

## Study of Myocardial Perfusion in Obese Individuals without Known Ischemic Heart Disease

Tufi Dippe Jr.,<sup>1</sup> Cláudio Leinig Pereira da Cunha,<sup>1</sup> Rodrigo Julio Cerci,<sup>2</sup> Arnaldo Lafitte Stier Jr.,<sup>2</sup> João Vicente Vítola<sup>2</sup>

Hospital de Clínicas da Universidade Federal do Paraná,<sup>1</sup> Curitiba, PR – Brazil

Clínica Quanta Diagnóstico e Terapia,<sup>2</sup> Curitiba, PR – Brazil

### Abstract

**Background:** Obesity is associated with an increased risk of type 2 diabetes mellitus (DM), ischemic heart disease (IHD) and cardiovascular mortality. Several studies have demonstrated the diagnostic and prognostic value of single photon computed tomography-myocardial perfusion scintigraphy (SPECT-MPI) in the evaluation of patients with suspected IHD, including in obese population. Data on clinical risk factors and their association with abnormal myocardial perfusion in obese patients are scarce in the Brazilian population.

**Objective:** To determine the factors associated with abnormal myocardial perfusion in obese individuals without known IHD.

**Methods:** We studied obese patients without known IHD who were referred for evaluation through SPECT-MPI between January 2011 and December 2016. Clinical variables and results of SPECT-MPI were obtained systematically. The distribution of continuous variables was assessed using the Shapiro-Wilk and Shapiro-Francia tests. We used the unpaired Student t test to compare the means of continuous variables with normal distribution and the Chi Square test for binomial variables analysis. A p value < 0.05 was considered statistically significant. The association of the clinical variables for the presence of factors associated with abnormal myocardial perfusion was determined by univariate and multivariate logistic regression analysis, and respective odds ratios (OR) and 95% confidence intervals (CI).

**Results:** The study sample consisted of 5,526 obese patients. Mean body mass index (BMI) of our patients was  $33.9 \pm 3.7$  kg/m<sup>2</sup>, 31% had DM, and myocardial perfusion abnormalities was observed in 23% of the total sample. The factors associated with abnormal myocardial perfusion on multivariate analysis were: age (OR: 1.02, 95% CI 1.01-1.03, p < 0.001), DM (OR: 1.57, 95% CI 1.31-1.88, p < 0.001), typical angina before the test (OR: 2.45, 95% CI: 1.82-3.31, p < 0.001), need for pharmacologic stress test (OR: 1.61, 95% CI: 1.26-2.07, p < 0.001), less physical effort evaluated in metabolic equivalents (METs) during the exercise treadmill test (OR: 0.89, 95% CI: 0.85-0.94, p < 0.001) and a lower post-stress left ventricular ejection fraction after stress (LVEF; OR: 0.989, 95% CI: 0.984-0.994, p < 0.001).

**Conclusion:** The factors associated with abnormal myocardial perfusion in obese patients without known IHD were age, DM, presence of typical angina, ventricular dysfunction, and inability to undergo physical stress as clinical variables, in addition to functional capacity during physical stress. (Arq Bras Cardiol. 2019; 112(2):121-128)

**Keywords:** Obesity; Diabetes Mellitus; Myocardial Perfusion Scintigraphy; Coronary Artery Disease.

### Introduction

According to the World Health Organization (WHO), obesity is defined as a body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>.<sup>1</sup> In 2016, more than 1.9 billion were overweight, 650 million of them obese.<sup>2</sup>

In Brazil, Vigitel 2016, a nationwide telephone survey of protective and risk factors for chronic diseases, sponsored by the Ministry of Health, revealed that 53.8% of Brazilian adults were above ideal body weight. The proportion of obese individuals older than 18 years was 18.9%.<sup>3</sup>

Obesity is an independent risk factor for cardiovascular disease. Besides, it increases the risk of traditional risk factors, such as systemic arterial hypertension (SAH), type 2 diabetes mellitus (DM) and dyslipidemias, leading to an increased incidence of ischemic heart disease (IHD), cardiovascular mortality and risk of sudden death.<sup>4-6</sup> Evidence from cohort studies have indicated that obesity is also an independent risk factor for coronary artery disease (CAD).<sup>7-9</sup>

Many studies have shown the diagnostic and prognostic value of single-photon emission computed tomography – myocardial perfusion imaging with (SPECT-MPI) in patients with suspected or confirmed IHD,<sup>10-12</sup> including obese patients.<sup>13-15</sup> Nevertheless, information on the predictive role of SPECT-MPI among Brazilian obese subjects are scarce.

The aim of this study was to determine factors associated with abnormal SPECT-MPI in a large population of obese subjects without known IHD.

**Mailing Address:** Tufi Dippe Jr. •

Rua Rocha Pombo, 920 apto. 501. Postal Code 80530-290, Juvevê, Curitiba, PR – Brazil

E-mail: tufidippejr@gmail.com, tufidippejr@bol.com.br

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## Methods

### Patients

Obese patients without known IHD who had undergone SPECT-MPI were studied between January 2011 and December 2016.

The following clinical data were prospectively collected using a standardized questionnaire – age, sex, weight, height, BMI, symptoms before the SPECT-MPI test (typical, atypical or no pain, and tiredness), previous heart disease or procedures (coronary cineangiography, acute myocardial infarction, myocardial revascularization surgery and coronary angioplasty), SAH, DM, dyslipidemia, smoking, use of medications and family history of IHD).

Regarding SPECT-MPI, we assessed the type of stress used during the test, treadmill test (TT) alone or combined with pharmacological stress test. Physical exertion during the tests was quantified by metabolic equivalents (METs). We also analyzed myocardial perfusion patterns (normal, ischemia alone or associated with fibrosis), and post-stress left ventricular ejection fraction (LVEF).

All tests were performed using a CardioMD (Philips, Milpitas, CA, USA) or a Vertex (ADAC, Milpitas, CA - USA) gamma camera. All images were reviewed immediately after acquisition, and an additional prone imaging was always obtained when the presence of artifacts was suspected. Both images were considered to define the type of myocardial perfusion defect and the final report also.

### Statistical analysis

All continuous variables are shown as mean and standard deviation, and all categorical variables as absolute values and percentages. Normal distribution of continuous variables was tested by Shapiro-Wilk and Shapiro-Francia tests.

Unpaired Student's t test was used to compare the means of continuous variables with normal distribution, and the chi-square test used for analysis of binominal variables. A p-value < 0.05 was considered statistically significant.

The association of clinical variables, type of the test stress, and left ventricular function with abnormal SPECT-MPI was analyzed by univariate logistic regression, followed by multivariate analysis. The respective odds ratio (OR) and 95% confidence intervals were also calculated.

All analyses were performed using a specific software, the Stata Statistical Software, Release 11 (College Station, TX: StataCorp LP).

## Results

### Demographic characteristics of the patients

From January 2011 to December 2016, a total of 5,526 obese patients were referred for SPECT-MPI. Table 1 shows demographic characteristics of the patients.

**Table 1 – Demographic characteristics of the patients without known ischemic heart disease and body mass index (BMI)  $\geq$  30kg/m<sup>2</sup> (n = 5,526)**

Characteristics	Mean (standard deviation) or number (percentage)
Age	59.4 (12.2)
BMI (kg/m <sup>2</sup> )	33.9 (3.7)
Male sex	2,605 (47.1%)
Diabetes mellitus	1,727 (31.5%)
Systemic arterial hypertension	4,106 (74.3%)
Family history of IHD	1,081 (19.5%)
Smoking	466 (8.4%)
Dyslipidemia	2,996 (54.2%)
<b>Symptoms before SPECT-MPI</b>	
Asymptomatic	2,996 (55.0%)
Atypical angina	1,210 (22.3%)
Typical angina	362 (6.6%)
Tiredness	878 (16.1%)
<b>Stress protocol</b>	
Physical	3,576 (64.7%)
Pharmacological	1,950 (35.3%)
Physical exertion, in METs	8.52 (2.37)
LVEF	59.2 (17.6)
LVEF > 50%	4,821 (92.9%)
LVEF 30 - 49%	330 (6.4%)
LVEF < 30%	38 (0.7%)
Abnormal SPECT-MPI	1,288 (23.3%)
Ischemia alone	1,228 (22.2%)
Ischemia > 10% of the LV	74 (1.3%)
Fibrosis alone	22 (0.4%)
Fibrosis and ischemia	38 (0.7%)

*BMI: body mass index; IHD: ischemic heart disease; METs: metabolic equivalents; LVEF: post-stress left ventricular ejection fraction; SPECT-MPI: myocardial perfusion imaging with single-photon emission computed tomography; LV: left ventricle.*

### Demographic characteristics of the patients by sex

The total sample was composed of 2,921 women and 2,605 men. Table 2 shows demographic characteristics of the patients by sex.

### Distribution of patients by BMI

Most patients (70.2%) were class I obese. Table 3 shows the distribution of the patients by BMI.

### Percentage of abnormal perfusion according to the BMI

Among obese individuals (n = 5,526), there was no statistically significant difference in the number of patients

**Table 2 – Demographic characteristics of the patients by sex**

	Men n = 2,605	Women n = 2,921	p value
Age; mean (SD)	56.7(11.8)	61.7(12)	< 0.0001
BMI (kg/m <sup>2</sup> ); mean (SD)	33.6(4.1)	34.2(3.3)	< 0.0001
Diabetes mellitus; n (%)	773 (29.7)	954 (32.7)	0.02
SAH; n (%)	1.843 (70.7)	2,263 (77.5)	< 0.001
Family history of IHD; n (%)	429 (16.5)	652 (22.3)	< 0.001
Smoking; n (%)	270 (10.4)	196 (6.7)	< 0.001
Dyslipidemia; n (%)	1,369 (52.5)	1,627 (55.7)	0.02
<b>Symptoms before SPECT-MPI; n (%)</b>			<b>&lt; 0.001</b>
Asymptomatic	1,701 (65.8)	1,295 (45.2)	
Atypical angina	433 (16.7)	777 (27.2)	
Typical angina	108 (4.2)	254 (8.9)	
Tiredness	343 (13.3)	535 (18.7)	
<b>Stress protocol; n (%)</b>			<b>&lt; 0.001</b>
Physical	1,895 (72.7)	1,681 (57.5)	
Pharmacological	710 (27.3)	1,240 (42.5)	
Physical stress in METs; mean (SD)	8.7 (2.2)	6.8 (2.1)	< 0.0001
%LVEF; mean(DP)	54.1 (18.4)	63.9 (15.5)	0.04
<b>LVEF; n(SD)</b>			<b>&lt; 0.0001</b>
LVEF > 50%	2,126 (89.4)	2,695 (95.9)	
LVEF 30 - 49%	227 (9.5)	103 (3.7)	
LVEF < 30%	25 (1.0)	13 (0.5)	
Abnormal SPECT-MPI abnormal; n (%)	475 (18.2)	813 (27.8)	< 0.001
Ischemia	436 (16.7)	792 (27.1)	
Ischemia > 10% of the LV	45(1.7)	29 (0.9)	0.017
Fibrosis alone	13 (0.5)	9 (0.3)	
Fibrosis and ischemia	26 (1)	12 (0.4)	

SD: standard deviation; BMI: body mass index; SAH; systemic arterial hypertension; IHD: ischemic heart disease METs: metabolic equivalents; LVEF: post-stress left ventricular ejection fraction; SPECT-MPI: myocardial perfusion imaging with single-photon emission computed tomography; LV: left ventricle

**Table 3 – Distribution of patients by body mass index**

BMI Classification	30.0 - 34.9 kg/m <sup>2</sup> Class I obesity*	35.0 – 39.9 kg/m <sup>2</sup> Class II obesity*	≥ 40.0 kg/m <sup>2</sup> Class III obesity*
Number (%) of patients	n = 3,880 (70.2%)	n = 1,207 (21.8%)	n = 439 (7.9%)

BMI: body mass index. \*World Health Organization<sup>1</sup>

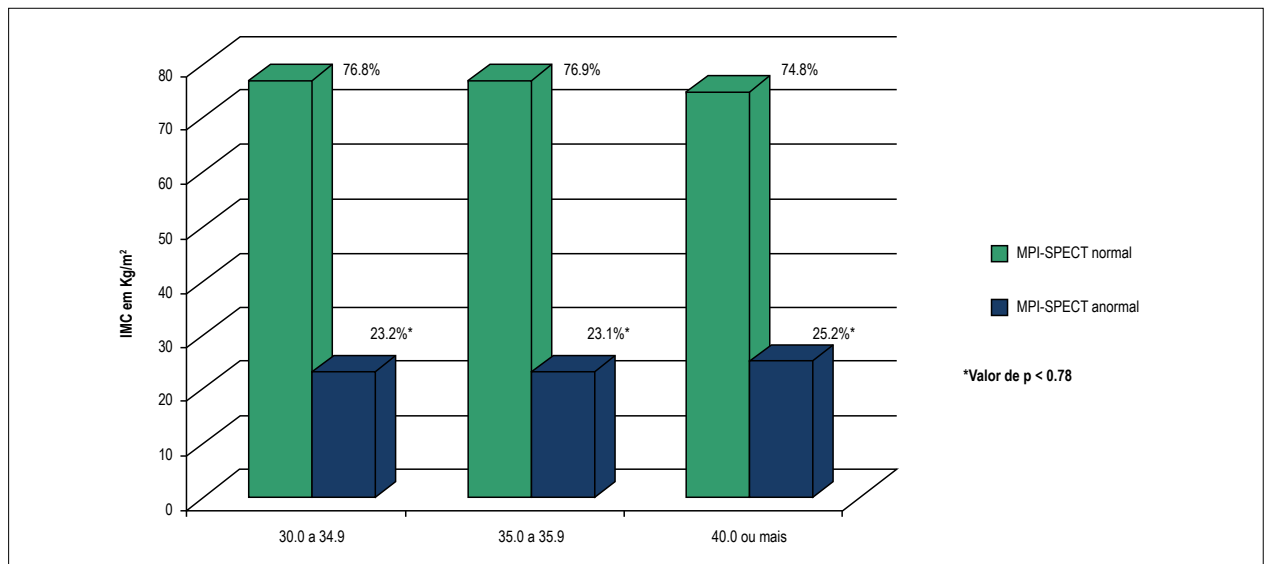
with abnormal SPECT-MPI according to BMI. Figure 1 shows the percentage of abnormal SPECT-MPI according to BMI.

#### Factors associated with abnormal myocardial perfusion

Univariate analysis revealed that the following factors were associated with abnormal myocardial perfusion – age (OR: 1.04; 95%CI: 1.04-1.05. p < 0.001), female sex (OR: 1.18; 95%CI: 1.18-1.21; p < 0.001), DM (OR: 1.96; 95%CI: 1.72-2.23. p < 0.001); SAH (OR: 1.79; 95%CI: 1.53-2.10; p < 0.001),

dyslipidemia (OR: 1.19; 95%CI: 1.04-1.34. p < 0.008), typical angina (OR: 1.96; 95%CI: 1.55-2.48; p < 0.001) or tiredness (OR: 1.29. IC 95%: 1.08-1.54. p = 0.004) before SPECT-MPI, lower stress test duration (mean) (OR: 0.81, 95%CI: 0.78-0.84; p < 0.001) and lower (mean) LVEF (OR: 0.996, 95%CI: 0.993-0.999, p < 0.041).

After multivariate analysis (Table 4), age, typical angina before SPECT-MPI, need of using the pharmacological stress protocol, less physical exertion (METs), and post-stress LVEF were found to be associated with abnormal myocardial perfusion.



**Figure 1** – Percentage of abnormal myocardial perfusion imaging with single-photon emission computed tomography (SPECT-MPI) according to BMI in the study population (n = 5,526) \*a p-value lower than 0.05 was considered statistically significant.

**Table 4** – Factors associated with abnormal perfusion after multivariate analysis in obese patients without known ischemic heart disease (n = 5,526)

	OR (95%CI)	Valor de p
Age; years	1.02 (1.01 - 1.03)	< 0.001
<b>BMI</b>		
30.0 - 34.9 kg/m <sup>2</sup>	Reference	
35.0 - 39.9 kg/m <sup>2</sup>	0.91 (0.73 - 1.12)	0.38
≥ 40.0 kg/m <sup>2</sup>	0.99 (0.68 - 1.45)	0.97
Male sex	0.82 (0.67 - 1.01)	0.052
Diabetes mellitus	1.57 (1.31 - 1.88)	< 0.001
Systemic arterial hypertension	1.21 (0.98 - 1.50)	0.08
Dyslipidemia	1.14 (0.96 - 1.36)	0.13
<b>Symptoms before the test</b>		
Asymptomatic	Reference	
Atypical angina	1.21 (0.97 - 1.49)	0.08
Typical angina	2.45 (1.82 - 3.31)	< 0.001
Tiredness	0.93 (0.72 - 1.20)	0.59
<b>Stress protocol; n (%)</b>		
Physical	Reference	
Pharmacological	1.53 (1.18-1.98)	< 0.001
Physical exertion, in METs	0.89 (0.85-0.93)	<0.001
<b>LVEF</b>		
LVEF > 50%	Reference	
LVEF 30 - 49%	7.42 (5.3-10.4)	<0.001
LVEF < 30%	10.2 (2.6-40.3)	<0.001

BMI: body mass index; METs: metabolic equivalents; LVEF: left ventricular ejection fraction. A p < 0.05 was considered statistically significant.

## Discussion

Our study reveals a strong association between obesity and other cardiovascular risk factors. Obesity is known to lead to insulin resistance, SAH, dyslipidemia, thromboembolism and sleep apnea and increase inflammatory markers, all known to be risk factors for CAD.<sup>4</sup> Obesity is an important factor in the pathogenesis and progression of CAD, with an almost linear relationship between BMI above 25 kg/m<sup>2</sup> and the risk of CAD.<sup>7</sup>

Xingping et al.<sup>12</sup> evaluated the relationship between BMI and the prognostic value of SPECT-MPI in 2,096 obese subjects without known CAD (mean age 62 ± 12 years). The authors reported a high prevalence of DM (22%), dyslipidemias (47%) and SAH (61%).<sup>12</sup> More recently, researchers of The Southern Community Cohort Study investigated the relationship between BMI and late mortality in young adults. At the end of the study, the total sample of obese individuals was 6,276 (mean age 50 ± 7.8 years). In this group, the authors also observed a high prevalence of risk factors – DM in 35.9%, dyslipidemias in 38.8% and SAH in 66.4%.<sup>13,14</sup>

The World Health Organization (WHO) believes that overweight and obesity are responsible for 44% of the risk for DM.<sup>1</sup> The International Diabetes Federation (IDF) estimates a prevalence of 10-12% of DM among adults in Brazil, which corresponds to 14.5 million people. In addition, the IDF estimates a 60% increase of new cases of DM in Latin America in the next 15 years.<sup>15</sup>

In the DIAD (Detection of Ischemia in Asymptomatic Diabetics) study, the authors assessed whether the screening for CAD could decrease the occurrence of cardiovascular events in symptomatic diabetic patients. A total of 1,123 patients were randomized to screening with SPECT-MPI or to no screening. After a mean follow-up of 4.8 years, the authors did not find any significant differences in cardiovascular event rate between the two groups.<sup>16</sup> The presence of DM significantly increases cardiovascular risk, and the need for diagnostic methods, including the rational use of nuclear medicine.<sup>17-19</sup>

A significant percentage of our study group (55%) were asymptomatic before the test, especially men. The high proportion of asymptomatic patients in our sample may be explained by several factors, including stratification of future events in patients at high cardiovascular risk, previous altered or inconclusive cardiologic tests, patients referred for preoperative assessment, and the presence of electrocardiographic abnormalities that limit the performance of TT (left branch bundle block, artificial pacemaker rhythm or ventricular preexcitation).<sup>20,21</sup>

Regarding preoperative assessment, the II Guidelines for Perioperative Assessment of the Brazilian Society of Cardiology suggests that indications for SPECT-MPI are similar to those of TT, *i.e.*, patients at estimated intermediate risk of vascular surgery complications, without severe cardiovascular conditions in the perioperative period. Also, SPECT-MPI would be the best choice for patients with physical impairment, changes in the ST segment that affect electrocardiography analysis, and in case of possible false positive results in TT.<sup>22</sup>

The decision to screen for IHD among obese patients should be similar to that in the general population, based mainly on clinical symptoms, chest pain and tiredness, and/or the presence of other associated risk factors. Besides, patients' ability to exercise and the presence of an interpretable electrocardiogram guide us in making decisions about the methods to be used.

Obese subjects are more likely to be screened for IHD, due to the higher presence of associated risk factors, tiredness, low functional capacity and musculoskeletal impairments.<sup>23,24</sup>

In 35% of our patients, a pharmacological stress was used, and this percentage was higher among women than men (42.5% versus 27.3%). This frequency was similar to that reported by Xingping et al.<sup>12</sup> (38%).

Duvall et al.,<sup>25</sup> evaluating the prognostic and diagnostic value of SPECT-MPI in 433 morbidly obese patients, observed that 77.4% of the patients used the pharmacological stress protocol, indicating a decreased functional capacity with increase of BMI. The use of pharmacological stress protocols is associated with low functional capacity, non-cardiac physical limitations, low motivation to exercise, left ventricular dysfunction, pulmonary diseases, abnormal electrocardiographic findings at rest (above mentioned), and inappropriate discontinuation of medications prior to the test (*e.g.*, beta-blockers).<sup>20,21</sup>

With respect to demographic differences by gender, most of our patients were women, who showed a more severe cardiovascular risk profile – higher mean BMI, and higher prevalence of associated risk factors (DM, SAH and dyslipidemias). In women, the rates of typical angina were lower, the use of pharmacological stress protocols was more common, and less physical effort during the test compared with men. The percentage of abnormal perfusion in SPECT-MPI was also higher in women than in men (27.8% versus 18.2%).

Studies have shown that women with diagnosis of CAD tend to be older, and present diffuse disease and a worse prognosis than men, including higher acute myocardial infarction and myocardial revascularization surgery. The use of effective diagnostic and prognostic methods, including nuclear medicine, is essential to reduce IHD morbimortality in this group.<sup>18,26</sup> In a previous study of our group, Cerci et al.,<sup>27</sup> in a study with 2,250 women, reported a strong, independent association between abnormal SPECT-MPI and mortality among women in Brazil.<sup>27</sup>

In our country, there is little information available about factors associated with abnormalities in myocardial perfusion in obese patients. Our data showed that age, DM, typical angina prior to the test, use of pharmacological stress, less physical effort in the test and lower mean post-stress LVEF were associated with perfusion abnormality. These findings corroborate previous studies on obese and non-obese subjects, with or without previous IHD. In the study by Xingping et al.,<sup>12</sup> predictive factors of cardiac mortality and abnormal SPECT-MPI in 2,096 obese subjects without known CAD were age, DM, use of pharmacological stress protocol and reduction of LVEF. Greater ability to exercise reduced mortality risk.<sup>14</sup> Korbee et al.<sup>15</sup> showed that an abnormal



SPECT-MPI, age, and previous heart failure were associated with major cardiovascular events and mortality in obese individuals during up to six years of follow-up following the test. These data have already been included in medical guidelines for appropriate indications of nuclear cardiology in patients with suspected CAD.<sup>28</sup>

If on the one hand obese individuals are at higher risk for CAD, on the other hand, these patients, particularly severely obese subjects, represent a challenging population concerning eligibility to all kinds of cardiac imaging tests.<sup>29,30</sup>

Obesity may affect the quality of SPECT-MPI images, reducing the specificity of the method due to diaphragmatic attenuation or increased extracardiac radiotracer activity. The use of higher doses of radiotracers, attenuation correction techniques, acquisition of images in prone position, among other techniques, may reduce the number of false-positive results related to obesity. Male sex and the use of physical stress protocol by the TT are associated with better quality of the images in obese patients undergoing SPECT-MPI.<sup>27,28</sup>

Positron-emission tomography (PET) with rubidium-82 seems to be the non-invasive method of choice for diagnostic and prognostic assessment of obese individuals with suspected CAD. Sensitivity and specificity of PET with rubidium-82 and SPECT-MPI are estimated to be 91% and 89%, and 87% and 73%, respectively.<sup>31</sup>

Chow et al.,<sup>32</sup> in a large multicentric study, evaluated the prognostic value (risk of overall and cardiac mortality) in 6,037 patients, 2,016 of them obese. After a mean follow-up period of 2.2 years, the authors concluded that PET with rubidium-82 improved the prognostic estimates of patients of all weight ranges. A normal PET was associated with a very low annual mortality in normal weight (0.38%), overweight (0.43%) or obese (0.15%) subjects.<sup>32</sup>

Although we do not have anatomic information of the patients referred for coronary angiography or coronary angiotomography following SPECT-MPI, we believe that the cases of abnormal SPECT-MPI encompass a wide pathophysiological range, including false-positive cases due to the presence of artifacts, IHD without an obstructive component (associated with endothelial dysfunction or coronary microcirculation impairment), and mostly obstructive CAD.

### Limitations

Our data were systematically collected using a standardized questionnaire administered by a nursing technician, nurses or physicians, and hence, some information regarding clinical variables were self-reported.

Most of patients had not undergone attenuation correction techniques, which help to reduce the percentage of abnormal SPECT-MPI associated with artifacts (false-positive results).

Our study was based on physiological variables and detection of ischemia; thus, we do not have anatomical information of patients that were referred for coronary angiography or coronary angiotomography based on SPECT-MPI results. For this reason, the actual percentage of false-positive cases and abnormal SPECT-MPI associated with obstructive CAD or other IHDs caused by endothelial dysfunction or impaired coronary microcirculation could not be determined.

### Conclusions

Factors associated with abnormal myocardial perfusion in obese patients without known IHD, after adjustment for relevant variables (multivariate analysis) were – age (2% increased risk per year older), DM (57% increased risk in diabetic patients), typical angina (245% increased risk in patients with typical angina as compared with symptomatic patients), use of pharmacological stress during (61% increased risk as compared with physical stress by TT), less physical exertion (expressed in METs) (10% reduced risk for each additional MET during TT) and post-stress LVEF (1% reduced risk for each 1% increase in LVEF).

### Author contributions

Conception and design of the research: Dippe Jr. T, Cunha CLP, Vítola JV; acquisition of data: Cerci RJ, Stier Jr. AL.; analysis and interpretation of the data: Dippe Jr. T, Cunha CLP, Cerci RJ, Vítola JV; statistical analysis: Cerci RJ; writing of the manuscript: Dippe Jr. T; critical revision of the manuscript for intellectual content: Dippe Jr. T, Cunha CLP, Stier Jr. AL., Vítola JV.

### Potential Conflict of Interest

There is no potential conflict of interest relevant to this article.

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### Study Association

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### Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital de Clínicas da UFPR under the protocol number 3026. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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