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Angiographic Parameters in Diagnosis of Microvascular Dysfunction in Patients with Heart Failure with Preserved Ejection Fraction

Mohammed I. El-Awady, Tamer M. Moustafa, Ahmed H. E. Soliman*, Moataz Elsanan
Department of Cardiology, Faculty of Medicine, Zagazig University, Egypt
***Corresponding author:** Ahmed Hassan Soliman, **E-Mail:** ahmed_soliman903@yahoo.com

ABSTRACT

Background: Heart failure with preserved ejection fraction (HFpEF) is a health care problem of epidemic proportions, currently accounting for roughly 3 million patients in the United States alone.

Objective: To study, using validated angiography indices, coronary blood flow and myocardial perfusion of the microcirculation to assess whether there is greater microvascular disease (MVD) in patients with microvascular angina and HFpEF compared to those who do not have.

Patients and methods: This retrospective study took place in El-Mahalla Cardiac Center on 160 patients with stable angina undergoing coronary angiography and echocardiography. All patients were subjected to complete history taking, full clinical examination, echocardiography, coronary angiography and angiography indices. Our patients were divided into two categories: 80 patients with HFpEF and 80 without HFpEF.

Results: There were statistically significant differences between the studied groups. We found lower myocardial blush grades (MBG) in three coronary arteries in HFpEF than non-HFpEF patients, with good statistical significance regarding MBG left anterior descending (LAD) and MBG left circumflex (LCX). Also, there was statistically significant difference between the studied groups regarding total MBG value. Between thrombosis in myocardial infarction frame count (TFC) and MBG, there was a good correlation. The best cutoff of total TFC in diagnosis in diagnosis of HFpEF was ≥ 98.55 with sensitivity of 92.5% and specificity of 73.8%. Also, the best cutoff of total MBG in diagnosis in diagnosis of HFpEF was ≤ 6.55 with sensitivity of 80% and specificity of 87.5%.

Conclusion: The HFpEF population has a greater involvement of microcirculation than patients without HFpEF.

Keywords: Angiography, Coronary microvascular dysfunction, Heart failure with preserved ejection fraction.

INTRODUCTION

A growing body of evidence has underscored the importance of coronary microvascular dysfunction (CMD), which manifests as the structural and functional abnormalities of coronary microvasculature, in a variety of cardiovascular diseases [(1)]. The prevalence of CMD is higher than ever thought in many clinical settings, and its presence is associated with worse clinical outcomes, especially when accompanied by myocardial ischemia or nonsignificant coronary artery disease (CAD) [(2)].

Heart failure is a complex medical syndrome that comes about from any structural or functional impairment of ventricular filling or ejection of blood. Strangeities of contracting and diastolic dyswork coexist, irrespective of ejection fraction (EF). EF is considered precious in classification of patients with heart failure since of differing sick person demographics, comorbid status, fate and response to therapies and since most medical trials selected persons based on EF. EF values are dependent on the shaping technique used, method of analysis and operator. Since other techniques may indicate strangeities in contracting work among patients with a preserved EF, it is suggested to use the terms preserved or small ejection fraction over preserved or reduced contracting work [(3)].

Chronic heart failure (CHF) affects nearly 6 million people in the United States and similar proportions in other industrialized countries. The prevalence is projected to rise substantially over the next 15 years, particularly in the >65 age group [(4)].

It causes substantial mortality and morbidity and represents a major disease and socioeconomic burden. CHF is a systemic syndrome involving the heart, vasculature, kidneys, and other organs, but it develops primarily as a result of diverse acquired and/or genetic structural and functional abnormalities of the heart. Forty percent to 50% of CHF patients have a form of heart failure in which left ventricular (LV) systolic function, as assessed by ejection fraction (EF) at rest, is relatively well preserved. This type of heart failure has come to be termed heart failure with preserved EF (HFpEF). The outcome of patients with HFpEF is on average slightly better than for those with reduced EF (HFrEF), but they still have substantial morbidity and mortality, e.g. 23% mortality over 3 years in a large meta-analysis [(5)].

Furthermore, the prevalence of HFpEF relative to HFrEF is rising. Although many trials have had limited power, treatments used for patients with HFrEF (e.g. inhibitors of the renin-angiotensin-aldosterone system, adrenergic blockers, biventricular pacemakers, and implantable defibrillators) have not been shown to reduce mortality in HFpEF. Current treatment is thus focused on comorbidities [(6)].

More recently, additional mechanisms have been discovered that are unrelated to diastolic function. Some studies shifts emphasis from LV afterload excess to coronary microvascular inflammation. This shift is supported by a favorable Laplace relationship in concentric LV hypertrophy and by all cardiac chambers showing similar remodeling and dysfunction. Myocardial remodeling in HFpEF differs from heart

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failure with reduced ejection fraction, in which remodeling is driven by loss of cardiomyocytes[7].

Whether HFpEF and HFrEF are distinct conditions or part of a spectrum has been debated, but it is clear that patient characteristics differ between the groups. HFpEF is especially common in the elderly. Patients with HFpEF are more likely to be female, have hypertension, obesity, metabolic syndrome, diabetes, atrial fibrillation, and to lead a sedentary lifestyle than those with HFrEF, and they are less likely to have ischemic heart disease. Transition of HFpEF to HFrEF may largely occur only in those who develop myocardial infarction. There is significant phenotypic and probably pathophysiologic heterogeneity among patients with HFpEF. An important question is whether defining more homogeneous subpopulations might allow a better understanding of the underlying pathophysiology and identification of groups that respond favorably to specific therapies. This idea is supported by a recent unbiased clustering analysis of nearly 400 carefully diagnosed HFpEF patients; in the analysis, three distinct patient groups could be identified, which differed in clinical and cardiac structural/functional characteristics as well as outcomes [8].

HFpEF was historically considered primarily to be a disorder of LV diastolic function (so-called "diastolic heart failure"). Although this is undoubtedly a major feature, it is evident that HFpEF results from a complex and variable interplay of multiple defects in LV hemodynamic and reserve function, including abnormalities of heart rate and rhythm, vascular stiffness and resistance, and ventricular-vascular coupling [9].

Clinical manifestations of HFpEF are similar to those observed in HFrEF and include shortness of breath including exercise induced dyspnea, paroxysmal nocturnal dyspnea and orthopnea, exercise intolerance, fatigue, elevated jugular venous pressure, and edema [10]. The diagnosis of HFpEF is more difficult than HFrEF and more likely to be inaccurate. It is generally accepted that abnormal LV diastolic function (with or without other cardiovascular pathology) is a fundamental component of HFpEF. Current American Heart Association (AHA) guidelines require the presence of signs or symptoms of heart failure, a preserved EF (EF≥50%), and objective evidence of LV diastolic dysfunction to diagnose HFpEF [10].

HFpEF is typically diagnosed with echocardiography. Techniques such as catheterization are invasive procedures and thus reserved for patients with co-morbid conditions or those who are suspected to have HFpEF but lack clear non-invasive findings. Catheterization represents more definitive diagnostic assessment as pressure and volume measurements are taken simultaneously and directly. In either technique the heart is evaluated for left ventricular diastolic function. Important parameters include, rate of isovolumic relaxation, rate of ventricular filling, and stiffness [11].

HFpEF has overtaken heart failure in the setting of reduced ejection fraction as the most common form of heart failure and now comprises more than 50% of all patients with heart failure. A substantial amount of research over the past few decades has revealed that HFpEF is heterogeneous in regard to underlying pathophysiologic mechanisms with both cardiac and noncardiac mechanisms. Among the cardiovascular processes are those that contribute to diastolic dysfunction, including LV hypertrophy, concentric remodeling, improper calcium handling, and abnormal relaxation [12].

Sucato *et al.* [13] studied, using validated angiography indices, coronary blood flow and myocardial perfusion of the microcirculation to assess whether there is greater MVD in patients with microvascular angina and HFpEF compared to those who do not have. They stated that analysis of microcirculation through angiography indices in patients with and without HFpEF has led to assess that the HFpEF population has a greater involvement of microcirculation than patients without HFpEF.

The aim of this work was to study, using validated angiography indices, coronary blood flow and myocardial perfusion of the microcirculation to assess whether there is greater MVD in patients with microvascular angina and HFPEF compared to those who do not have.

PATIENTS AND METHODS

This retrospective study took place in El-Mahalla Cardiac Center on 160 patients with stable angina undergoing coronary angiography and echocardiography. Our patients were divided into two categories: 80 patients with HFpEF and 80 without HFPEF (with EF >50%, no dyskinesia alterations) (in the HFPEF group, 47 females and 33 males; in control group, 45 females and 35 males).

Ethical consent:

The protocol was approved by our Zagazig University Institutional Review Board (ZU-IRB#2528/3-12-2018), which confirmed that all methods were performed in accordance with the relevant guidelines and informed written consent was obtained from all patients. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion criteria: Presence of chest pain, positive stress test, and epicardial coronary arteries free from stenosis at coronary angiography.

Exclusion criteria: Patients having positive biomarkers for myocardial infarction when they arrive to the emergency room or during hospitalization, and patients having an EF <50%.

All patients were subjected to:

- Complete history taking.
- Full clinical examination: General (head examination, abdominal examination and neurological assessment), and local examination (chest examination and heart examination).

Echocardiography to determine HFpEF using Phillips apparatus.

According to the latest guidelines of the European Society of Cardiology and American Heart Association [(10)], there are four criteria for the diagnosis of HFpEF: clinical signs of HF, symptoms of HF, normal or mild reduction in systolic function with LVEF >50% and with normal size of LV, and evidence of reduced diastolic LV function.

In our patients, we determined HFpEF by echocardiography (abnormalities of the mitral inflow pattern, tissue velocities (e), or the E/e ratio, left atrial volume index >34 mL/m^2, and increased LV mass index) [(10)].

- Coronary angiography.
- Angiography indices. TFC and MBG were calculated for each patient. According to three main coronary arteries (LAD, CX, and right coronary artery (RCA)), TMBS was obtained by summing up the MBG of each coronary area. TTFC was obtained from the sum of the TFCs of the three coronary arteries.

The MBG was also calculated carefully following the protocol described by **Gibson *et al.*[(14)]** MBGs were defined as follows: 0, no myocardial blush or contrast density; 1, minimal myocardial blush or contrast density; 2, moderate myocardial blush or contrast density, but less than that obtained during angiography of a contralateral or ipsilateral non–infarct-related coronary artery; and 3, normal myocardial blush or contrast density, comparable with that obtained during angiography of a contralateral or ipsilateral non–infarct-related coronary artery. When myocardial blush persisted ("staining"), this phenomenon suggested leakage of the contrast medium into the extravascular space and was graded 0. Besides, we used a new index, the TMBS. It was obtained by summing up the MBG of each coronary area. We intended to evaluate another index: the TTFC, which was obtained from the sum of the TFCs of the three coronary arteries.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for the Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Wilk test. Qualitative data were represented as frequencies and relative percentages. Chi square test (χ^2) was used to calculate difference between two groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P value < 0.05 was considered significant and <0.001 was considered highly significant.

RESULTS

There was statistically non-significant difference between the studied groups regarding age, gender or body mass index (table 1). Also, there was statistically non-significant difference between the studied groups regarding hemoglobin, total leucocytic count or serum creatinine (table 2).

Table (1): Comparison between the studied groups regarding demographic data

Parameter	Groups		Test	
	HFPEF group	Non-HFPEF group	χ^2/t	p
	N=80 (%)	N=80 (%)		
Gender: Female Male	 47 (58.8%) 33 (41.2%)	 45 (56.2%) 35 (43.8%)	0.102	0.749
Age (year): Mean ± SD	 57.8 ± 4.38	 57.24 ± 3.26	0.921	0.358
BMI: Mean ± SD	 30.9 ± 4.96	 29.75 ± 3.47	1.706	0.09

χ^2: Chi square test, t: T test

Table (2): Comparison between the studied groups regarding CBC and serum creatinine

Parameter	Groups		Test	
	HFPEF group	Non-HFPEF group	t	p
	Mean ± SD	Mean ± SD		
Hemoglobin (g/dl)	12.67 ± 1.37	12.37 ± 1.09	1.142	0.257
TLC	7.2 ± 1.3	7.19 ± 1.78	0.578	0.564
S. creatinine (mg/dL)	1.06 ± 0.19	1.01 ± 0.17	1.779	0.077

t: T test

There was statistically significant difference between the studied groups regarding total cholesterol, LDL cholesterol, HbA1cand triglycerides (significantly higher in HFpEF group) (table 3).

Table (3): Comparison between the studied groups regarding glycemic and lipid profile

Parameter	Groups		Test	
	HFPEF group	Non-HFPEF group	t	p
	Mean ± SD	Mean ± SD		
FBG (mg/dl)	181.16 ± 5.6	166.99 ± 5.96	1.815	0.071
HbA1c	7.74 ± 1.34	7.12 ± 1.52	2.737	0.007*
T cholesterol (mg/dL)	232 ± 39.95	214.59 ± 21.12	3.447	<0.001**
LDL.C (mg/dL)	183 ± 10.84	177.5 ± 17.68	2.372	0.019*
HDL.C (mg/dL)	31.8 ± 4.86	31.19 ± 5.97	0.712	0.487
TG (mg/dL)	202 ± 29.44	148.38 ± 34.11	10.654	<0.001**

t:T test. *: Statistically significant, **: Statistically highly significant

There was statistically significant difference between the studied groups regarding left atrial volume index (significantly higher in HFpEF group) (table 4).

Table (4): Comparison between the studied groups regarding echocardiographic data

Parameter	Groups		Test	
	HFPEF group	Non-HFPEF group	t	p
	Mean ± SD	Mean ± SD		
Ejection fraction	56.0 ± 2.01	60.9 ± 2.84	1.142	0.257
Left atrial volume index	34.8 ± 3.57	29.28 ± 3.45	9.954	<0.001**

t:T test, **: Statistically highly significant

There was statistically significant difference between the studied groups regarding mean E′ or E/e′ ratio) (table 5).

Table (5): Comparison between the studied groups regarding tissue Doppler data

Parameter	Groups		Test	
	HFPEF group	Non-HFPEF group	t	p
	Mean ± SD	Mean ± SD		
E	78.21 ± 21.14	77.24 ± 7.12	0.39	0.698
A	72.93 ± 30.44	73.88 ± 10.49	-0.264	0.793
E/A ratio	1.18 ± 0.42	1.08 ± 0.24	1.882	0.062
Mean E′	0.955± 0.165	1.008 ± 0.114	-2.364	0.019*
E/e′ ratio	61.54 ± 27.44	77.44 ± 10.01	-4.869	<0.001**

t:T test, *: Statistically significant, **: Statistically highly significant

There was statistically significant difference between the studied groups regarding TFC left anterior descending artery, left circumflex artery or total value (significantly higher in HFpEF group) (table 6).

Table (6): Comparison between the studied groups regarding TFC angiographic data

Parameter	Groups		Test	
	HFPEF group	Non-HFPEF group	t	p
	Mean ± SD	Mean ± SD		
TFC LAD	46.52 ± 3.62	42.31 ± 8.35	4.138	<0.001**
TFC LCX	34.22 ± 3.32	25.4 ± 1.27	22.194	<0.001**
TFC RCA	24.71 ± 2.92	25.0 ± 4.38	-0.496	0.620
Total TFC	105.44 ± 4.66	92.71 ± 9.89	10.42	<0.001**

t:T test, **: Statistically highly significant

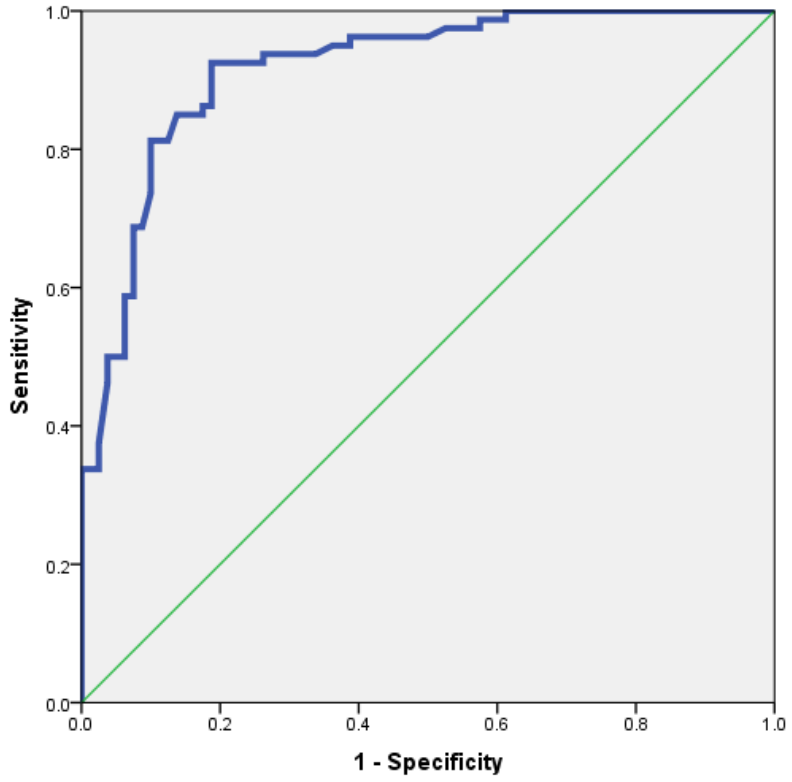
There was statistically significant difference between the studied groups regarding MBG left anterior descending artery, left circumflex artery or total value (significantly lower in HFpEF group) (table 7).

Table (7): Comparison between the studied groups regarding MBG angiographic data

Parameter	Groups		Test	
	HFPEF group	Non-HFPEF group	t	p
	Mean ± SD	Mean ± SD		
MBG LAD	2.12 ± 0.17	2.65 ± 0.35	-12.321	<0.001**
MBG LCX	2.01 ± 0.16	2.46 ± 0.24	-13.661	<0.001**
MBG RCA	2.12 ± 0.16	2.19 ± 0.26	-1.935	0.055
Total MBG	6.25 ± 0.38	7.3 ± 0.54	-14.174	<0.001**

t:T test, *: Statistically significant, **: Statistically highly significant

The best cutoff of total TFC in diagnosis in diagnosis of HFpEF was≥98.55 (Figure 1).

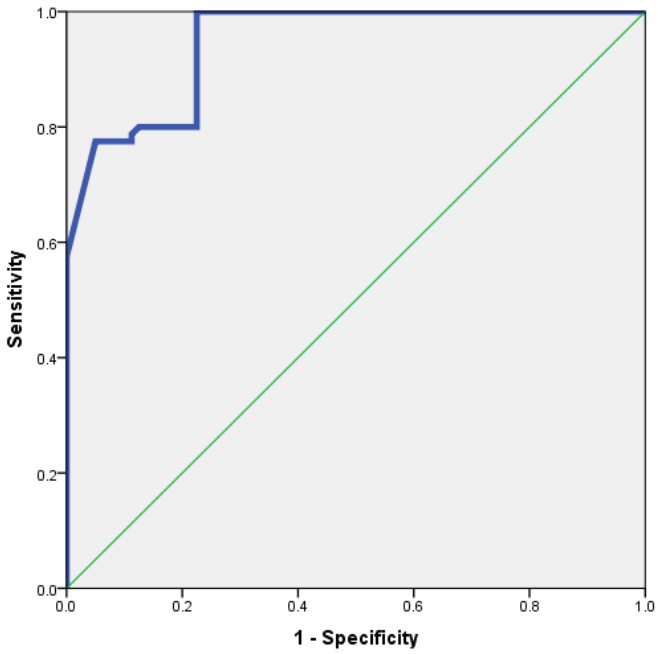


Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	p
≥98.55	0.917	92.5%	73.8%	77.9%	90.8%	83.1%	<0.001**

**: Statistically highly significant

Figure (1): ROC curve showing distribution of performance of total TFC in diagnosis of HFpEF among patients with ischemia.

The best cutoff of total MBG in diagnosis in diagnosis of HFpEF was≤6.55 (Figure 2).



Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	p
≤6.55	**0.947**	80%	87.5%	86.5%	81.4%	83.85	<0.001**

**: Statistically highly significant

Figure (2): ROC curve showing distribution of performance of total MBG in diagnosis of HFpEF among patients with ischemia.

DISCUSSION

HFpEF has overtaken heart failure in the setting of reduced ejection fraction (HFrEF; also known as systolic heart failure) as the most common form of heart failure and now comprises more than 50% of all patients with heart failure [(10)].

A substantial amount of research over the past few decades has revealed that HFpEF is heterogeneous in regard to underlying pathophysiologic mechanisms with both cardiac and noncardiac mechanisms. Among the cardiovascular processes are those that contribute to diastolic dysfunction, including LV hypertrophy, concentric remodeling, improper calcium handling, and abnormal relaxation [(7)].

Underlying causes of these "diastolic mechanisms" have included ischemia, alteration in cardiomyocyte myocardial stiffness including intrinsic cardiomyocyte stiffness related to abnormal calcium homeostasis, the cytoskeleton (e.g., microtubules and intermediate filaments or titin), as well as abnormalities in the extracellular matrix related to collagen and elastin [(13)].

We studied, using validated angiography indices, coronary blood flow and myocardial perfusion of the microcirculation to assess whether there was greater MVD in patients with microvascular angina and HFpEF compared to those who do not have.

This retrospective study took place in El-Mahalla Cardiac Center on 160 patients with stable angina undergoing coronary angiography and echocardiography. All patients were subjected to complete history taking, full clinical examination, echocardiography, coronary angiography and angiography indices.

Our patients were divided into two categories: 80 patients with HFpEF and 80 without HFpEF (in the HFPEF group, 47 females and 33 males; in control group, 45 females and 35 males). Mean age was 57.8 years in the HFpEF group and 57.24 years in non-HFpEF group. Statistically, there were non-significant differences between the studied groups regarding age or gender.

Also, **Sucato *et al.*** [(13)] evaluated myocardial perfusion and coronary blood flow through validated angiography indices to assess whether there was greater MVD in patients with microvascular angina and HFpEF compared to those who do not have. Their study was performed on a population of 286 patients that was divided into two categories: 155 patients with HFpEF and 131 without HFpEF (in the HFpEF group: 97 male, 58 female; in control group 81 male, 40 female). Mean age of the study subjects was 61 years.

In our study, there was statistically non-significant difference between the studied groups regarding body mass index. But, **Sucato *et al.*** [(13)] found that BMI was significantly higher in the HFpEF group than in the non- HFpEF group.

In our study, there were statistically non-significant differences between the studied groups regarding smoking, family history of ischemic heart disease or hypertension. Within HFpEF group, 38.7%, 36.2% and 60% were smokers, had positive family history and hypertensives respectively, while among non-HFpEF patients, 41.2%, 38.8% and 71.2% were smokers, had positive family history and hypertensives respectively. Also, **Sucato *et al.*[13]** found no significant difference between HFpEF and non-HPFPEF groups regarding the prevalence of hypertension, family history of CAD, and current/past smoker.

There was statistically non-significant difference between the studied groups regarding CRP level among patients with positive CRP. There was statistically non-significant difference between the studied groups regarding frequency of patients with positive CRP (68.8% within HFpEF group versus non-HFpEF group). **Sucato *et al.*[13]** found that serum level of fasting C reactive protein was also higher in HFpEF than in non-HFpEF groups, but this level of concentration did not show a statistically significant difference.

In our study, there were statistically non-significant differences between the studied groups regarding fasting blood glucose, or HDL cholesterol. But, there were statistically significant differences between the studied groups regarding total cholesterol, LDL cholesterol, HbA1c and triglycerides (significantly higher in HFpEF group). Also, **Sucato *et al.*[13]** found that the prevalence of hyperlipidemia was also significantly higher in HFpEF than in non-HFpEF groups. Plasma concentrations of LDL-C was significantly higher in patients with HFpEF than in non-HFpEF patients. Although the comparison of HDL-C and triglyceride levels did not show a statistically significant difference between HFpEF and non- HFpEF groups, patients without HFpEF had a significantly higher concentrations of HDL-C than patients with HFpEF (55 mg/dL vs. 52 mg/dL, respectively) and a lower level of triglyceride (142 mg/dL vs 158 mg/dL). Serum levels of fasting blood sugar was also higher in HFpEF than in non- HFpEF groups, but this level of concentration did not show a statistically significant difference.

In our study, there were statistically significant differences between the studied groups regarding left atrial volume index (significantly higher in HFpEF group), mean E' or E/e' ratio.

The use of coronary angiography indices like TFC and total TFC may be a useful tool to evaluate coronary microvascular alterations in patients with HFpEF. MBG has proved a reliable marker of MVD well correlated with TFC. Analysis of microcirculation in patients with and without HFpEF has led to assess that the HFpEF population has a greater involvement of microcirculation than patients without HFpEF [15].

Our study started to study the TFC on three coronary arteries; we showed that there was statistically non-significant difference between the studied groups regarding TFC right coronary artery, but, there were statistically significant differences between the studied groups regarding TFC left anterior descending artery, left circumflex artery or total value (significantly higher in HFpEF group), this indicated slow flow in HFpEF coronary microcirculation. Also, **Sucato *et al.*[13]** showed that patients with HFpEF had a longest TFC of three major coronary arteries (LAD, RCA and CX) than non- HFpEF patients.

We then studied coronary microcirculation perfusion through MBG: we found lower MBG in three coronary arteries (MBG LAD, 2.12 ± 0.17; MBG LCX 2.01 ± 0.16 and MBG RCA 2.12 ± 0.16) in HFpEF than non- HFpEF patients (MBG LAD 2.65 ± 0.35; MBG LCX 2.46 ± 0.24 and MBG RCA 2.19 ± 0.26), with good statistical significance regarding MBG LAD and MBG LCX. Also, there was statistically significant difference between the studied groups regarding total MBG value. Thus, total MBG value was lower in HFpEF than in non- HFpEF patients with good statistical significance. Also, **Sucato *et al.*[13]** found lower MBG on three coronary arteries (MBG LAD 2.1 ± 0.3; MBG RCA 2.1 ± 0.3; MBG CX 2.0 ± 0.32) in HFpEF than non- HFpEF patients (MBG LAD 2.6 ± 0.5; MBG RCA 2.2 ± 0.47; MBG CX 2.3 ± 0.4), with good statistical significance. Thus, TMBS was lower in HFPEF than in non- HFpEF patients with good statistical significance.

Between TFC and MBG, there was a good correlation, and the new index, TTFC, can be added to the other indices in the study of coronary microcirculation in these patients. The best cutoff of total TFC in diagnosis in diagnosis of HFpEF was ≥ 98.55 with area under curve of 0.917, sensitivity of 92.5%, specificity of 73.8%, positive predictive value of 77.9%, negative predictive value of 90.8% and accuracy of 83.1% ($p < 0.001$). Also, the best cutoff of total MBG in diagnosis of HFpEF was ≤ 6.55 with area under curve of 0.947, sensitivity of 80%, specificity of 87.5%, positive predictive value of 77.9%, negative predictive value of 90.8% and accuracy of 83.1% ($p < 0.001$).

Mohammed *et al.*[7] assessed coronary capillary density by histology in autopsy samples and found that coronary rarefaction was more prevalent in HFpEF patients compared to age-matched controls. In addition, it was correlated with increased myocardial fibrosis. **Sucato *et al.*[13]** analyzed microcirculation through angiography indices in patients with and without HFpEF, assessing that the HFpEF population has a greater involvement of microcirculation than patients without HFpEF.

Therefore, patients with HFpEF should be followed with a careful follow-up to assess any worsening of coronary artery stenosis, with greater attention to those who have cardiovascular risk factors, especially metabolic syndrome, which is often present in patients and that is, along with diabetes, a major cardiovascular risk factor; therefore, the need to

maintain total cholesterol in HFpEF patients than in non- HFpEF patients is a priority.

As far as therapeutic strategies, after prolonged treatment, as in hypertensive diabetic patients, the coronary reserve may increase. The clinical improvement of these patients is to be attributed to the role played by therapy on processes that are responsible for myocardial perfusion defects as alterations in repair mechanisms of microcirculation, which was found to be damaged at both structural and physiological levels [(16)].

The disease state of microcirculation in HFpEF patients allows us to affirm the absolute necessity to focus on this population (it is necessary to start early an appropriate treatment and it is necessary to follow a long-term follow-up) because this population have a subclinical microcirculation disease without clinical evidence, which could lead to an alteration of the quality of their lives in the future.

CONCLUSION

The new paradigm about HFpEF development identifies a systemic proinflammatory state induced by comorbidities as the cause of typical myocardial structural and functional alterations with a high prevalence of obesity, diabetes mellitus, chronic kidney disease, hypertension, and iron deficiency. In particular, there were significant higher metabolic syndrome incidences in HFpEF patients.

So, analysis of microcirculation through angiography indices in patients with HFpEF and without HFpEF has led to assess that the HFpEF population has a greater involvement of microcirculation than patients without HFpEF.

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