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Research Article

Myocardial Perfusion Imaging and Intraventricular Synchronism in Patients with Acute Coronary Syndrome. Is there a Sex Difference?

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Abstract

Background: Patients with a previous acute coronary syndrome (ACS) have a high risk of developing cardiac events during the first year. Thus, adequate assessment of myocardial ischemia and ventricular function is of crucial importance. In addition, the value of intraventricular synchronism as a marker of ischemia and the possible influence of sex is barely studied. Thus, the aim of this study was to assess the value of gated-SPECT myocardial perfusion imaging (including intraventricular synchronism evaluation) after ACS in women compared to men.

Methods: One-hundred sixty-seven patients (90 female, 58 ± 9 years; 77 male, 59 ± 10 years), referred from April 2011 to April 2014 with diagnosis of ACS were included. All underwent a stress-rest gated-SPECT myocardial perfusion imaging. A 48 months clinical follow-up was done.

Results: Men exercised more time and achieved more METS than women. Men showed slightly higher summed rest score and summed difference score than women, but summed stress score was significantly higher (11.61 ± 7.5 vs. 8.74 ± 7.9, respectively, p = 0.017). Although both phase standard deviation and histogram bandwidth were slightly higher in women compared to men, this difference was not significant. However, women had phase standard deviation and histogram bandwidth values twice as high as those reported as normal (phase standard deviation: 31.0 ± 19.4, histogram bandwidth: 90.7 ± 70.9). After four years, 82.2% of women and 61.4% of men were event-free.

Conclusion: Myocardial perfusion and intraventricular synchronism show differences comparing men and women after an ACS and gated-SPECT MPI can be useful to risk stratify these patients.

Keywords: *Myocardial Perfusion Imaging; Acute Coronary Syndrome; Sex; Gated-SPECT; Intraventricular Synchronism*

Abbreviations

ACS: Acute Coronary Syndrome; CABG: Coronary Artery Bypass Graft; CAD: Coronary Artery Disease; HBW: Histogram Bandwidth; LBBB: Left Ventricular Bundle Branch Block; LVEF: Left Ventricular Ejection Fraction; MHR: Maximal Heart Rate; MI: Myocardial Infarction; MPI: Myocardial Perfusion Imaging; NSTEMI: Non-ST Elevation Myocardial Infarction; PSD: Phase-Derived Standard Deviation; SDS: Summed Difference Score (SDS); SPECT: Single-Photon-Emission Tomography (SPECT); SRS: Summed Rest Score; SSS: Summed Stress Score; STEMI: ST Elevation Myocardial Infarction; ^{99m}Tc-MIBI: 99m-Technetium Methoxy-Isobutyl-Isonitrile; TID: Transient Ischemic Dilation

Introduction

Coronary artery disease (CAD) is the leading cause of mortality worldwide, both for women and men [1,2]. But for more than 2 decades, population case fatality rates for cardiovascular disease have been higher for women compared to men [3]. Although the cardiovascular mortality after an acute coronary syndrome (ACS) has been reduced in men in the last decade due to the improvement of diagnostic methods and patient-tailored management, the mortality rate among women has continued to increase, mainly due to the fact that women with ACS are less likely to undergo diagnostic and therapeutic procedures compared to men [4].

Patients with a previous ACS have a high risk of developing adverse cardiac events during the first year following the acute episode. Thus, adequate assessment of myocardial ischemia and ventricular function is of crucial importance. Stress myocardial perfusion imaging (MPI), particularly the extent and severity of myocardial perfusion defects, has been shown to predict the risk of future cardiovascular events [5,6]. It has been shown that perfusion abnormalities constitute the best predictor of myocardial infarction (MI), while post-stress left ventricular ejection fraction (LVEF) is the best predictor of cardiac death [5,7-9].

Gated single-photon-emission tomography (SPECT) MPI allows to measure perfusion and ventricular function, including the assessment of intraventricular synchronism by phase analysis [10,11], which can be significantly impaired soon after acute MI [12].

Nowadays, risk stratification after an ACS depends mainly on clinical, electrocardiographic and angiographic variables, but this approach has some limitations. In a previous work in post-ACS women [13], comparing ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI) patients, we reported that gated-SPECT MPI can be useful to risk stratify women after ACS, being summed stress score (SSS) and percentage of maximal heart rate (MHR) achieved during the stress test the best predictors of adverse cardiac events among NSTEMI patients. STEMI patients showed a more asynchronous behavior [13].

In addition, the value of intraventricular synchronism as a marker of ischemia and the possible influence of sex is barely studied. Thus, the aim of this study was to assess the value of gated-SPECT MPI (including intraventricular synchronism evaluation) after ACS in women compared to men.

Methods

Study Population

We studied 167 patients (90 female, mean age: 58 ± 9 years; 77 male, mean age: 59 ± 10 years), who were referred by their attending physicians to the Nuclear Medicine Department of the Institute of Cardiology from April 2011 to April 2014 with the following inclusion criteria: 25 years of age and older, with diagnosis of ACS prior to the MPI (mean: 2 months previously), able to exercise on treadmill or bicycle. Exclusion criteria were: pregnancy in case of women, previous coronary artery bypass graft (CABG) or any open-heart surgery, significant valvular disease, non-ischemic dilated cardiomyopathy, left ventricular bundle branch block (LBBB), arrhythmias which prevent the gated acquisition, or pacemaker implanted before the nuclear test.

Coronary risk factors were considered as follows: diabetes mellitus: fasting blood glucose ≥ 5.55 mmol/L (≥ 100 mg/dL) or treatment for diabetes; dyslipidemia: fasting plasma triglycerides ≥ 1.70 mmol/L (≥ 150 mg/dL) and/or HDL cholesterol < 1.29 mmol/L (< 50 mg/dL); high blood pressure: systolic blood pressure ≥ 130 mmHg or diastolic ≥ 85 mmHg or anti-hypertensive treatment; smoking history: patients were divided into current smokers, past smokers (defined as ≥ 6 months abstinence from smoking) and those who never smoked.

Each patient underwent a 99m-technetium methoxy-isobutyl-isonitrile (^{99m}Tc-MIBI) gated-SPECT MPI, following a two-day protocol: exercise stress/rest, including left ventricular dyssynchrony assessment by phase analysis. The patients included in the study were monitored by consultations and telephone calls (to patients or next of kin) at 1, 6, 12, 24, 36 and 48 months for the following adverse events: unstable angina, non-fatal MI, potentially lethal ventricular arrhythmia, percutaneous coronary intervention -PCI-, CABG, or death.

This study complies with the ethical standards laid down in the 1964 Declaration of Helsinki and all subsequent revisions. The review board and ethics committee of the Institute of Cardiology approved the study, and informed consent was obtained from all patients prior to the inclusion in the study. Patient anonymity was maintained during data analysis.

Gated-SPECT MPI

The first day of the study all patients underwent a symptom-limited treadmill exercise stress test (MTM-1 500 med, Schiller, Switzerland) following the Bruce protocol. At peak exercise, a dose of 740 MBq of ^{99m}Tc-MIBI was administered intravenously, and the patient continued to exercise for an additional period of 60 - 90 seconds when possible. Post-stress images were acquired at 60 minutes after tracer injection, using a rotating dual-head gamma camera (Nucline Spirit DHV, Mediso, Hungary) equipped with low energy, high-resolution, parallel-hole collimators, with a 20% energy window centered on the 140 keV photopeak. Sixty-four projections (20 seconds per projection), eight frames/cycle, with a 64 x 64 matrix were obtained over a 180^0 orbit. The following day, rest images were acquired at 60 minutes after the intravenous injection of 740 MBq of ^{99m}Tc -MIBI. Imaging was always performed in a supine position.

SPECT images were reconstructed using OSEM with 3 iterations and 10 subsets and filtered by a Butterworth filter, power 10, using a cut-off frequency of 0.3 cycles/mm. No attenuation or scatter correction was applied. All patients were studied 72 hours after the withdrawal of cardiovascular medication.

SPECT image interpretation

Semi-quantitative visual interpretation of images employed short-axis and vertical long-axis tomograms divided into 17 segments [14]. Each segment was scored by the consensus of two expert independent observers who were unaware of the clinical and angiographic data, using a five-point scoring system (from 0 = normal to 4 = absence of myocardial uptake). Disagreements, including any score in each SPECT segment were resolved by consensus. Segments with reduced tracer uptake were considered to be reversible defects if the score decreased ≥ 1 point from stress to rest. Summed stress, summed rest and summed difference scores (SSS, SRS and SDS) were obtained. If the summed difference score was 4 or greater it was considered as presence of stress-induced ischemia.

The assessment of regional wall motion was performed by visual inspection of gated tomograms in cine mode for semi-quantitative scoring. The LV myocardium was divided into 17 segments. Segmental wall motion was classified as: normal, hypokinesis, akinesis or dyskinesis. An operator independent analysis of regional wall motion and LVEF was made using dedicated software (Emory Cardiac Toolbox -ECTb-, Syntermed, Inc., Atlanta, Georgia, USA). The difference between LVEF from post-stress and rest acquisitions was defined as Delta LVEF (Delta LVEF = post-stress LVEF - rest LVEF). The left intraventricular mechanical dyssynchrony was evaluated at rest and post-stress by using the phase analysis of the gated SPECT MPI included in the ECTb, previously described [15].

Statistical analysis

Categorical variables are expressed as numbers and percentages and compared when necessary with the chi-square test and the Fisher exact test. Continuous variables are expressed as mean ± standard deviation (SD). For independent observations, the nonpaired Student t- test was applied. The Kaplan-Meier method was used to calculate event-free survival rates, and log-rank test was used for comparison of survival curves by sex. A value of $p < 0.05$ was considered significant.

Results

Patient characteristics

Clinical characteristics of patients are shown in table 1. There were no significant differences between both groups regarding age and presence of high blood pressure, diabetes mellitus and dyslipidemia. All diabetic patients were type 2, with disease duration of 5 ± 1 years prior to the ACS. More women than men had STEMI and NSTEMI, while more men had unstable angina. Smoking habit was more frequent among women. Chest pain (mainly typical) as symptom referred by the patients before the gated-SPECT was significantly more frequent among men: 66.2% vs. 45.6% among women. Sixty-eight women (76%) were postmenopausal.

Stress results

Stress characteristics are presented in table 2. Maximal blood pressure and percentage of maximal heart rate were not significantly different between both groups. Men exercised more time (8.0 ± 2.0 vs. 6.8 ± 1.7 min, $p < 0.0001$), as well as achieved more METS (6.3 ± 2.1 vs. 4.4 ± 1.4, $p < 0.0001$) than women. Women complained of chest pain at stress more frequently than men (51.1% vs. 31.2%, $p = 0.007$), while these showed more ST depression during stress (37.7% vs. 12.2%, $p < 0.001$).

Variables	Sex		Total n = 167	p
	Female n = 90	Male n = 77		
Age (years, mean ± SD)	58.3 ± 9.6	59.1 ± 9.9	58.7 ± 9.8	0.587
Current smokers Past smokers	24 (26.7%) 18 (20.0%)	16 (20.8%) 37 (48.1%)	40 (24.0%) 55 (32.9%)	0.001
Dyslipidemia	33 (36.7%)	36 (46.8%)	69 (41.3%)	0.123
Diabetes Mellitus	24 (26.7%)	16 (20.8%)	40 (24.0%)	0.240
High Blood Pressure	66 (73.3%)	58 (75.3%)	124 (74.3%)	0.455
STEMI NSTEMI Unstable Angina	54 (60.0%) 7 (7.8%) 29 (32.2%)	28 (36.4%) 0 (0.0%) 49 (63.6%)	82 (49,1%) 7 (4.2%) 78 (46.7%)	< 0,001
Chest Pain	41 (45.6%)	51 (66.2%)	92 (55.1%)	0.007
Family History of CAD	26 (28.9%)	5 (6.5%)	31 (18.5%)	< 0.0001

Table 1: *Patient characteristics.*

CAD: Coronary Artery Disease; NSTEMI: Non ST-Elevation Myocardial Infarction; STEMI: ST-Elevation Myocardial Infarction.

Variables	Female n = 90	Male n = 77	p
Exercise duration (min)	6.8 ± 1.7	8.0 ± 2.0	< 0.0001
Peak systolic BP	167.7 ± 20.4	171.7 ± 25.7	0.261
Peak diastolic BP	97.1 ± 11.4	95.4 ± 11.3	0.366
% MHR achieved	92.5 ± 6.4	91.7 ± 10.0	0.567
METS	4.4 ± 1.4	6.3 ± 2.1	< 0.0001
Chest pain at stress	46 (51.1%)	24 (31.2%)	0.007
ST depression	11 (12.2%)	29 (37.7%)	<0.001

Table 2: *Stress results.*

BP: Blood Pressure; MHR: Maximal Heart Rate.

Gated-SPECT MPI

Male patients showed slightly higher SRS and SDS than women. SSS was significantly higher in male: 11.61 ± 7.5 than in women: 8.74 ± 7.9 ($p = 0.017$). In both groups there was a significant change between SSS and SRS (from 8.74 ± 7.9 to 6.01 ± 6.6 in women and from 11.61 ± 7.5 to 7.66 ± 7.1 in men, $p < 0.0001$).

Transient ischemic dilation (TID) was not different between both groups: 1.0 ± 0.1 (female) vs. 1.0 ± 0.3 (male), $p = 0.118$.

Ventricular function and intraventricular synchronism variables are presented in table 3. LVEF (at rest and post-stress) and delta LVEF were not significantly different between both groups. Although both phase-derived standard deviation (PSD) and histogram bandwidth (HBW) were slightly higher in women compared with men, this difference was not significant. In both groups PSD did not change between rest and post-stress, while HBW showed a minor reduction in women (from 90 to 87 degrees) and an increase in men (from 76 to 80 degrees).

Variables	Female n = 90	Male n = 77	p
Myocardial perfusion			
SSS	8.74 ± 7.9	11.61 ± 7.5	0.017
SSR	6.01 ± 6.6	7.66 ± 7.1	0.125
SDS	2.73 ± 4.6	3.95 ± 3.5	0.053
Ventricular function			
LVEF at rest (%)	62.1 ± 12.9	62.5 ± 12.4	0.835
LVEF post-stress (%)	61.8 ± 13.1	63.1 ± 13.1	0.554
Delta LVEF	1.10 ± 6.37	1.53 ± 11.8	0.213
Intraventricular synchronism			
PSD at rest (degrees)	31.0 ± 19.4	27.9 ± 18.5	0.316
PSD post-stress (degrees)	31.0 ± 19.7	27.0 ± 19.1	0.239
HBW at rest (degrees)	90.7 ± 70.9	76.7 ± 57.3	0.185
HBW post-stress (degrees)	87.4 ± 64.0	80.3 ± 63.7	0.480

***Table 3**: Ventricular function and intraventricular synchronism.*

HBW: Histogram Bandwidth; LVEF: Left Ventricular Ejection Fraction; PSD: Phase Standard Deviation;

SSS: Summed Stress Score; SRS: Summed Rest Score; SDS: Summed Difference Score.

Follow-up

Forty-five adverse cardiac events appeared during the follow-up: 16 (17.8%) in women and 29 (38.6%) in men. In the whole study population, SSS (12.32 ± 6.7 vs. 9.49 ± 8.0 p = 0.038) and SDS (5.15 ± 5.2 vs. 2.82 ± 3.7 p = 0.018) were significantly higher in patients who developed adverse events (Table 4).

After four years, 82.2% (74/90) of female patients and 61.4% (48/77) of male patients were event-free (Figure 1). There were five deaths (three cardiac and two non-cardiac). Only one woman died of cardiac cause.

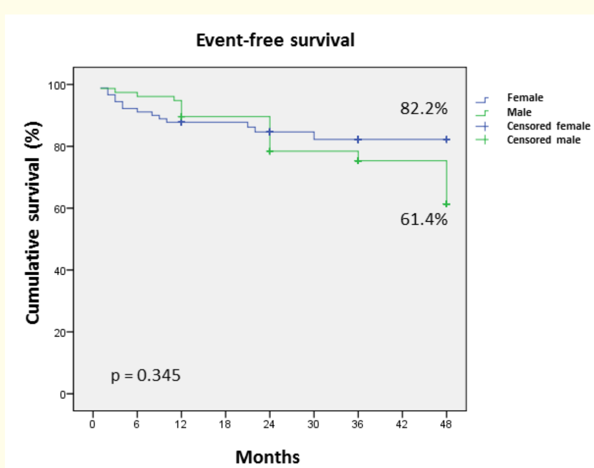

***Figure 1:** Survival in acute coronary syndrome patients (women compared with men) 48 months after gated SPECT, Kaplan-Meier curve (90 women vs. 77 men).*

Variables	Adverse events		p
	Yes n = 34	No n = 133	
SSR	7.18 ± 6.5	6.67 ± 7.0	0.691
SSS	12.32 ± 6.7	9.49 ± 8.0	0.038
SDS	5.15 ± 5.2	2.82 ± 3.7	0.018
TID	1.05 ± 0.1	1.01 ± 0.3	0.245
LVEF at rest	61.5 ± 13.5	62.5 ± 12.4	0.621
LVEF post-stress	62.1 ± 13.9	63.2 ± 13.0	0.594
Delta LVEF	0.04 ± 6.4	1.53 ± 11.8	0.328

Table 4: *Gated-SPECT variables and occurrence of adverse events.*

LVEF: Left Ventricular Ejection Fraction; SSS: Summed Stress Score; SRS: Summed Rest Score; SDS: Summed Difference Score; TID: Transient Ischemic Dilation.

Discussion

In the present work, men exercised more time and achieved more METS than women after an ACS. Male patients showed slightly higher SRS and SDS than women, but SSS was significantly higher. Although both PSD and HBW were slightly higher in women compared with men, this difference was not significant. However, in both groups PSD did not change between rest and post-stress. To the best of our knowledge, there are no previous reports of the synchronism behavior after ACS comparing women and men.

Only two risk factors were significant different between women and men: family history of CAD and current smoking habit, both more frequent in women. More men presented with unstable angina and more women had STEMI and NSTEMI in our study, which may be explained by the bias represented for the SPECT indications. After an ACS men are sent more frequently to invasive angiography, while women are mainly sent to non-invasive studies.

Myocardial perfusion, left ventricular function and intraventricular synchronism

Although there is an extensive body of evidence as to the value of stress myocardial perfusion SPECT and PET for risk stratification in women and men presenting with symptoms of stable ischemic heart disease [16-22], as far as we know, there is no published data on the comparison of perfusion, function and intraventricular synchronism between women and men in the short- and medium-term post-ACS.

Although values of sensitivity and specificity are slightly higher in male compared to female patients, there are no significant differences in SPECT performance for the diagnosis of CAD [23]. Vitola., *et al*. [24] reported that men showed positive SPECT findings more frequently than women (34.9% vs. 27.0%, respectively), as well as more severe perfusion defects (SSS > 13 in 11.0% vs. 4.9% in women). This coincided with our study, where male patients showed more extensive perfusion defects, in relation with more frequent multivessel disease compared to women. However, the ventricular function was not significantly different between both groups.

Asynchronous motion often appears in patients with myocardial infarction and has been associated with infarct size [25] and left ventricular remodeling at six-month follow-up [26]. Experimental and clinical reports have demonstrated that dyssynchrony results in decreased cardiac output, slowed relaxation rates, reduced peak filling velocity, and increased myocardial energy demand [27,28] and may be associated with abnormalities of myocardial perfusion [29,30].

In a previous work comparing STEMI and NSTEMI in women [13] we found that patients with STEMI, with more abnormal contraction patterns due to the presence of transmural myocardial infarction, had the more asynchronous behavior both at rest and post-stress, considering both phase variables (PSD and HBW).

In the present study, although both women and men had higher PSD and HBW than the reported normal ones [15], it results interesting that this finding was more pronounced in women, who had PSD and HBW values twice as high as those reported as normal. This may be explained by the fact that women showed more STEMI than men in our sample.

Hida., *et al.* [31] reported that the mechanisms responsible for dyssynchrony are the temporal contraction delay (as in LBBB), and the heterogeneous contraction due to fibrosis and ischemia, which could explain our results. Other authors, such as Haugaa., *et al*. [32], also suggested that the mechanical dispersion of the contraction may be a representation of the scar tissue scatter within the myocardium, as well as a substrate for arrhythmia and sudden cardiac death. Another finding which also may support the value of intraventricular synchronism to assess CAD patients is that the PSD did not reduce post-stress (normal behavior) among our cases.

Follow-up

In a review of individual patient-level data from three established ACS registries published by Bugiardini., *et al.* [33], despite presenting with higher risk characteristics and having higher in-hospital and six months risk of death, women with ACS and obstructive CAD were apparently treated less aggressively with secondary preventive drugs than were men, being less likely to receive aspirin, beta-blockers and statins at discharge. Overall, coronary revascularization appears to be performed in a similar proportion of women and men, once angiography has been performed and the coronary anatomy is known. Nevertheless, substantial geographic variation exists in the relative rate of coronary angiography in men and women. For instance, in a group of 16 736 patients who were admitted with ACS (85% men and 15% women), El-Menyar., *et al.* reported that gender discrepancy exists in many aspects of ACS patients and the mortality rate was higher in women of all age groups, which may be due to underestimation of patient risk [4].

Al-Fiadh., *et al.* [34] reported that female sex was associated with a higher rate of major adverse cardiac events (MACE) (10.1% vs. 6.4%, $p < 0.001$) at 30 days than male sex. After 12 months, as in our cases, there was no significant difference in mortality, MACE, and revascularization between women and men.

In 2 225 women referred for SPECT-MPI not immediately after ACS, and followed by a period of 3.7 ± 1.4 years, Cerci., *et al.* [35] reported that SPECT MPI significantly risk stratified the population: patients with abnormal scans showed significantly higher death rates compared to patients with normal scans (13.1% vs. 4.0%, respectively, $p < 0.001$). The survival rate at 4 years was of 96% in patients with normal scans, while it was of 89.2% and 80.3% in those with mild/moderate defects and severe defects, respectively. On the other hand, Santos., *et al.* [36] in a group of 4 628 diabetic patients did not find a difference according to sex.

It is well known that SSS > 8, ≥ 10% of abnormal myocardium, ≥ 10% of ischemic myocardium, as well as post-stress LVEF lower than rest LVEF, are features that can be considered as high-risk indicators of future cardiac adverse events [37,38]. Thus, it seems that these same features can also help to risk stratify patients after ACS, independently of sex. Although in our patients we did not find any significant relationship between synchronism status and adverse cardiac events, this is a topic which needs more research with bigger samples, probably considering some cut-off values.

Due to under-representation of females in major clinical trials, there are limited data on whether recent changes in the management of ACS patients resulted in corresponding changes in the short- and long-term outcomes of women hospitalized with ACS [39]. Although our work was not designed as a treatment trial, this might represent an interesting line of future research.

Limitation

This is a single-center prospective observational study with a small sample, possibly influenced by selection and referral bias, as is the case in many observational studies.

Conclusion

Myocardial perfusion and intraventricular synchronism show differences comparing men and women after an ACS and gated-SPECT MPI can be useful to risk stratify these patients.

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