The practical value of technetium-99m-MIBI SPET to differentiate between ischemic and non-ischemic heart failure presenting with exertional dyspnea

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Abstract

Objective: We aimed to differentiate ischemic heart failure (HF) from non-ischemic HF in patients presenting with non-acute onset exertional dyspnea using technetium-99m methoxyisobutylisonitrile gated single photon emission tomography (^{99m}Tc-MIBI gSPET) imaging. **Subjects and Methods:** One hundred and seventy nine consecutive patients with exertional dyspnea without concomitant chest pain referred to ^{99m}Tc-MIBI gSPET imaging were included in this study. All patients had a newly diagnosed HF with reduced ejection fraction (HFrEF). Imaging findings were compared between ischemic HF and non-ischemic HF groups. **Results:** Of the 179 patients, 127 had ischemic HF and 52 had non-ischemic HF. There was no difference between ischemic and non-ischemic groups in terms of age, gender, body mass index, any smoking history, diabetes mellitus, history of hypertension and hyperlipidemia. Global dysfunction of left ventricle was more common in non-ischemic HF group than ischemic HF group (82.7% vs 41.7% respectively, P<0.001). Presence of severe (3+/4+) ischemia and large perfusion defect were higher in ischemic HF group compared to non-ischemic HF group (45.7% vs 15.4%, P<0.001 and 23.6% vs 3.8%, P=0.003, respectively). Summed stress score (SSS), summed rest score and summed difference score were higher in ischemic HF group compared to non-ischemic HF group (P<0.001, P<0.001, and P=0.021, respectively). In multivariate analysis, absence of global dysfunction (P<0.001, OR=10.338, 95%CI: 3.937-27.405) and SSS (P<0.001, OR=1.208, 95%CI: 1.090-1.339) were the independent predictors of ischemic HF. Absence of global dysfunction had 58.3% sensitivity and 86.7% specificity for diagnosis of ischemic HF at gSPET imaging in patients presenting with newly diagnosed HF and exertional dyspnea without concomitant chest pain (AUC=0.705, 95%CI: 0.632-0.771, P<0.001), whereas SSS>8 had 65.4% sensitivity and 75.0% specificity (AUC=0.732, 95%CI:0.661-0.795, P<0.001). **Conclusion:** Absence of global dysfunction and SSS on SPET imaging were the independent predictors of ischemic etiology of HF presenting with dyspnea without concomitant chest pain. These findings had a low sensitivity, but acceptable specificity.

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Introduction

The distinction between ischemic and non-ischemic heart failure (HF) is clinically important in terms of management and prognosis [1]. Unfortunately, this distinction is not always possible on clinical grounds. Although chest pain is commonly associated with ischemic etiology, some patients may present with only exertional dyspnea leading to limitation of their physical activity [2]. In the subgroup of patients having exertional dyspnea (non-acute onset) without concomitant chest pain, the differentiation between ischemic HF and non-ischemic HF becomes more complex. While cardiac catheterization has been the gold standard for the differentiation of these conditions [3], non-invasive imaging tests are always favorable in distinguishing ischemic from non-ischemic etiologies, because of their low risk and cost as compared to catheterization.

Dyspnea is an independent predictor of mortality in patients undergoing cardiac stress imaging [4]. However, published clinical studies using thallium-201 ($^{201}TlCl_2$) imaging and radionuclide ventriculography [3, 5, 6], or echocardiography [7, 8], technetium-99m-methoxyisobutylisonitrile (sestamibi) gated single photon emission tomography (^{99m}Tc-MIBI gSPET) imaging [9], 13-N ammonia positron emission tomography (PET) [10] do not specifically randomize or investigate this subgroup of patients with reduced ejection fraction (EF) and exertional dyspnea without concomitant chest pain, which is relatively a common encounter in clinical practice.

The aim of the study was to investigate the value of ^{99m}Tc-MIBI gSPET imaging in the differentiationbetween ischemic and non-ischemic forms of HF with reduced ejection

fraction (HFrEF) presenting with symptoms of exertional dyspnea without concomitant chest pain.

Subjects and Methods

Study population

We retrospectively evaluated 994 consecutive patients who were referred to CardioCheck Nuclear Imaging Center, Ankara, Turkey from April 2014 to April 2015, for myocardial perfusion imaging (MPI). These patients were for the first time, clinically diagnosed with heart failure and had reduced left ventricular (LV) ejection fraction (HFrEF). Inclusion criteria were: newly diagnosed HFrEF within the last 4 weeks (documented EF$\leqslant$40% by transthoracic echocardiography within the last 4 weeks) and exertional dyspnea (New York Heart Association functional class II) without concomitant chest pain. Exclusion criteria were as follows: stable angina pectoris (SAP), acute onset dyspnea, history of unstable angina (UAP) or myocardial infarction (MI), previous percutaneous coronary intervention (PCI) or previous coronary artery bypass grafting or known coronary artery disease (CAD), inability to perform treadmill exercise, previous history of heart failure, decompensated HF, primary valvular heart disease (VHD), hypertrophic cardiomyopathy (HCMP), LV aneurysm, previous history of peripheral arterial disease (PAD) or cerebrovascular disease (SVD), previous history of diabetes mellitus (DM) for more than 7 years [11], left bundle branch block (LBBB) on ECG, ECG findings consistent with previous MI or ischemia, and active pulmonary diseases or pulmonary diseases with unstable symptoms. Patients with pulmonary diseases (such as chronic obstructive pulmonary diseases or asthma) who had stable symptoms with or without drug therapy within last 3 months were not excluded. A total of 789 patients were excluded as follows; 352 with SAP or history of UAP/MI or known CAD/PCI (including 45 patients with active pulmonary diseases), 32 with history of acute onset dyspnea (including 7 patients with active pulmonary diseases), 124 with New York Heart Association class III functional status or inability perform treadmill exercise (including 19 patients with active pulmonary diseases), 69 with previous history of HF, 29 with primary VHD, 7 with HCMP, 26 with LV aneurysm, 59 with history of PAD or SVD, 53 with LBBB and 38 with ECG findings consistent with previous MI/ischemia. The remaining 205 patients underwent exercise stress MPI. Our imaging center has routinely requested the information about coronary angiography (CAD) result (if it is performed) from referring physicians or referring hospitals or the patients. A total of 179 patients were undergone CAG within 15 days after MPI and none of them experienced cardiac events during this time, and the remaining 26 patients not. Of the 179 patients (study population), those eligible for analyses were divided into two groups: the ischemic HF and the non-ischemic HF according to CAG results. Single photo emission tomography imaging findings were compared between the ischemic HF and non-ischemic HF groups. The study was conducted in accordance with the rules of the 1964 Declaration of Helsinki. All patients gave their written informed constent.

Definitions of ischemic and non-ischemic HF

According to the recent guidelines of the American College of Cardiology HF, HFrEF is defined as the clinical diagnosis of HF with LV EF $\leqslant$40% [12]. In the presence of LVEF $\leqslant$40%, ischemic HF (ischemic cardiomyopathy) or non-ischemic HF (non-ischemic cardiomyopathy) was defined by using angiographic criteria. Ischemic etiology of HF was defined as the presence of any major epicardial coronary vessels (left anterior descending artery [LAD], left circumflex artery [LCX] and right coronary artery [RCA]) with $\geqslant$75% diameter stenosis [13] or left main coronary artery (LMCA) with $\geqslant$50% diameter stenosis, whereas non-ischemic etiology of HF was defined as having normal coronary arteries or epicardial coronary arteries with less than 50% diameter stenosis. The number-of-diseased-vessels classification was defined as the number of vessels (LAD, CX and RCA) with $\geqslant$75% diameter stenosis (0, 1, 2, 3) [13]. Left main coronary artery with $\geqslant$50 diameter stenosis was accepted as 2 vessels disease.

Imaging technique and test description

All patients underwent a symptom-limited treadmill exercise test using modified Bruce protocol (2-minute stages, 1 metabolic equivalent [MET] increment per stage) and monitoring with a 12-lead electrocardiogram, heart rate and blood pressure during stress and recovery. Using the same day rest-stress imaging protocol, we performed ^{99m}Tc-MIBI imaging at rest 45 minutes after intravenous (i.v.) injection of 370-555MBq ^{99m}Tc-MIBI. Stress imaging was performed 3 to 5 hours later (mean 3.4hrs), 10-15 minutes after the i.v. injection of 370-555MBq ^{99m}Tc-MIBI at peak exercise. All images were acquired using a Siemens single-head SPET gamma camera (Siemens Nuclear Medicine Group, Hoffman Estates, Illinois) and a low energy high resolution collimator. Each imaging set was acquired over a 180 degrees arc starting from 45 degrees right anterior oblique to 45 degrees left posterior oblique, 64 projections in circular orbit, 64 by 64 matrix size, 25 seconds per projection for stress and 20 seconds per projection for rest. All images were processed using a low-pass Butterworth filter, with a cut-off frequency at the range of 0.35-0.45 and an order of 5.

Test interpretation

Interpretation of myocardial perfusion images was performed by two experienced clinicians certified by the American Board of Nuclear Cardiology and the American Board of Nucear Medicine and they were blind to any clinical information or patients' identity. Perfusion defect severity was expressed by the five point model semiquantitative scoring system (0=normal perfusion, 1=mild decrease in perfusion, 2=moderate decrease in perfusion, 3=severe decrease in perfusion, 4=absent perfusion) and defect size was expressed semiquantitatively as a percentage of the entire left ventricle (LV); small represents 5% to 10%, medium 10% to 20% and large $\geqslant$20% of the entire LV. Also, a standard 17-

segment model and semiquantitative scoring system was used for grading perfusion and function [14]. For the assessment of myocardial perfusion on stress and rest imaging, each segment was scored on a scale of 0 to 4 (0=normal activity, 1=mild, 2=moderate, 3=severe reduction in photon activity, 4=complete absence of photon activity). For each image, a summed stress score (SSS) and a summed rest score (SRS) was calculated by adding the segment scores. A summed difference score (SDS) was derived for each image by subtracting the SRS from the SSS. Additionally, specific patterns of perfusion imaging such as increased lung uptake and transient LV dilatation were also recorded. Pulmonary/myocardial ratios of ^{99m}Tc-MIBI at standardized times on immediate post stress acquisitions and on delayed tomographic acquisitions were also measured.

Statistical analysis

The variables were investigated using an analytical method: the one sample Kolmogorov-Smirnov test to determine whether or not they were normally distributed. Continuous variables were expressed as mean±standard deviation or median (min-max) in the presence of abnormal distribution, and categorical variables as percentages. Comparisons between groups of patients were made by using χ^2 test for categorical variables, independent samples t test for normally distributed continuous variables, and Mann-Whitney U test when the distribution was skewed. We used univariate logistic regression analysis to quantify the association of variables with ischemic HF. The presence of 2 or more defects, the presence of 3+/4+ defect severity, the presence of a large defect, the absence of global dysfunction, the presence of segmental wall motion abnormalities, SSS, SRS and SDS were entered into the multivariate logistic regression model with a forward stepwise method in order to determine the independent predictor factors of ischemic HF. All statistical procedures were performed using SPSS software version 14.0 (SPSS Inc., Chicago, IL) except sensitivity and specificity analyses. The receiver operating characteristic (ROC) curve analysis was used to compare the diagnostic performance (sensitivity and specificity) of the multivariate predictor of non-ischemic HF evaluated in the study. Statistical analyses were performed using software MedCalc for Windows, version 9.5.1.0 (MedCalc Software, Mairiakerke, Belgium; personal license of MBY). A P value of 0.05 was considered as statistically significant.

Results

A total of 179 patients were identified and included in the present analysis. The mean age was 59±12 years and 113 (63.1%) of them were males. Ischemic HF was diagnosed after CAG in 127 patients and non-ischemic HF in 52 patients. Baseline characteristics of the study population are presented in Table 1. There was no difference between ischemic and non-ischemic groups in terms of age, gender, body mass index, any smoking history, diabetes mellitus, history of hypertension and hyperlipidemia. Mean duration of dyspnea was 7.6±4.0 months in the ischemic group and 8.5±4.2 months in the non-ischemic group (P=0.22). The median LVEF was 33% in the ischemic group and 33% in the non-ischemic group (P=0.65). In the ischemic group, 32 (25.2%) patients had one-vessel disease (29 patients with proximal LAD stenosis and 3 patients with proximal stenosis of dominant LCX), 60 (47.2%) patients had two-vessels disease, and 35 (27.6%) patients had three-vessels disease.

Results from MPI are shown in Table 2. Segmental wall motion abnormality was more common in the ischemic group than in the non-ischemic group (58.3% vs 21.2% respectively, P<0.001) whereas global dysfunction of the left ventricle was more common in the non-ischemic group than in the ischemic group (82.7% vs 41.7% respectively, P<0.001). Defect number ⩾2 on MPI was more common in ischemic group than non-ischemic group (50.4% vs 30.8% respectively, P=0.017). Patients with ischemic HF had more severe and larger defects than non-ischemic HF (45.7% vs 15.4%, P<0.001; 23.6% vs 3.8%, P=0.003, respectively). The SSS, SRC and SDC values were statistically higher in the ischemic HF group compared to the non-ischemic HF group (P<0.001, P<0.001, and P=0.015, respectively).

Clinical and imaging variables were entered into univariate analyses for the prediction of ischemic HF. Results of univariate and multivariate analyses for the prediction of ischemic HF are presented in Table 3. In the study group, univariate analyses identified five predictors of ischemic HF: defect number ≥2 (P=0.018, OR=2.286, 95%CI:1.153-4.530), presence of 3+/4+ defect severity (P<0.001, OR=4.623, 95%CI: 2.015-10.606, large defect (P=0.006, OR=7.732, 95%CI: 1.732-33.677), absence of global dysfunction (P< 0.001, OR=6.671, 95% CI:2.996-14.851), segmental wall motion abnormality (P<0.001, OR=5.204, 95%CI: 2.450-11.052), SSS (P<0.001, OR=1.201, 95%CI: 1.114-1.317), SRS (P<0.001, OR=1.282, 95%CI: 1.148-1.431), and SDS (P=0.021, OR=1.144, 95%CI: 1.021-1.282). Multivariate analysis of factors with P<0.1 in univariate analysis showed that absence of global dysfunction (P<0.001, OR=10.338, 95%CI: 3.937-27.405) and SSS (P<0.001, OR=1.208, 95%CI: 1.090-1.339) were the independent predictors of ischemic HF.

In patients with newly diagnosed HF and exertional dyspnea without concomitant chest pain, absence of global dysfunction showed 58.3% sensitivity and 86.7% specificity for the diagnosis of ischemic HF at MPI (AUC=0.705, 95% CI: 0.632-0.771, P<0.001), whereas SSS>8 had 65.4% sensitivity and 75.0% specificity (AUC=0.732, 95%CI:0.661-0.795, P<0.001).

Discussion

We found that larger, more severe defects and defects more than one were associated with ischemic HF and global left ventricular dysfunction was associated with non-ischemic HF. Furthermore, the ischemic HF group has higher SSS,SRS and SDS values compared to the non-ischemic HF group. In multivariate analysis, absence of global LV dysfunction and

Table 1. *Baseline characteristics of study population*

Characteristics	All patients (n=179)	Ischemic HF (n=127)	Non-ischemic HF (n=52)	P
Age	59±12	59±12	60±14	0.513
Male, n (%)	113 (63.1)	46(59.8)	37 (71.2)	0.154
Dyspnea duration (month)	7.9±4.1	7.6±4.0	8.5±4.2	0.220
Atypical chest pain	55 (30.7)	38 (29.9)	17 (32.7)	0.715
Body mass index (kg/m^2)	25.4±4.6	24.8±4.0	25.8±5.0	0.215
Smoking, n (%)	64 (35.8)	46 (36.2)	18 (34.6)	0.859
Hypertension, n (%)	99 (55.3)	70 (55.1)	29 (55.8)	0.937
Diabetes mellitus, n (%)	63 (35.2)	44 (34.6)	19 (36.5)	0.810
Hyperlipidemia, n (%)	66 (36.9)	51 (40.2)	15 (28.8)	0.154
Alcohol, n (%)	19 (10.6)	12 (9.4)	7 (13.5)	0.600
COPD, n (%)	46 (25.7)	29 (22.8)	17 (32.7)	0.237
Ejection fraction, %	33 (25-39)	33 (25-39)	33 (25-39)	0.650
Atrial fibrillation, n (%)	43 (31.9)	22 (42.3)	21 (25.3)	0.039
WBC, $10^9/L$	8.3±2.3	8.2±2.2	8.6±2.5	0.399
Hemoglobin, g/dL	13.4±1.9	13.5±1.8	13.1±2.1	0.291
Platelet count, K/mm^3	243±58	243±57	242±60	0.888
BUN, mg/dL	30.6 (22-45)	30.6 (25-43)	30.6 (22-45)	0.926
Creatinine, mg/dL	1.1±0.4	1.0±0.4	1.1±0.4	0.447
AST, U/L	34±9	33±8	35±9	0.420
ALT, U/L	37±11	37±10	38±12	0.292
Total cholesterol, mg/dL	185±34	184±36	186±27	0.653
LDL cholesterol, mg/dL	123±24	122±25	127±20	0.174

(continued)

Characteristics	All patients (n=179)	Ischemic HF (n=127)	Non-ischemic HF (n=52)	P
HDL cholesterol, mg/dL	38±6	38±6	37±6	0.215
Triglyceride, mg/dL	195±74	192±73	204±77	0.311
BNP pg/mL	162±59	165±55	152±66	0.209
Medication				
ASA	127 (71.3)	85 (67.5)	30 (57.9)	0.215
ACEI/ARB, n (%)	153 (85.5)	107 (84.3)	46 (88.5)	0.623
Beta blocker, n (%)	165 (92.2)	120 (94.5)	45 (26.5)	0.120
CaCB, n (%)	41 (22.9)	34 (26.8)	9 (17.3)	0.249
Diuretic, n (%)	139 (77.7)	97 (76.4)	42 (80.8)	0.658
Statin, n (%)	68 (38.0)	51 (40.2)	17 (32.7)	0.350
Warfarin, n (%)	40 (22.5)	25 (19.8)	15 (28.3)	0.266

ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; ASA: acetylsalicylic acid; BNP: B-type natriuretic peptide; BUN: blood urea nitrogen; CaCB: calcium channel blockers; COPD: chronic obstructive pulmonary disease

Table 2. *SPET imaging results between the ischemic HF and non-ischemic HF groups*

Characteristics	All patients (n=179)	Ischemic HF (n=127)	Non-ischemic HF (n=52)	P
High values for immediate acquisition, n (%)	28 (15.6)	21 (16.5)	7 (13.5)	0.774
High values for delayed acquisition, n (%)	19 (10.6)	13 (10.2)	6 (11.5)	0.793
Transient LV dilatation, n (%)	21 (11.7)	16 (12.6)	5 (9.6)	0.759
Defect number ⩾2, n (%)	80 (44.7)	64 (50.4)	16 (30.8)	0.017
Defect severity 3+/4+, n (%)	66 (36.9)	58 (45.7)	8 (15.4)	<0.001
Large defect, n (%)	32 (17.9)	30 (23.6)	2 (3.8)	0.003
Global dysfunction, n (%)	96 (53.6)	53 (41.7)	43 (82.7)	<0.001
Segmental wall motion abnormality, n (%)	85 (47.5)	74 (58.3)	11 (21.2)	<0.001
SSS	13.3±6.3	14.8±6.7	9.7±3.0	<0.001
SRC	10.1±4.5	11.1±4.7	7.7±2.7	<0.001
SDC	3.2±4.0	3.6±4.5	2.0±1.9	0.015
SSS >8, n (%)	96 (53.6)	83 (65.4)	13 (25.0)	<0.001

HF: heart failure; LV: left ventricle; SDC: summed difference score; SSS: summed stress score; SRS; summed rest score

Table 3. *Univariate and multivariate predictors of ischemic heart failure in the study population*

Variable	Univariate			Multivariate		
	P	OR	95%CI	P	OR	95%CI
Defect number ⩾2	0.018	2.286	1.153-4.530			
Defect severity 3+/4+	<0.001	4.623	2.015-10.606			
Large defect	0.006	7.732	1.732-33.677			
Absence of global dysfunction	<0.001	6.671	2.996-14.851	<0.001	10.338	3.937-27.405
Segmental wall motion abnormality	<0.001	5.204	2.450-11.052			
SSS	<0.001	1.201	1.114-1.317	<0.001	1.208	1.090-1.339
SRC	<0.001	1.282	1.148-1.431			
SDC	0.021	1.144	1.021-1.282			

SDC: summed difference score; SSS: summed stress score; SRS; summed rest score

SSS were the independently predicting factors of ischemic HF. These findings had relatively low sensitivity, but acceptable specificity.

Since heart failure may result from variety of acquired and hereditary disorders, the differentiation of ischemic from non-ischemic hearts disease has important prognostic and therapeutic implication [15]. Ischemic etiology is an independent predictor of mortality in patients with left ventricular dysfunction [1]. Specific therapeutic interventions are possible in ischemic HF [16, 17]. Of great importance is the recognition of jeopardized myocardium and responsible stenosis in CAD since revascularization may significantly improve LV function.

Cardiac nuclear imaging is currently useful in almost every step from diagnosis to treatment of cardiac diseases. It can provide information on left and right ventricular function, etiology of heart failure, myocardial ischemia and viability, dyssynchrony of LV and exercise capacity [18-20]. However, data of the role of stress imaging for diagnosis of CAD in patients having dyspnea as the primary referral symptom are limited.

Dyspnea is a subjective symptom that can be caused by a variety of diseases such as HF, CAD, valvular diseases, pulmonary diseases, obesity and anemia [21]. Dyspnea is a common symptom and has been demonstrated that patients presenting to a chest pain unit with dyspnea at admission have worse outcome than patients without dyspnea [22]. In a study by Bergeron et al. (2004) patients with unexplained dyspnea without chest pain had a higher likehood of ischemia than patients with only chest pain [23]. During follow up, patients with dyspnea and without chest pain had a higher incidence of MI, cardiac death and all-cause of mortality than patients with chest pain alone [23]. Balaravi et al. (2006) demonstrated a high prevalence of abnormal (45%) and high risk (11%) SPET scans in older overweight patients without known CAD who were referred for stress SPET imaging to evaluate dyspnea [24]. In a study including 17,991 patients undergoing MPI SPET, patients were divided into five categories according to their symptoms at presentation (asymptomatic, non-anginal chest pain, atypical chest pain, typical angina and dyspnea). After a mean follow up of 2.7±1.7 years, the rate of cardiac death and death from any cause was significantly higher among patients with dyspnea than among patients with other or no symptoms at presentation [4]. In a meta-analysis by Argulian et al. (2014), no statistically significant difference in the incidence of ischemia on stress imaging between patients with dyspnea and patients with chest pain was found, but during the follow-up period, all-cause of mortality was higher in patients with dyspnea compared with patients with chest pain (OR:2.57, 95%CI:1.75- 3.76, P<0.001) [25].

In idiopathic dilated cardiomyopathy LV wall motion and myocardial perfusion abnormalities on $^{201}TlCl_2$ tomography were heterogeneous and not evenly distributed [6]. It was reported that radionuclide ventriculography and exercise testing with $^{201}TlCl_2$ perfusion imaging were not able to differentiate ischemic from non-ischemic HF due to the presence of LV segmental wall motion abnormalities and segmental perfusion abnormalities in non-ischemic HF [26]. Conversely, other researchers showed that large severe defects were independent predictors of the presence of ischemic disease in patients with LVEF <35% who underwent $^{201}TlCl_2$ scintigraphy [3]. In another study with $^{201}TlCl_2$ imaging and dipyridamole, large defects were more common in patients with CAD than in patients with idiopathic dilated cardiomyopathy [5]. Technetium-99m-MIBI was used in a previous study by Danias

et al. (1998), performed with gSPET. Summed stress, rest, and reversibility perfusion defect scores were significantly lower in non-ischemic HF patients compared with ischemic HF patients [9]. The discrepancy between these studies can be partly explained by utilization of planar imaging methods with its inherently lower sensitivity and specificity compared to SPET imaging and employment of $^{201}TlCl_2$, which has less favorable imaging characteristics over ^{99m}Tc due to its lower energy emission (69-83keV) compared to ^{99m}Tc (140keV) and consequent higher soft tissue attenuation. A subsequent clinical study included 164 patients with unknown CAD and LV EF ⩽40% as tested by gSPET. These patients underwent subsequent CAG and showed a cutoff SSS value of >8 with 87% sensitivity and 63% specificity for diagnosing ischemic HF [27, 28]. This cutoff value was identified in 86% patients with ischemic HF and an 37% patients with non-ischemic HF [27]. Other researchers studied stress/rest gSPET with technetium-99m-MIBI MPI as an initial investigative tool in 201 hospitalized patients with new-onset HF [29]. The incidence of reversible perfusion abnormalities was found to be low, and 56% had a SDS of zero indicating absence of any ischemia despite resting abnormalities [28, 29]. Also, the mean SSS in patients with extensive CAD was 17.07±8.24 compared to 7.38±9.42 in patients without extensive CAD [28, 29]. Due to inconsistent results as compared to previous studies, the authors concluded that patients with new-onset HF differ in important pathophysiologic ways from those with chronic HF because chronic HF patients may have had pharmacological and/or mechanical interventions that alter LV structure, function, and ischemic burden [29]. This pathophysiologic theory seems to be valid not only for the previous studies investigating HF patients with various clinical statuses, but also for our study including newly diagnosed HF patients presenting primarily with dyspnea.

Up to 60% of patients with ischemic HF have no angina [30], and the assessment strategy for these patients continues to be debated [29]. Our study differs from previous studies investigating ischemic HFrEF patients with various symptoms, since it only includes HFrEF patients with dyspnea as a primary symptom which represents the majority of ischemic HF patients in daily clinical practice. Angina indicates chest discomfort (pain), whereas dyspnea implies difficulty breathing (breathlessness or shortness of breath) [24]. Using a clear-cut definition to differentiate from each other may not be exactly true in all patients, because some patients may use overlapping terms such as “tightness” or “suffocating” in order to describe their symptoms, but, patients' self-reported symptoms of dyspnea and chest pain were reported to be important in predicting cardiovascular outcomes [4]. In the present study, patients were asked to provide a definite answer (either "yes" or “no”) for questions such as “Do you experience shortness of breath”, “Do you experience chest pain”, etc. Previous studies have suggested that dyspnea is likely to represent an angina equivalent symptom in patients with known CAD [31]. But, contrary to expectations, the published literature failed to show a high frequency of inducible myocardial ischemia in CAD patients presenting with dyspnea, and reported an incidence of inducible myocardial ischemia between 10% and 40% in these studies [23, 25, 31]. On the other hand, among patients with not known CAD, there was no difference in the incidence of inducible myocardial ischemia in patients with dyspnea and those with chest pain [25]. Patients with highly variable exercise/functional status and LV systolic capacity (LV EF) were included in these studies [4, 23, 25, 31, 32]. Furthermore, in order to investigate scintigraphic variables which are valuable to determine (ischemic or non-ischemic) heart disease etiology, a highly specific group of patients with HFrEF and not known CAD, presenting primarily with dyspnea but had the capacity to perform exercise stress test were included in our study. The present study was performed with ^{99m}Tc-MIBI SPET and the presence of any of the following 8 scintigraphic criteria: large defect, multiple defect, 3+/4+ defect, abnormal segmental wall motion, absence of global LV dysfunction, SSS, SRS and SDS were associated with ischemic HF, but the absence of global dysfunction and SSS was the independent predictors of ischemic HF. Patients without global left ventricular dysfunction were found to have 10 times higher risk of having ischemic HF than patients with global dysfunction. Although the absence of global dysfunction and a SSS >8 had a low sensitivity, they had an acceptable specificity in our study.

Only a few studies have evaluated the role of SPET in the diagnosis of CAD in patients with dyspnea without concomitant chest pain. For patients with reduced LVEF and dyspnea, determining the cause as ischemic and non-ischemic is important for prognostic and treatment. Although coronary angiography has been the gold standard, revascularization is not indicated in non-ischemic HF. Besides, some patients may have limitations or increased risk for complications for invasive angiography. A non-invasive and accurate technique is desirable. Our findings may serve to evaluate the etiology of LV dysfunction without intervention in patients allergic to contrast media or having high risk for contrast nephropathy.

Study limitations

Main limitations of this study are its small sample size and retrospective design. Further large-scale prospective studies will be required to validate our results. The other limitation is the lack of pulmonary function testing data. All patients were able to perform exercise tests and all had New York Heart Association functional class II. More severe dyspnea as a primary symptom may have different significance. Patients intolerant to exercise stress test were excluded. Of these patients, results of dipyridamole stress test with ^{99m}Tc-MIBI SPET had been taken into consideration as valuable data to determine the ischemic origin of MPI abnormalities and the abnormal hemodynamic response [33]. Additionally, coronary artery calcium measurements by computed tomography can be used as an adjunct to SPET imaging for increasing diagnostic accuracy which is found to have both diagnostic and prognostic value in patients with CAD when used with SPET [34, 35]. Furthermore, multi-center studies are warranted to support our findings and test their prognostic value in this special subgroup of patients.

In conclusion, among patients with exertional dyspnea and LV EF <40%, those with ischemic etiology had more often severe and large LV perfusion defects, and higher SSS, SRC and SDS values than patients with non-ischemic etiology as studied on gSPET. Absence of the global LV dysfunction and SSS were the only independent predictive factors of ischemic HF on gSPET.

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