



## Brief Communications

### Left Ventricular Dysfunction Secondary to Ischemia in Women With Angina and Normal Coronary Angiogram. Five Years Follow-Up

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#### Abstract

**Introduction:** To assess if myocardial ischemia evidenced through both perfusion abnormalities and post-stress left ventricular ejection fraction reduction by gated single photon emission tomography (SPECT) myocardial scintigraphy in women with angina and normal coronary angiograms, as well as the presence of endothelial dysfunction, can predict cardiac events during a medium term follow-up.

**Methods:** Thirty-two postmenopausal women (mean age:  $58 \pm 8$  years) with angina and normal coronary epicardial arteries were included. Each underwent technetium-99m methoxyisobutylisonitrile gated-SPECT myocardial scintigraphy (2-day protocol: exercise stress – rest), and brachial artery endothelial function measured by ultrasonography. All patients were followed during 5 years. Cardiac death and acute coronary syndromes (ACS) were considered as end points.

**Results:** The most prevalent risk factors were high blood pressure (66% of patients), smoking habit (47%), and obesity (38%). Forty-four percent of patients experienced angina both during stress and at rest. In thirteen cases (41%), the gated-SPECT was abnormal (small to moderate reversible perfusion defects and post-stress LVEF reduction  $\geq 5\%$ ); while in 19 (59%) was normal. Fourteen patients (44%) showed a brachial artery vasodilator responsiveness after 5 minutes of ischemia lower than 5%, which in 8 cases coincided with the presence of an abnormal gated-SPECT. There were one cardiac death and five ACS. Seventy-nine percent of patients with normal scintigraphy, and 84% of those with abnormal scintigraphy were free of cardiac events at five years; while 78% of patients with normal brachial vasodilatory response, and 85% of those with an abnormal response were free of cardiac events.

**Conclusions:** The presence of myocardial ischemia evidenced by gated-SPECT, as well as endothelial dysfunction, are not suggestive of a worse prognosis at medium term in postmenopausal women with angina and normal coronary angiograms.

#### Introduction

In patients who have typical exertional angina and a positive electrocardiographic (ECG) exercise stress test without significant coronary stenosis (syndrome X), [1] coronary microcirculation abnormalities have been shown to play a pathophysiological role [2-4]. At least half the patients diagnosed with cardiac syndrome X have some microvascular coronary dysfunction [5].

Data from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE) study have shown a 2.5% annual risk of adverse cardiac events, including death, myocardial infarction, stroke, and congestive heart failure in subjects with microvascular coronary dysfunction [5,6]. Gulati et al [7] have found a five-year annualized event rate for cardiovascular events of 7.9% among women with normal epicardial coronary arteries.

A few studies performed with isotopic techniques have shown a decrease in the left ventricular ejection fraction (LVEF) during exercise in approximately 30% of patients with syndrome X [8,9]. We have found that stress-induced ischemia is associated with post-stress LVEF reduction as a probable manifestation of myocardial stunning (persistent contractile dysfunction despite reperfusion after ischemia) in postmenopausal women with typical angina and normal coronary angiography [10,11].

Nonetheless, to our knowledge, there are no data so far regarding the prognostic value of gated-single photon emission tomography (SPECT) myocardial perfusion imaging (MPI) in postmenopausal women with angina and nonobstructive coronary artery disease.

#### Objectives

To investigate if myocardial ischemia evidenced through both perfusion abnormalities and post-stress LVEF reduction by gated-SPECT MPI in women with angina and normal coronary angiograms, as well as the presence of endothelial dysfunction, can predict cardiac events at a medium term follow-up (FU).

#### Material and Methods

We included 32 postmenopausal female patients (mean age:  $58 \pm 8$  years) with typical angina and without previous myocardial infarction (MI), selected on the basis of having had a coronary angiogram (performed between May 2004 and December 2005), which disclosed no evidence of coronary artery disease, defined as no angiographic luminal irregularities. Patients were excluded if they had a history of estrogen replacement therapy.

Each underwent technetium-99m methoxy-isobutyl-isonitrile (99mTc-MIBI) gated-SPECT (2-day protocol: exercise stress-rest), as well as endothelial function measured by ultrasonography of the brachial artery, as previously described by Celermajer et al [12]. All patients were studied 72 h after the withdrawal of cardiovascular medication. The use of sublingual nitroglycerin was allowed only in case of chest pain.

This study complies with the Declaration of Helsinki. The ethics committee of the Institute of Cardiology approved the study, and written informed consent was obtained from all patients prior to their inclusion in the study.

#### - Study endpoints

Patients were followed at one; three and five years after inclusion, taking into account the following endpoints: cardiac death and admission due to acute coronary syndrome (ACS).

#### - Statistical Analysis

Categorical variables are expressed as numbers and percentages. Continuous variables are expressed as mean  $\pm$  standard deviation. Associations and comparisons between variables were done by chi-square test and Fisher's exact test (for categorical variables) and by the Wilcoxon signed ranks test in case of the continuous variables. A Cox-Mantel test was used to obtain the survival function. A value of  $p < 0.05$  was considered significant.

## Results

The most prevalent risk factors were high blood pressure (66%), smoking habit (47%), and obesity (38%). Fifty percent of patients had dyslipidemia. Fourteen patients (44%) experienced angina both during stress and at rest.

In thirteen cases (41%), the gated-SPECT MPI was abnormal (small to moderate reversible perfusion defects); while in 19 (59%) was normal. Ventricular volumes and LVEF are presented in Table 1. Only LVEF and end-systolic volume (ESV) showed significant differences between rest and stress. Twenty-one patients (66%) showed reduction of post-stress LVEF. Of these, 13 (41% of the total) exhibited a post-stress LVEF reduction  $\geq 5\%$ . Among the cases with abnormal MPI, six (46%) also exhibited a post-stress LVEF reduction  $\geq 5\%$ .

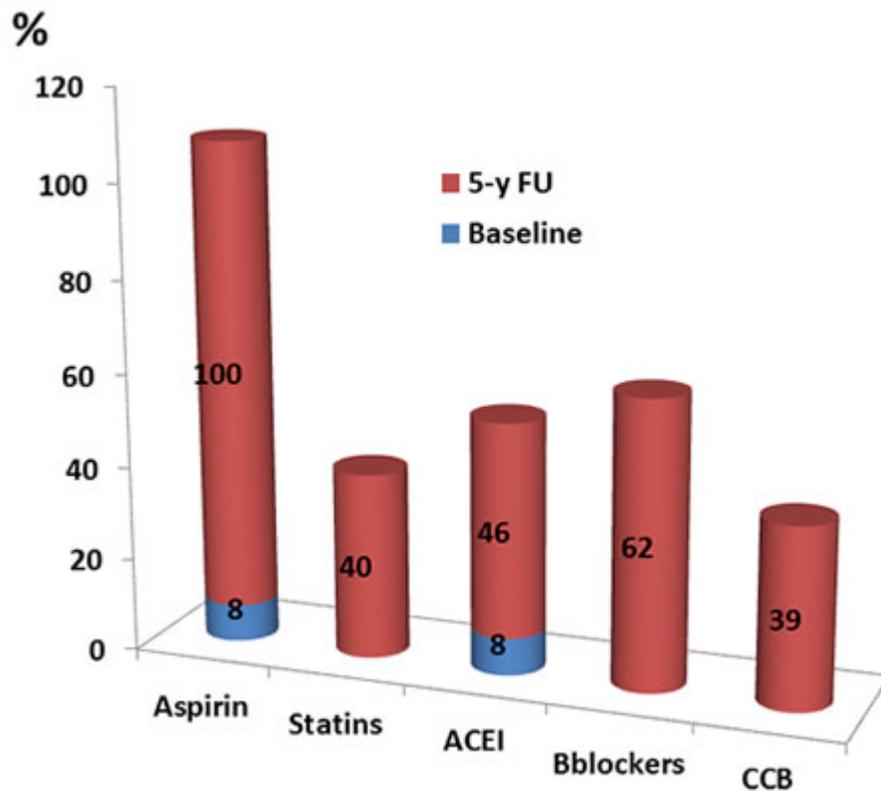
Variable	Rest	Stress	p
End-diastolic volume (ml)	79 $\pm$ 28	78 $\pm$ 30	0.38
End-systolic volume (ml)	28 $\pm$ 14	31 $\pm$ 18	0.03
Stroke volume (ml)	50 $\pm$ 16	50 $\pm$ 13	0.92
LVEF (%)	65 $\pm$ 7	62 $\pm$ 8	0.02

**Table 1.** Ventricular function

LVEF: left ventricular ejection fraction. Values are expressed as mean  $\pm$  SD

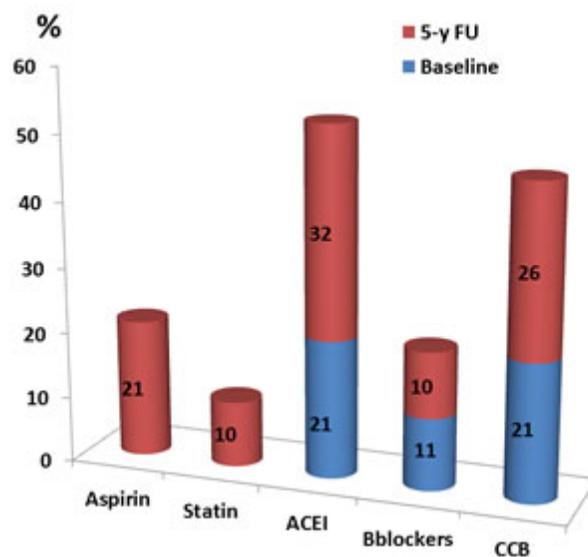
Fourteen patients (44%) showed brachial artery vasodilator responsiveness lower than 5% after five minutes of ischemia, which in eight cases coincided with the presence of an abnormal perfusion and in ten coincided with a reduction of post-stress LVEF in the gated-SPECT.

Figures 1 and 2 present the treatment prescribed according to the MPI results, baseline vs. five-years of FU. In patients both with abnormal (**Figure 1**) or normal (**Figure 2**) perfusion on MPI, aspirine, statins, ACE inhibitors, betablockers and calcium channel blockers were more frequently prescribed after inclusion in the study, but only among those with abnormal MPI the difference was statistically significant in the case of the prescription of aspirin and betablockers ( $p=0.0001$  and  $p=0.005$ , respectively).



**Figure 1.** Treatment prescribed according to the MPI results, baseline vs. five-years of follow-up, in patients with abnormal perfusion on MPI. Aspirine, statins, ACE inhibitors, betablockers and calcium channel blockers were more frequently prescribed after inclusion in the study, but only aspirin and betablockers were significantly different between baseline and follow-up ( $p=0.0001$  and  $p=0.005$ , respectively).

MPI: myocardial perfusion imaging, ACEI: angiotensin-converting enzyme inhibitors, Bblockers: betablockers, CCB: calcium channel blockers, 5-y FU: five-years follow-up



**Figure 2.** Treatment prescribed according to the MPI results, baseline vs. five-years of follow-up, in patients with normal perfusion on MPI, pNS

MPI: myocardial perfusion imaging, ACEI: angiotensin-converting enzyme inhibitors, Bblockers: betablockers, CCB: calcium channel blockers, 5-y FU: five-years follow-up

There were one cardiac death at three years of FU and five admissions due to ACS: three patients with a non-ST elevation myocardial infarction (non-STEMI) at two, three and four years of FU, and two cases with an ST-elevation myocardial infarction (STEMI) at three and four years of FU. Four out of six (67%) adverse events appeared in patients with normal perfusion on MPI. Seventy-nine percent of patients with normal MPI, and 84% of those with abnormal MPI were free of cardiac events at five years; while 79% of cases with  $\Delta\text{LVEF} > -5\%$  and 85% of those with  $\Delta\text{LVEF} \leq -5\%$  were free of cardiac events. Seventy-eight percent of patients with normal brachial vasodilatory response, and 85% of those with an abnormal response were free of cardiac events.

### Discussion

Our results show that in a group of postmenopausal women with angina and normal epicardial coronary arteries, 79% of patients with normal MPI and 84% of those with abnormal MPI were free of cardiac events at five years of FU. Percentages of event-free patients were similar if post-stress LVEF and abnormal brachial vasodilatory response were considered.

Until recently, the prognosis of women with angina without nonobstructive coronary artery disease was thought to be benign [13,14], and such patients were treated almost only with reassurance that they do not have heart disease. Nowadays, this notion has been challenged, with new evidence showing that these women have a high risk of future cardiac events [7,15,16].

Endothelial dysfunction in microvascular angina has been explained as a generalized process that can involve both coronary and peripheral conduit arteries and is similar to that observed in patients with organic atherosclerotic disease [17]. About 44% of our patients showed brachial artery vasodilator responsiveness lower than 5% after five minutes of ischemia, which can be considered a manifestation of endothelial dysfunction. There was a coincidence of 62% between abnormal vasodilator responsiveness and the presence of stress-induced ischemia and reduction of post-stress LVEF in the gated-SPECT, and this may be explained by the fact that myocardial ischemia might occur during coronary vasoconstriction associated with coronary endothelial dysfunction.

Post-stress LVEF measured by gated-SPECT slightly but significantly decreases after an ischemic insult, whereas it remains mostly unchanged, with a tendency to increase, if there is no ischemia [18,19]. We have previously found that stress-induced ischemia is associated with post-stress LVEF reduction as a probable manifestation of myocardial stunning in postmenopausal women with typical angina and normal coronary angiography [10,11]. In the present study, 41% of the patients exhibited a post-stress LVEF reduction  $\geq 5\%$ . Among the cases with abnormal MPI, six (46%) also exhibited a post-stress LVEF reduction  $\geq 5\%$ . This LVEF reduction seems to be owing to the increase of ESV caused by endocardial ischemia.

In a previous study [10], we have suggested that the combination of stress-induced ischemia, endothelial dysfunction and regional myocardial stunning, expressed by the post-stress LVEF reduction, should be regarded with concern as a sign suggesting impaired prognosis in these patients with cardiac syndrome X. Nonetheless, among our cases, four out of six (67%) adverse events appeared in patients with normal perfusion on MPI.

In this regard, it should be considered that in patients with normal epicardial coronary arteries and myocardial ischemia demonstrated by MPI, either by abnormal perfusion or by post-stress LVEF reduction, a more intensive treatment was prescribed, both to achieve a better control of coronary risk factors and to treat the ischemia. In our cases, aspirin, statins, ACE inhibitors, betablockers and calcium channel blockers were more frequently prescribed, but only among those with abnormal MPI the difference was statistically significant in the case of the prescription of aspirin and betablockers.

This present investigation was not designed as a treatment trial, and thus the association of a better prognosis and the intensification of treatment in patients with abnormal MPI do not prove a causal relationship between the two.

Nevertheless, rather than viewing this study as showing gated-SPECT as a test with negative prognostic value in cardiac syndrome X female patients, and in spite of the small sample, which in fact is a limitation of the study, cardiologists might consider the results as a positive message: postmenopausal women with angina and nonobstructive coronary artery disease, receiving contemporary medical care both to control coronary risk factors and to treat ischemia, may have a better prognosis at medium term.

### Conclusions

The presence of myocardial ischemia evidenced by gated-SPECT, as well as endothelial dysfunction, may not suggest a worse prognosis at medium term in postmenopausal women with angina and normal coronary angiograms who have received more intensive treatment after abnormal MPI results.

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