure with reduced ejection fraction; HFmrEF — heart failure with mildly reduced ejection fraction; HFpEF — heart failure with preserved ejection fraction

62 ± 11 years, and 63% were males. The mean value of BMI was 28.11 ± 3.95 kg/m^2 (24% had normal weight, 50% were obese, and 26% were overweight). 73% of the patients had hypertension, 28% were diabetic, and 76% had dyslipidemia. Current smokers comprised 25% of the study population, whereas ex-smokers and never-smokers were 57% and 18%, respectively. Additionally, 60% of the patients had single vessel disease. Furthermore, the mean eGFR was 96 ± 32 mL/min/1.73 m^2. According to LVEF, 26% of the patients were diagnosed with HFrEF, 28% with HFmrEF, and 46% with HFpEF. Also, the mean FMD was 5.05 ± ± 2.78%, and the mean PWV was 8.91 ± 2.49 m/s.

Population study characteristics according to LVEF category

There were no significant differences among the study groups regarding age (HFrEF: 62 ± 11 vs. HFmrEF: 61 ± 11 vs. HFpEF: 61 ± 11, p = 0.64), eGFR (HFrEF: 93 ± 32 vs. HFmrEF: 94 ± 32 vs. HFpEF: 94 ± 33, p = 0.97), and male sex (HFrEF: 61% vs. HFmrEF: 63% vs. HFpEF: 64%, p = 0.10). Interestingly, single-vessel CAD was more frequent in subjects with HFpEF compared to subjects with HFmrEF and HFrEF (HFrEF: 56% vs. HFmrEF: 64% vs. HFpEF: 73%, p = 0.049; Table 2). FMD displayed an improvement in patients with HFmrEF and HFpEF, contrary to patients with HFrEF (HFrEF: 4.74 ± 2.35 vs. HFmrEF: 4.97 ± 2.81 vs. HFpEF: 5.94 ± 3.46, p = 0.01; Table 2).

Evaluation of arterial function according to LVEF classification: Factors affecting arterial function

Our results revealed a stepwise impairment of FMD according to HF classification (HFpEF: 5.94 ± 3.46% vs. HFmrEF: 4.97 ± 2.80% vs. HFrEF: 4.74 ± 2.35%, p = 0.01; Fig. 1A). PWV values did not differ among the study groups (HFpEF: 8.89 ± 2.50 m/s vs. HFmrEF: 8.83 ± 2.50 m/s vs. HFrEF: 8.87 ± 2.51, p = 0.91; Fig. 1B). Also, galectin-3 levels were similar between the study groups (HFrEF: 9.50 [8.26, 16.39] vs. HFmrEF: 10.02 [8.74, 14.58] vs. HFpEF: 9.66 [5.78, 53.00], p = 0.61; Table 2). In order to examine whether any demographic or clinical parameters affected FMD, we performed a multiple linear regression analysis, in which we included all variables possibly affecting FMD (i.e., age, sex, BMI, hypertension, diabetes mellitus, dyslipidemia, smoking, number of vessel disease and HF group) (Table 3). FMD was reduced in patients with HFrEF compared to HFpEF by approximately 1.0% (b coefficient: 0.990, 95% confidence interval [CI]: 0.166–1.814, p = 0.019) independently of the aforementioned confounders (Table 3). Regression analysis revealed that FMD was inversely associated with age and BMI (Table 3).

Cardiovascular events

The median follow-up period of the study population was 48 months (interquartile range: 36, 76 months). During follow-up 30 patients died, 14 patients suffered a stroke, 41 patients were hospitalized for HF deterioration, 69 patients underwent angiography, and 28 patients suffered a MI. In total 38.2% developed a MACE.

Left ventricular ejection fraction was not associated with MACE (HFrEF: 38.2% vs. HFmrEF: 41.2% vs. HFpEF: 34.0%, p = 0.24). FMD was impaired in subjects who presented a MACE, compared to those without a MACE (4.51 ± 2.35% vs. 5.32 ± 2.67%, p = 0.02). Interestingly, patients

Table 2. Characteristics of the study population according to heart failure category

Variable	HFrEF	HFmrEF	HFpEF	P
Age [years]	62 ± 11	61 ± 11	61 ± 11	0.64
Male sex	61%	63%	64%	0.10
Body mass index [kg/m^2]	27.75 ± 4.33	27.93 ± 3.47	28.18 ± 3.86	0.75
Hypertension	68%	78%	78%	0.09
Diabetes mellitus	27%	31%	24%	0.50
Dyslipidemia	76%	69%	84%	0.07
Smoking:				0.40
Current smokers	29%	28%	25%	
Ex-smokers	57%	56%	48%	
Never-smokers	14%	16%	27%	
eGFR [mL/min/1.73 m^2]	93 ± 32	94 ± 32	94 ± 33	0.97
Single vessel disease	56%	64%	73%	0.049
Stable clinical condition [months]	16 (10, 29)	16 (11, 26)	15 (10, 23)	0.23
Flow mediated dilatation [%]	4.74 ± 2.35	4.97 ± 2.81	5.94 ± 3.46	0.01
Pulse wave velocity [m/s]	8.97 ± 2.51	8.83 ± 2.50	8.89 ± 2.50	0.91
Galectin-3 [ng/mL]	9.50 (8.26, 16.39)	10.02 (8.74, 14.58)	9.66 (5.78, 53.00)	0.61

Data are presented as mean ± standard deviation for normally distributed data or as median with interquartile range for parametric and non-parametric data. Categorical variables are presented as valid percentages. Abbreviations — see Table 1.

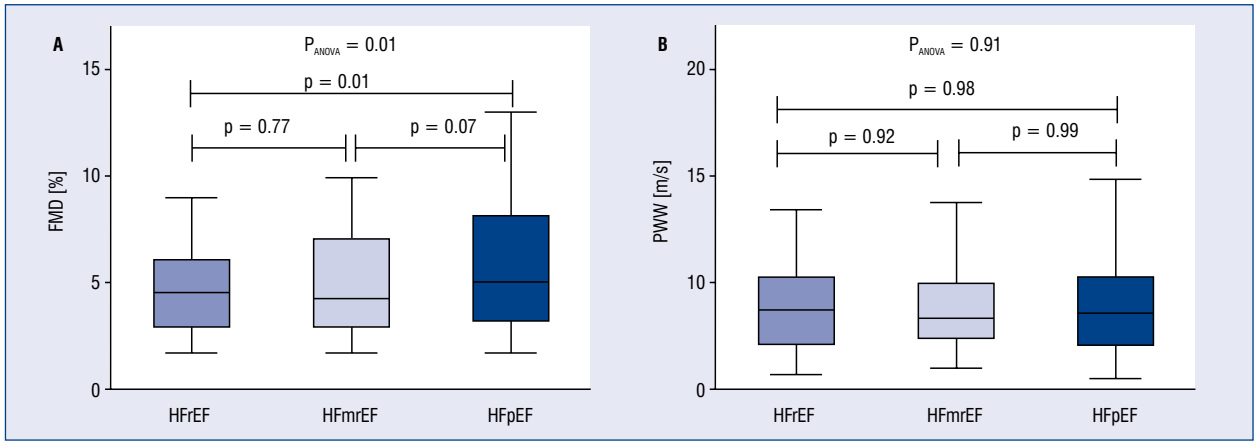

Figure 1. Box plots of arterial function parameters (arterial stiffness and endothelial function) according to left ventricular ejection fraction (EF) classification; **A.** Flow-mediated dilatation (FMD) values according to heart failure (HF) classification; **B.** Pulse wave velocity (PWV) values according to HF classification. Abbreviations — see Table 1.

in the highest tertile of galectin-3 presented more MACEs compared to the subjects of the other tertiles (36% vs. 5.9%, p = 0.01) (**Suppl. Fig. 1A–D**). According to ROC analysis (**Suppl. Fig. 2A–C**), LVEF category and the highest tertile of galectin-3 did not display any prognostic capability for MACE (LVEF: area under the curve [AUC] = 0.526, 95% CI: 0.453–0.599, p = 0.49, highest tertile of galectin-3: AUC = 0.600, 95% CI: 0.486–0.713, p = 0.11, respectively). On the other hand, FMD had the greatest prognostic capability for MACE (FMD: AUC = 0.608, 95% CI: 0.532–0.685, p = 0.006). Last but not least (**Suppl. Fig. 3A–C**), ROC analysis for LVEF, FMD, and galectin-3 (highest tertile) displayed no prognostic value for the combined end-point of rehospitalization for HF and/or death (LVEF: AUC = 0.504, 95% CI: 0.394–0.614, p = 0.94; FMD: AUC = 0.591, 95% CI: 0.460–0.722, p = 0.15; highest tertile of galectin-3: AUC = 0.532, 95% CI: 0.393–0.671, p = 0.67).

Table 3. Multiple linear regression analysis for the association of flow-mediated dilatation (FMD) with heart failure (HF) group and multiple confounders.

	Regression analysis for the association of FMD (dependent variable) with HF group after adjustment for multiple cardiovascular risk factors		
	b coefficient	95% CI	P
Age [years]	–0.04	(–0.07, –0.02)	0.003
Male sex	–0.70	(–1.58, 0.18)	0.118
Body mass index [kg/m^2]	–0.12	(–0.19, –0.04)	0.003
Hypertension	0.11	(–0.63, 0.84)	0.772
Diabetes mellitus	–0.07	(–0.74, 0.60)	0.836
Dyslipidemia	0.09	(–0.64, 0.84)	0.792
Smoking			
Never-smokers (reference category):			
Ex-smokers	–0.07	(–0.93, 0.79)	0.882
Current smokers	0.30	(–0.68, 1.29)	0.544
Single vessel disease [%]	–0.13	(–0.75, 0.49)	0.692
HFrEF (reference category):			
HFmrEF	0.14	(–0.54, 0.81)	0.692
HFpEF	0.99	(0.17, 1.81)	0.019

For categorical variables the reference category was set as female sex and the absence of: hypertension, diabetes mellitus, hyperlipidemia, multi-vessel coronary artery disease, smoking history, and heart failure with reduced ejection fraction (HFrEF); HFmrEF — heart failure with mildly reduced ejection fraction; HFpEF — heart failure with preserved ejection fraction; CI — confidence intervals

Discussion

In this prospective cohort study we evaluated the effects of galectin-3, brachial artery FMD, and carotid-femoral PWV on cardiovascular prognosis in patients with ischemic HF according to LVEF [16]. Interestingly, FMD was significantly improved in patients with HFpEF in contrast to patients with reduced EF, independently of possible confounders. Arterial stiffness, assessed by PWV, was not associated with LVEF. Furthermore, FMD was impaired in patients who developed a MACE during follow-up, and patients in the highest tertile of galectin-3 exhibited more MACEs. Our results did not indicate an association between MACE and LVEF category. Lastly, single-vessel CAD was more frequent in patients with HFpEF.

Deteriorated endothelial function has been linked to the development and progression of ischemic HF [15]. Indeed, endothelial dysfunction is associated with decreased production of NO and reduced vascular relaxation [7]. Endothelial dysfunction favors the production of vasoconstrictors, and the proliferation of vascular smooth muscle cells and extracellular matrix, which is implicated in cardiac remodeling and decreased cardiac output in HF [17]. In our study, FMD demonstrated a stepwise improvement with the increase of EF, and specifically patients with HFpEF demonstrated higher levels of FMD, independently of possible confounders. Evidence from the literature shows that FMD has an inverse association with LVEF in patients with chronic HF, but this is statistically non-significant in regression analysis models [18].

As for HFpEF, the literature reveals that coronary microvascular rarefaction, cardiac hypertrophy, and fibrosis induce LV diastolic dysfunction and impaired coronary flow reserve [19]. Microvascular rarefaction might be a significant contributor of diastolic dysfunction in older patients with HFpEF [20]. Similar associations have been demonstrated for obese patients, who display a worse profile of microvascular rarefaction, myocardial and pericardial fibrosis, and abnormal filling pressure of LV [21]. Our study did not find an association between PWV and LVEF. PWV is a marker of arterial stiffness, and higher levels of central PWV have been linked to the incidence of HF in the community [22]. PWV is also a marker of ageing, and higher values have been found in patients with HFrEF and HFpEF as well as in patients with HFmrEF [23–25]. Also, other published data indicate that HFpEF exhibits similar aortic stiffness with the group of HFrEF despite

the presence of higher central blood pressures and wave reflections [26].

On the other hand, in our study FMD levels were deteriorated in patients who had more MACEs during follow-up. Persistently elevated levels of FMD have been correlated to worse cardiovascular prognosis in patients with chronic ischemic HF [27]. Moreover, there is evidence that FMD is associated with deteriorated prognosis among patients with advanced HF [28].

As for cardiovascular prognosis, our data showed that MACE was not linked to LVEF category. To date, patients with HFmrEF have a better prognosis than those with HFrEF [29]. Observational studies indicate that patients with HFpEF display better prognosis than those with HFrEF [30]. Indeed, in the MAGGIC meta-analysis, the group with HFpEF had decreased adjusted mortality risk compared to those with HFrEF [31]. Nevertheless, EF may vary with time in the same individual; therefore, patients who progress to HFrEF might have worse prognosis than patients who remain clinically stable or progress to a better clinical status [32, 33].

In our study, the presence of single-vessel CAD was more frequent in the group with HFpEF, to a less extent in patients with HFmrEF, and less frequently in HFrEF. Interestingly, HFmrEF is defined as HF with mildly-reduced EF (compared to HF with mid-range EF in the former guidelines of HF) because patients might benefit from the therapeutic approaches of the HFrEF category [1, 4]. Surprisingly, HFmrEF shares common characteristics with HFrEF, which might be attributed to the presence of underlying CAD, contrary to the group of HFpEF [4]. It is widely perceived that patients with multivessel CAD, compared to those with single-vessel or two-vessel disease, have decreased alteration in EF during dipyridamole stress echocardiography test, indicating the severity of the disease [34]. On the other hand, multivessel CAD has been linked to higher in-hospital incidence of HFpEF in patients who present with acute MI [35]. Consequently, HF is a more complex entity which is not solely explained by the evaluation of EF per se [36].

Lastly, patients with the highest levels of galectin-3 displayed more MACEs in our study. Indeed, higher levels of galectin-3 are linked to worse cardiovascular prognosis in patients with chronic ischemic HF due to the development of cardiac remodeling and associations with biomarkers of oxidative stress, inflammation, and renal dysfunction [37]. This seems reasonable because galectin-3 is a well-established marker of fibrosis participating in the processes of apoptosis, angiogenesis, and inflammation [38]. The clinical utility of galectin-3 is under investigation and has received a class IIb recommendation in the guidelines for HF as a possible risk factor, revealing the need for future studies to determine its possible role in HF diagnosis [39].

Limitations of the study

Our study had several limitations. To begin with, we did not display information about NYHA functional status of the patients and concurrent medications of the patients. Moreover, we did not perform an assessment of natriuretic peptides. EF may vary with time in the same individual, and this should be taken into account when interpreting cardiovascular prognosis. Also, the small size of our study population should be considered for the evaluation of the statistical significance of the results. The effects of other under-evaluated confounders might also affect the robustness of our results. Finally, our results cannot provide an etiologic explanation of the association of FMD and galectin-3 with cardiovascular prognosis.

Conclusions

Flow-mediated dilatation is significantly deteriorated in patients with HFrEF of ischemic etiology independently of confounders, and it displays a linear increase with the improvement of EF. Decreased FMD levels are associated with the incidence of MACE during follow-up in patients with ischemic HF, although LVEF per se does not affect survival. Also, higher levels of galectin-3 might serve as a risk factor of worse cardiovascular prognosis in patients with ischemic HF.

Conflict of interest: None declared

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