The Impact of Gender Difference on the Effects of Preinfarction Angina on Microvascular Damage With Reperfused Myocardial Infarction

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ABSTRACT

Background: Few studies have addressed gender differences in evoking preconditioning. In an experimental study, it was reported that the preconditioning effect disappeared after gonadectomy.

Objectives: We sought to determine the effects of preinfarction angina (PA) on myocardial damage using intravenous contrast echocardiography.

Methods: We studied 334 consecutive patients with anterior myocardial infarction (AMI) who underwent successful angioplasty. All patients underwent myocardial contrast echocardiography (MCE) 14 days after percutaneous coronary intervention (PCI). Contrast defect was calculated as contrast defect area/myocardial area. Typical angina occurring in the 24-hour period preceding myocardial infarction was present in 133 patients (29 women) (group PA) and absent in 201 patients (43 women) (group non-PA). All women were postmenopausal.

Results: The contrast defect size and peak creatinine phosphokinase (max CPK) level in women were both significantly higher than that of men in group PA ($18.3\% \pm 6.3\%$ vs $11.9\% \pm 9.0\%$; $P < 0.01$ and 5000 ± 599 IU/L vs 2672 ± 221 IU/L; $P < 0.005$). The functional status of the myocardium among group PA, as expressed by risk area wall motion score index, was better in men than in women at 14 days (1.1 ± 0.8 vs 1.7 ± 0.8 ; $P < 0.01$) and at 6 months (0.7 ± 0.4 vs 1.6 ± 0.6 ; $P < 0.01$). However there were no significant gender differences in group non-PA. Multivariate regression analysis showed that the female gender ($P < 0.05$) was a significant independent predictor for microvascular damage.

Conclusions: These findings suggest that preconditioning effects were attenuated in women with reperfused AMI.

Introduction

It has been shown in a number of experimental models that episodes of ischemia occurring before myocardial infarction (MI) can reduce infarct size.^{1,2} However, these studies have been predominantly conducted in male animals.³ Recently, it has been shown that preinfarction angina may attenuate the development of the no-reflow phenomenon, and thus preserve both microvascular function and tissue perfusion after reperfusion.⁴ In an experimental study, a gender difference, which was estrogen-dependent, has been shown in the tolerance to ischemia-reperfusion injury.⁵ After a gonadectomy, the hearts of female mice had a depressed function and increased infarction after ischemia and reperfusion. Moreover, preconditioning had no beneficial effects. Thus, this current study investigated whether there was a gender difference in the tolerance to ischemia reperfusion injury.

Methods

Patients

Between April 1998 and August 2007, 334 consecutive patients with their first anterior myocardial infarction (AMI) underwent primary percutaneous transluminal coronary angioplasty (PTCA; for single vessel disease) or stent implantation, or both, of the totally occluded or subtotally occluded coronary artery (degree of occlusion was based on: thrombolysis in myocardial infarction [TIMI] flow grade 0 or 1) within 24 hours of the onset of AMI symptoms. Patients meeting any of the following criteria were excluded: age >90 years, documented history of variant angina, a previous MI and/or previous revascularization, left main coronary stenosis, or severe left ventricular dysfunction (ejection fraction <0.20). Patients were also ineligible if they had had a previous MI, coronary artery bypass graft, or other cardiac surgery. Preinfarction angina was defined as classic angina (chest pain, chest discomfort, or left

arm or jaw pain episodes lasting <30 min). Data were collected from interviews on admission as to whether patients ever experienced preinfarction angina in the 24 hour preceding the MI. Preinfarction angina was present in 133 patients (29 women) (group PA) and absent in 201 patients (43 women) (group non-PA). All women were postmenopausal.

Echocardiographic Studies

Baseline left ventricular regional wall motion and volumes were assessed in all patients using 2-dimensional echocardiography 14 days after PTCA. Myocardial contrast echocardiography (MCE) was performed 14 days after the MI. A follow-up echocardiography was performed 6 months later to assess contractile recovery and left ventricular volume changes over time.

Echocardiographic images were recorded with commercially available systems, equipped with second harmonic imaging and harmonic power Doppler (Philips Sonos-5500). The images were digitally stored on magneto-optical disks and S-VHS videotapes for off-line analysis. The left ventricle was divided into 16 segments, as visualized using apical 4-chamber, 2-chamber, and long axis views. For the purpose of this study, the myocardial risk area was defined as the area occupied by dysfunctioning segments in the echocardiogram, performed in the acute phase of the MI. A regional wall motion score index (WMSI) in the risk area was calculated. Two independent observers, who had no knowledge of the patients' data, evaluated the wall motion of 16 myocardial segments, as endorsed by the American Society of Echocardiography. The wall thickening of each myocardial segment was scored as follows: 4 = dyskinesia; 3 = akinesia; 2 = severe hypokinesia; 1 = hypokinesia; and 0 = normokinesia or hyperkinesias.⁶ The wall motion score (WMS) was calculated as the sum of the scores within the area at risk.

The contrast agent used in the MCE procedure in this study was Levovist (Schering AG, Berlin, Germany), a suspension of galactose microparticles in sterile water, injected into a cubital vein at a dose of 10 mL volume of 300 mg/mL, with slow bolus. The contrast media suspension was first administered as a 2 mL bolus and then as an infusion (1 mL/sec). Apical views were systematically explored, and harmonic power Doppler technology and interrupted transmission imaging at end-systole were used. Evaluation of MCE studies was performed off-line by 2 experienced cardiologists blinded to the clinical angiographic data and the eventual presence and location of wall motion abnormalities. A myocardial segment was considered opacified at MCE if it showed enhancement after contrast injection. A contrast defect was considered as absent of contrast enhancement in 1 region compared with others in the same view. The following formula was used to assess the relative contrast

defect area: (total contrast defect area/total myocardial area) $\times$ 100.

Angiographic Analysis

The TIMI study flow grade and the presence of angiographically visible collaterals were evaluated after the recanalization procedure. Collateral channels were graded according to the method reported by Rentrop et al⁷; good collateral flow was defined as grade 2 or 3. PTCA was considered successful when the residual stenosis was <25% in the presence of TIMI grade 3 flow.

Time to Treatment

Time to treatment for PCI was measured with reperfusion time. This interval was defined as the time from symptom to the time of first balloon inflation or use of another therapeutic interventional device such as a stent or a thrombectomy catheter.

Statistical Analysis

Data are presented as mean $\pm$ SD. The statistical significance of differences between groups was determined with the Student *t* test for unpaired data. Differences in prevalence were assessed by χ^2 tests. A 1-way analysis of variance (ANOVA) was used to analyze the difference in cardiac function and infarct size. Univariate and multivariate analysis was used to determine the factor of contrast defect size. The variables included age, the presence of diabetes mellitus, smoking, hypertension, time to reperfusion, preinfarction angina, and female gender. Diabetes mellitus was defined as a fasting glucose level >126 mg/dL or/and receiving relevant therapy, and hyperlipidemia was defined as a serum cholesterol >240 mg/dL (6.2 mmol/L) or receiving antihyperlipidemic treatment on admission. A *P* < 0.05 was considered statistically significant. Odds ratios and 95% confidence intervals were calculated. Data were analyzed with the use of SPSS software (version 10, SPSS, Chicago, IL).

Results

Clinical and Angiographic Data

Patient demographics and baseline characteristics, together with in-hospital clinical laboratory and angiographic variables and follow-up therapy of patients are listed in Table 1.

Women were older than men in both groups. In group PA, a higher percentage of diabetes mellitus and smoking was observed in men compared with women. Max CPK levels in women were significantly higher than those in the men in group PA (5000 ± 599 IU/L vs 2672 ± 221 IU/L; *P* < 0.005). However, there was no significant deference in group non-PA (men: 5390 ± 414 IU/L vs

Table 1. Clinical Characteristics

	Group PA (n = 133)		Group Non-PA (n = 201)	
	Men (n = 104)	Women (n = 29)	Men (n = 158)	Women (n = 43)
Age (yrs)	59 ± 11	69 ± 12 ^a	61 ± 11	71 ± 12 ^a
Diabetes mellitus (%)	34 (33)	6 (19) ^a	41 (26)	13 (31)
Smoking (%)	66 (63)	0 (0) ^a	96 (61)	8 (19) ^a
Hypertension (%)	46 (44)	11 (38)	54 (34)	5 (45)
Hyperlipidemia (%)	38 (37)	11 (38)	68 (43)	19 (45)
Reperfusion time (hr)	4.3 ± 3.0	6.6 ± 3.6	4.4 ± 2.8	5.6 ± 4.7
Max CK (IU/L)	2672 ± 221 ^b	5000 ± 599	5390 ± 441	4828 ± 897
TIMI grade 3 flow (%)				
Pre-PTCA	13 (12)	1 (4) ^a	61 (9)	0 (0) ^a
Post-PTCA	84 (81)	25 (87)	141 (89)	37 (87)
Good collateral (2,3)	21 (20)	1 (4) ^b	19 (12)	4 (10)
Medical treatment				
ACE-inhibitor (%)	94 (90)	20 (69)	114 (72)	42 (97)
Statin (%)	26 (25)	9 (31)	54 (34)	14 (33)
β-Blocker (%)	33 (32)	12 (42)	55 (35)	26 (60)

Abbreviations: ACE, angiotensin-converting enzyme; CK, creatine phosphokinase; PA, preinfarction angina; PTCA, percutaneous transluminal coronary angioplasty; TIMI, thrombolysis in myocardial infarction.
Values are mean ± SD.
^a $P < 0.05$ vs men of same group.
^b $P < 0.05$ vs other groups.

women: 4828 ± 341 IU/L; $P = \text{ns}$). In group non-PA, a smaller percentage of preprocedure TIMI grade 3 flow was observed in women compared with men. While in group PA, a smaller percentage of good collateral was observed in women compared with men. Reperfusion time for women was slightly longer than men in both groups, but it was not statistically significant.

The Extent of Microvascular Damage

All patients were analyzed with MCE. Microvascular damage, expressed as a contrast defect, was significantly greater in group non-PA ($17.2\% \pm 10\%$) than in group PA ($12.2\% \pm 9\%$; $P = 0.002$). There were no significant gender differences in the contrast defect in group non-PA (men: $16.1\% \pm 6.1\%$ vs women: $16.4\% \pm 4.4\%$; $P = \text{ns}$). However, in group PA, the contrast defect area of women was significantly greater than that of men ($18.3\% \pm 6.3\%$ vs $11.9\% \pm 9.0\%$; $P < 0.01$; Figure 1).

Functional Status

The echocardiography performed within 14 days after AMI, indicated that the WMSI of men in group PA was better than all other groups (1.1 ± 0.8 vs 1.7 ± 0.8 [group PA women] vs 1.7 ± 0.9 [group non-PA men] and vs 1.9 ± 0.8 [group non-PA women], $P < 0.01$). A similar finding in favor of group PA men was observed for the WMSI on the 6-month follow-up echocardiogram: WMSI was 0.7 ± 0.4 (group PA men) vs 1.6 ± 0.6 (group PA women) vs 1.7 ± 0.8 (group non-PA men) and vs 1.6 ± 0.8 (group non-PA women), $P < 0.01$ (Figure 2).

No differences were seen between the 4 groups in left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV) on the 14-day echocardiogram (Table 2). However, the left ventricular ejection fraction (LVEF) of men in group PA was better than the other groups: $59\% \pm 13\%$ vs $52\% \pm 7\%$ (group PA women) vs $49\% \pm 4\%$ (group non-PA men) vs $50\% \pm 2\%$ (group non-PA women), $P < 0.05$. There were no significant differences

Figure 1. Size of contrast defect between group PA and group non-PA. Contrast defect of men in group PA was significantly greater than all other groups (group PA women: $18.3\% \pm 6.3\%$ vs group PA men: $11.9\% \pm 9.0\%$ vs group non-PA men: $16.1\% \pm 6.1\%$ vs group non-PA women: $16.4\% \pm 4.4\%$; $P < 0.01$ vs other group).

Figure 2. Comparison of risk area WMSI. The WMSI of men in group PA was better than all other groups after 2 weeks and 6 months after AMI. Two weeks after AMI; group PA men: 1.1 ± 0.8 vs group PA women: 1.7 ± 0.8 vs group non-PA men: 1.7 ± 0.9 and vs group non-PA women: 1.9 ± 0.8 , $P < 0.01$ vs other group. 6 months after MI; group PA men: 0.7 ± 0.4 vs group PA women: 1.6 ± 0.6 vs group non-PA men: 1.7 ± 0.8 and vs group non-PA women: 1.6 ± 0.8 , $P < 0.01$ vs other group.

in the 6-month echocardiogram among the 4 groups for LVEDV and LVESV. However, at follow-up, similar between-group differences in LVEF were observed to those seen on the 14-day echocardiogram. Men in group PA had better LVEF results than the other groups: $62\% \pm 7\%$ vs $54\% \pm 3\%$ (group PA women) vs $56\% \pm 5\%$ (group non-PA men) vs $54\% \pm 7\%$ (group non-PA women), $P < 0.05$ (Table 2).

Determinants of Microvascular Damage

To determine the independent factors related to the development of microvascular damage, we performed univariate and multivariate analysis. Multivariate analysis revealed that preinfarction angina and female gender were

Table 2. Echocardiographic Studies

	Group PA		Group Non-PA	
	Men	Women	Men	Women
Baseline				
LVEDV (mL/m ²)	98 ± 7	92 ± 11	103 ± 4	88 ± 7
LVESV (mL/m ²)	46 ± 4	49 ± 6	52 ± 3	53 ± 7
LVEF (%)	59 ± 13 ^a	52 ± 7	49 ± 4	50 ± 2
Follow-up				
LVEDV (mL/m ²)	92 ± 6	96 ± 11	101 ± 7	99 ± 11
LVESV (mL/m ²)	36 ± 4	48 ± 8	51 ± 5	53 ± 9
LVEF (%)	62 ± 7 ^a	54 ± 3	56 ± 5	54 ± 7

Abbreviations: LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; PA, preinfarction angina.

Values are mean ± SD.

^a $P < 0.05$, (compared with other group).

independent predictors for the extent of contrast defect (Table 3).

Discussion

The main findings of the present study were that preinfarction angina was associated with attenuated left ventricular dysfunction and microvascular damage, but only in men, as these effects disappeared in women.

In experimental situations, the hearts of female mice have been shown to have depressed function and increased infarction zone after ischemia and reperfusion. Turcato et al⁸ reported that hearts from females have greater inherent resistance to ischemic injury, possibly involving increased signaling via the phosphorylated prosurvival kinase, Akt. Ischemic preconditioning has been demonstrated to protect the hearts of a variety of experimental species. However in female mice, while gonadectomy increased infarct size and depressed left ventricular developed pressure, preconditioning did not exert any demonstrable beneficial effects.⁵ In contrast, the beneficial effects of ischemic preconditioning in the male mouse heart completely disappeared after gonadectomy or gonadectomy and estrogen substitution, suggesting that not only estrogens, but also androgens, may be involved in the development of preconditioning in the male.

There are several documented beneficial actions that might provide estrogen-induced myocardial protection. First, estrogen activates the myocardial mitochondrial ATP-sensitive potassium channels.⁹ Second, estrogen

Table 3. Univariate and Multivariate Analysis for the Extent of Contrast Defect

Risk factor	OR	95% CI	P Value	
Univariate analysis				
Age	0.098	−0.002	+0.119	0.0551
Diabetes mellitus	0.276	−2.120	+2.671	0.8210
Smoking	−1.521	−3.835	+0.793	0.1996
Hypertension	0.411	−2.794	+1.972	0.7344
Time to reperfusion	0.058	−0.016	+0.132	0.2741
Preinfarction angina	−4.412	−6.742	−2.708	0.0002
Female gender	4.087	1.279	+6.869	0.0045
Multivariate analysis				
Age	0.046	−0.072	+0.163	0.4441
Diabetes mellitus	0.926	−1.507	+3.359	0.4540
Smoking	0.743	−3.476	+1.990	0.6422
Hypertension	0.677	−3.110	+1.756	0.5842
Time to reperfusion	0.046	−0.027	+0.120	0.2265
Preinfarction angina	−3.695	−6.113	−1.277	0.0029
Female gender	3.385	0.116	+6.653	0.0424
Abbreviations: CI, confidence interval; OR, odds ratio.				

Abbreviations: CI, confidence interval; OR, odds ratio.

decreases the influx of calcium during ischemia,¹⁰ and reduces the severity of contraction band necrosis.¹¹ Third, estrogen reduces both myocardial infarct size and occurrences of ischemia, and reperfusion-induced ventricular arrhythmias, which appear to be mediated by an increase in the production of nitric oxide and the opening of Ca^{2+} -activated K^{+} channels.¹² Fourth, Kim et al reported that the protective effect of estrogen may be mediated by its antioxidant properties.¹³ Fifth, estrogen reduces leukocyte adherence and migration in infarct tissue through reducing expression of cytokines and leukocyte adhesion molecules.^{14–16} In this study, all the women were postmenopausal, and therefore they did not receive the benefit of estrogen.

Our data showed no differences were seen between the group PA women and group non-PA at microvascular damage, expressed as a contrast defect and WMSI. Only group PA men received the benefit of preinfarction angina. These results lead the collateral evidence that women independently predict poorer outcomes in patients with ST-elevation myocardial infarction and more often complicated cardiogenic shock compared to men.^{18,19}

Study Limitations

The present findings do not represent the outcome of a prospective randomized trial. This is a retrospective analysis of anterior ST-segment elevation myocardial infarction subjects.

Conclusion

Our data suggest that preinfarction angina was associated with attenuated left ventricular dysfunction and microvascular damage, but only in men, as these effects disappeared in women. Gender differences in any preconditioning effects were not fully resolved in our study. The causality of preconditioning effects is shown, but not proven.

In summary, preconditioning effects of preinfarction angina were attenuated in postmenopausal women with reperfused anterior myocardial infarction. This finding may help in providing a solution to the problem of clinically poor prognosis of this cardiac condition.

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The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

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