Angina with Normal Epicardial Coronary Arteries: Does Gender Imply any Difference in Ischemia Detection?

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Abstract

To evaluate if gender implies any difference in ischemia detection both by perfusion and function abnormalities using gated-SPECT myocardial scintigraphy in patients with typical angina, normal coronary angiography, and endothelial dysfunction, 31 women (Group I) and 20 men (Group II) were studied. Each underwent technetium-99m methoxy-isobutyl-isonitrile myocardial scintigraphy, brachial artery endothelial function measured by ultrasonography and lipidogram. Five female and eight male patients showed a reversible perfusion defect with post-stress left ventricular ejection fraction (LVEF) reduction greater than 5%, associated with endothelial dysfunction in three women and four men. There was no significant difference neither in presence of endothelial dysfunction, nor in LVEF post-stress minus LVEF at rest (ΔLVEF): -2.71% in women vs. -2.41% in men. In patients with typical angina, normal coronary angiography and abnormal SPECT myocardial scintigraphy (both by perfusion and post-stress left ventricular ejection fraction reduction), gender does not account for differences in the detection of ischemia.

INTRODUCTION

Patients who have typical exertional angina and a positive electrocardiographic exercise stress test without significant coronary stenosis (syndrome X)[1] show transient myocardial perfusion abnormalities [2] and metabolic evidence of myocardial ischemia [3,4] in response to appropriate methods of provoking ischemia.

Coronary microcirculation abnormalities have been shown to play a pathophysiological role in patients with cardiac syndrome X. It has been demonstrated that preserved systemic endothelial function appears to rule out the occurrence of transient single-photon emission computed tomographic (SPECT) defects in patients with syndrome X [5]. Myocardial stunning, expressed by post-stress ventricular function reduction as a heart response to an acute ischemia, and assessed by gated-SPECT, might be considered another approach to the evaluation of ischemia in these patients [6].

It is well known that syndrome X is more frequent in women than in men[7]. Nevertheless, gender does not appear to make a difference in the diagnosis of ischemia in these patients when evidenced through perfusion and function abnormalities by gated-SPECT myocardial scintigraphy with technetium-labeled compounds.

Chest pain with normal coronary arteries may have different causes, not all dependent on a heart condition, and our main objective is to contribute to the refining of diagnostic tools for ischemia. In the present study, we hypothesize that both in men and in postmenopausal women with syndrome X, in spite of their anatomical differences, myocardial ischemia can be detected in a similar way using nuclear cardiology tests.

METHODS

STUDY POPULATION

We studied 31 postmenopausal female and 20 male patients with typical angina and without previous myocardial infarction, selected on the basis of having had a coronary angiogram (performed between May 2004 and December 2006) which disclosed no evidence of coronary artery disease, defined as no angiographic luminal irregularities. Female 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), and endothelial function measured by ultrasonography of the

brachial artery. A lipidogram was also made.

This study complies with the Declaration of Helsinki. The Review Board of the Institute of Cardiology approved the study, and written informed consent was obtained from all patients.

MYOCARDIAL SCINTIGRAPHY

Two 99mTc-MIBI scintigraphies were performed by the gated-SPECT technique: physical stress and rest 24 hours apart. The first day of the study all patients underwent a symptom-limited exercise stress test carried out in the upright position using a bicycle ergometer (MEDIFIT 400L) with 25 W load increment every two minutes and continuous monitoring of symptoms, electrocardiogram, heart rate and blood pressure. At peak exercise, a dose of 740 MBq of 99mTc-MIBI was administered intravenously, and the patient continued to exercise for an additional period of 60-90 seconds. Images were acquired 45 minutes to one hour after the injection, with a rotating dual-head gamma camera (Sopha) equipped with a low-energy, high-resolution parallel-hole collimator centered on the 140 keV photopeak with a 20% window. Thirty-two projections (25 seconds per projection), 8 frames/cycle, with a 64x64 matrix were obtained over an 1800 orbit. Filtered back-projection was then made with a low-resolution Butterworth filter with a cutoff frequency of 0.25 cycles per pixel, order 7. No attenuation or scatter correction was applied. The following day, rest images were acquired one hour after the intravenous injection of 740 MBq of 99mTc-MIBI.

All patients were studied 72 hours after the withdrawal of cardiovascular medication. Use of sublingual nitroglycerin was allowed if chest pain occurred.

SCINTIGRAPHIC IMAGE INTERPRETATION

Semiquantitative visual interpretation of images employed short-axis and vertical long-axis tomograms divided into 17 segments for each patient [8]. 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 in image interpretation, including every score in each SPECT segment, were resolved by consensus. Segments with reduced tracer uptake were considered to be reversible defects if the activity score increased ≥ 1 point from stress to rest.

The assessment of regional wall motion was performed by visual inspection of gated SPECT perfusion images in cine mode for semiquantitative scoring, and quantitative images were used for objective confirmation of visually abnormal wall motion. A six-point scoring system was used for wall motion: 5=dyskinesis, 4=akinesis, 3=severe hypokinesis, 2=moderate hypokinesis, 1=mild hypokinesis, 0=normal motion. An operator-independent analysis of regional wall motion, left ventricular ejection fraction (LVEF), LV end-diastolic volume (EDV), LV end-systolic volume (ESV) and LV stroke volume (SV) was made using a MultiDim Analysis software (Sopha).

ASSESSMENT OF ENDOTHELIAL FUNCTION

Endothelial function was evaluated by ultrasound measurement of flow-mediated, endothelium-dependent vasodilatation of the brachial artery, as previously described by Celermajer et al [9]. Patients were tested in a supine position. Under resting conditions (after ten minutes of relaxation), ultrasound images of the brachial artery above the antecubital fossa in the longitudinal plane were obtained using high-resolution ultrasound equipment (Philips) with a 10-MHz linear transducer. Reactive hyperemia (for flow-mediated endothelium-dependent vasodilatation assessment) was induced by a five-minute inflation of a blood pressure cuff around the forearm to 200 mmHg for five minutes and subsequent release. The diameter of the brachial artery was assessed 60 seconds after deflation of the cuff.

All images were recorded on S-VHS video tape, and measurements were made by an ultrasound specialist blinded to test conditions and patient identity. Brachial artery diameter measurements were made using electronic calipers at end-diastole, simultaneous with the electrocardiographic R waves, over four cardiac cycles, and averaged. Changes in arterial diameter with reactive hyperemia were expressed as the percentage of change from resting baseline, providing an index of endothelial function. An increase higher than 5% after deflation of the cuff, compared to baseline value was considered normal [10].

All patients were studied 72 hours after the withdrawal of cardiovascular medication. Use of sublingual nitroglycerin was allowed if chest pain occurred.

LIPIDOGRAM

Lipid fractions were analyzed in EDTA-treated plasma. Total cholesterol and triglycerides were analyzed by enzymatic methods. HDL cholesterol was isolated after addition of heparin and 2 mol/L $MnCl_2$.

STATISTICAL ANALYSIS

Continuous variables were expressed as mean ± 1 standard deviation (SD). Discrete variables were compared by means of the chi-square test and continuous data were analyzed by Mann-Whitney test.

A value of $p < 0.05$ was considered significant.

RESULTS

PATIENT CHARACTERISTICS AND RISK FACTORS

Patients were divided into two groups: Group 1: Female patients (n=31), and Group 2: Male patients (n=20). Clinical characteristics by sex are shown in Table 1.

Figure 1

Table 1: Characteristics of the Patients

	Group 1 (n = 31)	Group 2 (n = 20)	p
Age (years)	58 ± 8	54 ± 9	NS
BMI	28 ± 4	27 ± 4	NS
High Blood Pressure	22 (71%)	15 (75%)	NS
Diabetes Mellitus	9 (29%)	2 (10%)	NS
Smoking Habit	16 (52%)	13 (65%)	NS
Rest Angina	8 (26%)	5 (25%)	NS
Stress Angina	9 (29%)	6 (30%)	NS
Rest & Stress Angina	14 (45%)	9 (45%)	NS
Total-Cholesterol	195 ± 25	196 ± 41	NS
HDL-Cholesterol	40 ± 10	38 ± 18	NS
LDL-Cholesterol	130 ± 29	129 ± 38	NS
VLDL-Cholesterol	26 ± 12	35 ± 19	0.04
Triglycerides	129 ± 57	170 ± 98	0.04

BMI: Body Mass Index

Except age, BMI and lipid values, the rest of variables are expressed in number of patients with percent in parenthesis

Age and BMI are expressed as mean ± standard deviation. Lipid values are expressed as mean ± standard deviation in mg/dl

There was no significant difference regarding risk factors or type of angina. However, while there were more diabetic women, there were more current smokers and slightly more hypertensive patients among the males.

Men had higher levels of VLDL-cholesterol and triglycerides (p=0.04, Table 1).

MYOCARDIAL PERFUSION

Among female patients, exercise-stress provoked angina in five cases (associated with ST-segment depression in one patient); there was an asymptomatic ST-segment depression in three cases and an episode of paroxysmal supraventricular tachycardia at maximal load in another patient. Three men had angina at maximal load (in one case asociated with ST-segment depression).

In female patients, reversible perfusion defects induced by exercise appeared in five patients. In all cases, this was associated with post-stress LVEF reduction greater than 5%. The localization of the perfusion defects were: three anterior, one inferior and inferoseptal, and one anterior / anteroseptal / inferoseptal. Three of these five patients also showed endothelial dysfunction. Seven patients had fixed defects (in anterior and anteroseptal segments), which in six patients were associated with post-stress LVEF reduction greater than 5%. Four of these seven women also showed endothelial dysfunction. Nineteen patients had a normal myocardial perfusion, but in 16 cases a post-stress LVEF reduction greater than 5% was found, which in six patients was associated with endothelial dysfunction.

In male patients, exercise-induced reversible defects appeared in eight cases: three anteroapical, one anteroapical and septal, one inferior and inferoseptal, two inferior and one anterior and inferior. In all cases there was also a post-stress LVEF reduction greater than 5%, which in four patients coincided with endothelial dysfunction. Two patients had fixed defects in the inferior segment, with a post-stress LVEF reduction greater than 5% and endothelial dysfunction. Eleven patients had normal perfusion, which in three cases coincided with a post-stress LVEF reduction greater than 5% and endothelial dysfunction.

VENTRICULAR FUNCTION

Comparison between LVEF and ventricular volumes at rest and post-stress is presented in Table 2. Male patients had a significantly minor LVEF and higher ventricular volumes.

Figure 2

Table 2: Ventricular Function and Volumes

	Group I (n = 31)	Group II (n = 20)	p
LVEF at rest (%)	65 ± 7	60 ± 12	0.02
LVEF at stress (%)	63 ± 8	58 ± 12	0.04
EDV at rest (ml)	79 ± 28	128 ± 64	0.0003
EDV at stress (ml)	78 ± 30	127 ± 61	0.0004
ESV at rest (ml)	28 ± 14	57 ± 40	0.005
ESV at stress (ml)	31 ± 18	61 ± 42	0.004
SV at rest (ml)	51 ± 15	72 ± 19	0.0001
SV at stress (ml)	50 ± 13	72 ± 18	0.00002

EDV: end-diastolic volume; ESV: end-systolic volume; LVEF: left ventricular ejection fraction; SV: stroke volume

Variables are expressed as mean ± standard deviation

 LVEF (LVEF post-stress minus LVEF at rest) was -2.71% in Group I patients (women) vs. -2.41% in Group II (men), p=NS. Patients with reversible perfusion defects in both groups also showed a moderate hypokinesis congruent with the localization of the perfusion defects.

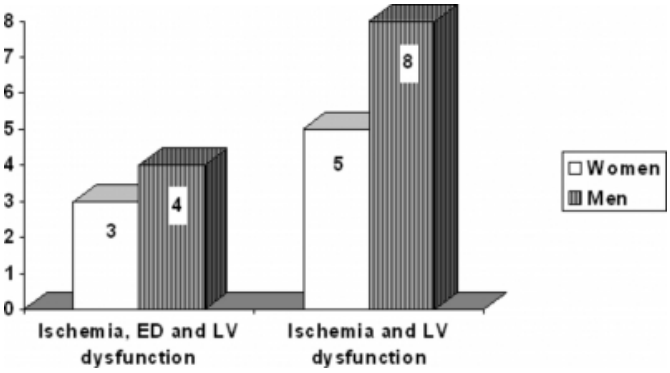
ENDOTHELIAL FUNCTION

Endothelial dysfunction was found in a similar proportion in both groups (45% of women and 50% of men, p=NS). The brachial artery vasodilator responsiveness after five minutes of ischemia was similar in both groups of patients (5% in women vs. 4% in men; p=NS).

Figure 1 shows the concordance among stress-induced myocardial ischemia, post-stress left ventricular dysfunction and endothelial dysfunction in both groups. All patients with stress-induced ischemia also had a post-stress left ventricular dysfunction. But in these patients, endothelial dysfunction was present in 60% of the women and in 50% of the men.

Figure 3

Figure 1: Concordance among stress-induced myocardial ischemia, left ventricular dysfunction and endothelial function in both groups of patients. The white bars represent women and the black bars, men. The first pair of bars corresponds to those patients who showed myocardial ischemia, post-stress ventricular dysfunction and endothelial dysfunction. The second pair shows those who only had stress-induced ischemia and left ventricular dysfunction.



ED: endothelial dysfunction; LV: left ventricular. p=NS

Association of the three manifestations was found in 10% of the whole group of women and in 30% of the men (p=NS).

DISCUSSION

Our study demonstrates an association between brachial artery flow-mediated dilation as a measurement of endothelial dysfunction, post-stress LVEF reduction and myocardial ischemia in 10% of postmenopausal patients with normal coronary angiography but in whom symptoms of chest pain are an important component of their clinical status, as well as in 30% of men with the same clinical presentation, with no significant difference regarding gender.

It has been found that patients with cardiac syndrome X have a high prevalence of cardiovascular risk factors, such as smoking, dyslipidemia, obesity and estrogen deficiency, which may trigger endothelial dysfunction [11]. Among our cases, the main risk factors were high blood pressure and smoking. Overweight was also present in both groups. In general, the lipid values were normal, except for reduced HDL-cholesterol values in women which were consistent with postmenopause, explaining the absence of difference in men of a similar age. Triglycerides and VLDL were abnormal in men and higher than in women (p=0.04).

MYOCARDIAL PERFUSION, ENDOTHELIAL

DYSFUNCTION AND ISCHEMIA IN CARDIAC SYNDROME X

Coronary endothelial dysfunction can be detected in some patients with minimally obstructive coronary artery disease and angina [12,13,14,15,16,17], and endothelial dysfunction in microvascular angina has been explained as a generalized process that can involve both coronary and peripheral conduit arteries, similar to that observed in patients with epicardial atherosclerotic disease [18]. In our patients, endothelial dysfunction was found in 45% of women and 50% of men. It has been reported that endothelial-dependent responses in the peripheral circulation may be modulated by steroid hormones, showing an impairment of endothelial function in postmenopausal women with syndrome X [19]. Thus, it could be hypothesized that estrogen deficiency may contribute to the development of microvascular angina through endothelial dysfunction and, therefore, postmenopausal women do not show any significant difference from men regarding the frequency of endothelial dysfunction, as was found in our patients.

Myocardial ischemia may occur during coronary vasoconstriction associated with coronary endothelial dysfunction. Transient abnormalities in myocardial perfusion have been demonstrated in approximately 30% of patients with cardiac syndrome X [20,21]. In a previous study with a group of 59 women with syndrome X [6], we found that perfusion defects appeared with physical stress in 20% of cases, 75% of whom also showed a post-stress LVEF reduction greater than 5%. These results have led us to further investigate whether this post-stress stunning (which is a manifestation of ischemia) is an explanation for the occurrence of reversible perfusion defects. In the present work, which is part of that ongoing study, we found that reversible perfusion defects induced by exercise appeared in five women and in eight men, in all cases associated with post-stress LVEF reduction greater than 5% and regional wall motion abnormalities, which supports the concept of regional stunning. This is consistent with our hypothesis.

Seven female patients showed fixed perfusion defects that could be attributed to attenuation defects due to breast tissue. In fact, these defects were all in anterior or anteroseptal localization, the area most frequently associated with breast attenuation. But in six cases this was associated with a post-stress LVEF reduction greater than 5%. Two men also had a fixed defect in the inferior segment, which in part might be explained by attenuation due to diaphragmatic tissue.

Microvascular angina has been consistently found in cardiac syndrome X patients and is suggested as a cause for segmental myocardial blood flow abnormalities and heterogeneous myocardial perfusion [22]. Thus, alterations in coronary microcirculation seem to be a more plausible explanation for the finding of reversible myocardial perfusion defects among our patients with normal coronary arteries.

In the cases without perfusion defects, other explanations for the clinical setting could be suggested, such as abnormal pain perception [23,24,25].

VENTRICULAR FUNCTION

Myocardial stunning, defined as myocardium with persistent contractile dysfunction despite the restoration of perfusion after a period of ischemia [26], represents a heart response to an acute ischemia which persists for some time after the restoration of adequate blood flow. There are different clinical settings in which myocardial stunning has been demonstrated [27,28], but it can also develop after silent or symptomatic ischemic episodes during daily activities and after diagnostic stress tests (either by physical or by pharmacological stress) provoking an ischemic response [26,29,30,31].

Post-stress left ventricular ejection fraction (LVEF) measured by gated-SPECT slightly but significantly decreases after an ischemic insult; however, it remains mostly unchanged, with a tendency to increase, if there is no ischemia [32,33]. According to Borges-Neto et al [34], the difference between stress and rest LVEF calculations (ΔLVEF) for nonischemic patients is + 1% (stress higher than rest), while ΔLVEF in patients with stress-induced ischemia has been reported as – 4% (rest higher than stress).

Gated-SPECT offers the possibility of assessing perfusion and function with the same test, and using technetium-labeled compounds, such as sestamibi and tetrofosmin, allows the evaluation of 45 minutes to one hour post-stress LVEF, a feasible and reliable means of analyzing myocardial stunning [35,36,37]. In a previous work [6], we found a significant ΔLVEF minus value in syndrome X female patients with reversible perfusion defects (-5.2% vs. -1.8% in those without reversible defects, $p<0.001$), associated with a higher post-stress end-systolic volume. In the present study, all patients with reversible perfusion defects and the 27% of men and the 84% of women with normal perfusion showed post-stress LVEF reduction greater than 5%.

Because it has been shown that in ischemic patients, exercise-induced LV dysfunction (myocardial stunning) continues for at least one hour, and that the extent of LVEF reduction is determined by the severity of ischemia [38], myocardial stunning should be taken into account as a response to acute ischemia due to physical stress in microvascular angina, although definite proof of this would require further study. However, in those cases without reversible perfusion defects, but with post-stress left ventricular dysfunction, a generalized dysfunction caused by a microvascular abnormality might be considered a possible explanation for the clinical picture.

CONCLUSION

In patients with typical angina, normal coronary angiography and abnormal SPECT myocardial scintigraphy (both by perfusion and post-stress left ventricular ejection fraction reduction), gender does not account for differences in the detection of ischemia.

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