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## Evaluation of the influence of age and gender on the relationships between infarct size, infarct severity, and left ventricular ejection fraction in patients successfully treated with primary percutaneous coronary intervention

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**Background.** Female sex and advanced age have adverse prognostic meaning in acute myocardial infarction. Whether gender and/or age influence the relationship between infarct size, infarct severity, and left ventricular ejection fraction (LVEF) is unclear.

**Methods.** We examined 460 patients (359 men) with acute myocardial infarction submitted to successful primary percutaneous coronary intervention. Infarct size, infarct severity, and LVEF were evaluated with perfusion gated SPECT at one month of index infarction.

**Results.** There were no significant correlations between age and infarct size or infarct severity, and between age and LVEF. Moreover, elderly age ( $\geq 75$  years) did not influence the relationship between LVEF and infarct size or infarct severity. Conversely, there was a significant gender-related difference in the relationship between LVEF and infarct size ( $F = 20.5$ ,  $P < .00001$ ), and between LVEF and infarct severity ( $F = 8.6$ ,  $P < .005$ ). In practice, there was a steeper decrease in LVEF in case of moderate to large infarct size in women than in men.

**Conclusion.** With increasing infarct size, LVEF decreases more sharply in women than in men. Conversely, age does not influence the relationship between infarct dimensions and LVEF. (J Nucl Cardiol 2010)

**Key Words:** Age • gated SPECT • gender • infarct size • infarct severity • left ventricular ejection fraction

### INTRODUCTION

Age is an independent adverse prognostic factor in patients with acute myocardial infarction.<sup>1-3</sup> The use of primary percutaneous coronary intervention (PCI) has improved the prognosis in elderly patients, but age remains an unfavorable predictor also in this setting.<sup>4-9</sup> The mechanisms through which age influences the prog-

nosis are still uncertain. Risk factor profile, angiographic variables and the rate of PCI success do not completely explain the worse prognosis of older patients.<sup>6,7</sup> Whether a larger final infarct size could play a role is unclear. Previous echocardiographic data suggested that elderly patients had a larger infarct zone.<sup>10</sup> However, studies using Tc-99m-sestambi imaging in the thrombolytic era suggested that older patients did not show larger infarct size nor a significantly lower left ventricular ejection fraction (LVEF), although their prognosis was worse than in their younger counterparts.<sup>11,12</sup>

As regards gender, it is known that women show a worse prognosis than men, but this is seemingly related to older age, high-risk factor profile, and unfavorable angiographic features and not to an intrinsic adverse prognostic meaning of female sex.<sup>13,14</sup> Furthermore, previous data suggest that female sex is associated with a smaller infarct size.<sup>15,16</sup> However, the interaction between gender, infarct size, and LVEF has not been established.

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Currently, gated SPECT is the state-of-the-art modality for myocardial perfusion scintigraphy.<sup>17</sup> This method allows the assessment of left ventricular (LV) function during a perfusion scan, and has been reported to be accurate and reproducible.<sup>18-23</sup> In a previous study, we had demonstrated that the relationship between infarct size, infarct severity, and LV functional parameters, all simultaneously derived from a single gated SPECT, is significantly related to the infarct location.<sup>24</sup> Aim of the present study was to evaluate whether the relationships of infarct size and severity vs. LVEF were somehow influenced by age and/or gender in patients submitted to successful primary PCI for acute myocardial infarction.

## MATERIALS AND METHODS

### Patient Population and Study Protocol

The patient population included consecutively the patients admitted from January 2001 until May 2008 to our Cardiology Department because of their first acute myocardial infarction within 6 hours of symptom onset who were submitted to successful primary percutaneous coronary intervention with stenting of the infarct-related vessel, and who were then referred to our Nuclear Medicine laboratory for the assessment of infarct size at one-month. The diagnosis of acute myocardial infarction required the presence of typical chest pain lasting more than 30 minutes together with  $>0.1$  mV ST segment elevation in at least two contiguous electrocardiographic leads. Successful primary percutaneous coronary intervention was defined as Thrombolysis In Myocardial Infarction (TIMI) grade 3 coronary flow in the treated vessel with a residual stenosis  $<20\%$ .<sup>25</sup> ST-segment elevation resolution was evaluated at 30 minutes after PCI.<sup>26</sup> All patients underwent a control angiography at least one-month after index infarction to exclude the occurrence of restenosis of the infarct-related artery. Six-month follow up data were obtained by outpatient visit or telephone interview, and the occurrence of hard events (cardiac death, nonfatal myocardial infarction, hospitalization for congestive heart failure) was registered.

### Gated SPECT

Gated SPECT acquisition began 60 minutes after resting  $^{99m}\text{Tc}$ -sestamibi injection (740 MBq), using a double-head camera (either Picker Irix, Philips Medical System, Andover, MA, USA or SKYlight, Philips Medical Systems, Milpitas, CA, USA) equipped with high-resolution collimators,  $180^\circ$  rotation arc, 34 projections, 60 seconds/projection, 8-frames/heart cycle,  $64 \times 64$  matrices. The studies were reconstructed using filtered backprojection without attenuation or scatter correction and realigned along the heart axis. Infarct size was measured from representative short-axis circumferential count profile curves, with the defect threshold set at 60% of peak uptake.<sup>24,27</sup> Perfusion defects were identified as infarcted

myocardium and expressed as a percentage of the LV.<sup>24,27</sup> In case of detectable perfusion defects, infarct severity was defined as the lowest minimal/maximal counts ratio in the short-axis slices examined for infarct size evaluation; therefore, the lower the ratio the more severe the defect.<sup>24,27-30</sup> The measurement of LVEF was performed by an automated and validated method.<sup>18</sup>

### Statistical Analysis

Variables are expressed as mean value  $\pm$  standard deviation or as median (25th, 75th percentile) as appropriate. The correlation between continuous variables was calculated using the Pearson's correlation coefficient. The comparisons between groups were performed by the Student *t* test for unpaired samples with the Bonferroni correction or the Mann-Whitney *U* test as appropriate. The comparison of proportions was made with the Fisher exact test. The relationships between gender, age, infarct size, infarct severity, and LVEF were analyzed with stepwise multiple linear regression analysis and the analysis of covariance (ANCOVA). The predictors of events at follow up were evaluated using the Cox proportional hazard model. Survival curves were constructed using the Kaplan-Meier method and compared with the log-rank test. A *P* value  $<0.05$  was considered statistically significant.

## RESULTS

The study cohort included 460 patients (359 men and 101 women, mean age  $64 \pm 12$  years, range 23-93). The mean interval between index infarction and gated SPECT was  $35 \pm 7$  days. At the time of gated SPECT all patients were asymptomatic. Table 1 summarizes the main features of the patient population and compares them in men vs. women. Female patients were significantly older, and more frequently hypertensive. Their infarct size was significantly smaller and infarct significantly less severe than those of male patients, and their LVEF significantly higher.

Table 2 compares the features of elderly ( $\geq 75$  years) patients vs. the other patients. Patients in the older age group were more frequently female, had a more severe risk factor profile as regards hypertension and cholesterol, a more severe coronary artery disease pattern with higher prevalence of multivessel disease, and a more severe clinical presentation as indicated by the incidence of Killip class  $> I$ . The infarct size and the infarct severity were similar in the two age groups. The LVEF was comparable as well.

In the whole patient population there was a significant inverse correlation between infarct size and LVEF ( $r = -.643$ ,  $P < .00001$ ) and a significant correlation between infarct severity and LVEF ( $r = .639$ ,  $P < .00001$ ). There were no correlations between age

**Table 1.** Features of the patient population divided according to gender

	<b>Males (n = 359)</b>	<b>Females (n = 101)</b>	<b>P</b>
Age, years, mean $\pm$ SD	62.3 $\pm$ 11.5	71.2 $\pm$ 11.9	<.0001
Family history of coronary artery disease, n (%)	29 (8)	6 (6)	NS
Systemic hypertension, n (%)	137 (38)	56 (55)	<.005
Hypercholesterolemia (total cholesterol >200 mg/dL), n (%)	140 (39)	32 (32)	NS
Recent history of past smoking or current smoker, n (%)	143 (40)	28 (28)	<.05
Diabetes mellitus, n (%)	40 (11)	19 (19)	NS
Time interval symptoms–PCI, min, mean $\pm$ SD	185 $\pm$ 80	202 $\pm$ 87	NS
Anterior infarct location, n (%)	152 (42)	36 (36)	NS
Killip class > I, n (%)	42 (12)	19 (19)	NS
Multivessel coronary artery disease, n (%)	138 (38)	44 (44)	NS
Collateral Rentrop grade $\geq$ 1, n (%)	39 (11)	8 (8)	NS
TIMI grade before PCI, median (25th, 75th percentile)	0 (0,0)	0 (0,1)	NS
Baseline ST-segment elevation, mm, median (25th, 75th percentile)	3 (2,5)	3 (2,4)	<.05
30-minute ST-segment elevation, mm, median (25th, 75th percentile)	1 (0,2)	1 (0,2)	NS
ST-segment elevation resolution, %, mean $\pm$ SD	67.4 $\pm$ 28.1	69.9 $\pm$ 30.8	NS
Infarct size, %, mean $\pm$ SD	18.1 $\pm$ 14	8.8 $\pm$ 10	<.0001
Infarct severity, mean $\pm$ SD	0.43 $\pm$ 0.13	0.50 $\pm$ 0.13	<.0001
LVEF, %, mean $\pm$ SD	46.2 $\pm$ 10.9	54.6 $\pm$ 13.8	<.0001

**Table 2.** Features of the patient population divided according to age

	<b>Age &lt; 75 years (n = 362)</b>	<b>Age <math>\geq</math> 75 years (n = 98)</b>	<b>P</b>
Female sex, n (%)	56 (15)	45 (45)	<.00001
Family history of coronary artery disease, n (%)	34 (9)	1 (1)	<.005
Systemic hypertension, n (%)	138 (38)	55 (56)	<.003
Hypercholesterolemia (total cholesterol >200 mg/dL), n (%)	148 (41)	24 (24)	<.005
Recent history of past smoking or current smoker, n (%)	164 (45)	7 (7)	<.00001
Diabetes mellitus, n (%)	42 (12)	17 (17)	NS
Time interval symptoms–PCI, min, mean $\pm$ SD	186 $\pm$ 82	199 $\pm$ 82	NS
Anterior infarct location, n (%)	152 (42)	36 (37)	NS
Killip class > I, n (%)	38 (10)	23 (23)	<.002
Multivessel coronary artery disease, n (%)	130 (36)	52 (53)	<.005
Collateral Rentrop grade $\geq$ 1, n (%)	41 (11)	6 (6)	NS
TIMI grade before PCI, median (25th, 75th percentile)	0 (0,0)	0 (0,2)	NS
Baseline ST-segment elevation, mm, median (25th, 75th percentile)	3 (2,5)	3 (2,4.125)	NS
30-minute ST-segment elevation, mm, median (25th, 75th percentile)	1 (0,2)	1 (0,2)	NS
ST-segment elevation resolution, %, mean $\pm$ SD	69.4 $\pm$ 27.7	62.7 $\pm$ 31.8	NS
Infarct size, %, mean $\pm$ SD	16.7 $\pm$ 14.1	13.8 $\pm$ 12.6	NS
Infarct severity, mean $\pm$ SD	0.44 $\pm$ 0.13	0.46 $\pm$ 0.13	NS
LVEF, %, mean $\pm$ SD	47.5 $\pm$ 11.6	50 $\pm$ 13.6	NS

and infarct size or infarct severity, and between age and LVEF.

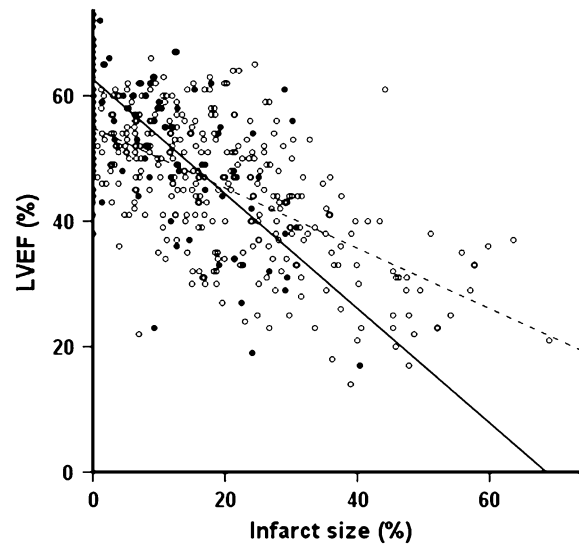
According to stepwise multiple regression analysis examining gender and all other parameters listed in Table 1 that were significantly different between the gender groups, the significant predictors of LVEF were infarct severity, infarct size, gender, and baseline ST segment elevation, with a final model adjusted  $R^2 = .470$  (Table 3). ANCOVA demonstrated a significant effect of gender on the relationship between LVEF, infarct size, and infarct severity:  $F = 12.4$  ( $P < .0005$ ) when both covariates were considered together,  $F = 10$  ( $P < .002$ ), and  $F = 19$  ( $P < .00002$ ), respectively, for infarct size and infarct severity examined separately. The ANCOVA test for parallelism showed a significant difference in the relationship between LVEF, infarct size, and infarct severity between males and females:  $F = 7$  ( $P < .001$ ). The difference was larger for the relationship between LVEF and infarct size than for that between LVEF and infarct severity:  $F = 20.5$  ( $P < .00001$ ) and  $F = 8.6$  ( $P < .005$ ), respectively. These data indicate that the relationship between LVEF and infarct size, and to a minor degree that between LVEF and infarct severity, are modulated by gender. As shown in Figure 1, the relationship between infarct size and LVEF appears clearly steeper in women than in men, with small infarcts showing higher LVEF and larger ones lower LVEF in female than in male patients.

As regards age, including in stepwise multiple regression analysis the age group and all variables listed in Table 2 that were significantly different between elderly and other patients, the significant predictors of LVEF were infarct severity, infarct size, Killip class  $> 1$ , and gender, with a final model adjusted  $R^2 = .480$  (Table 4). ANCOVA did not demonstrate age-related differences in the relationship between LVEF, and infarct size and infarct severity, neither examined together nor separately.

During follow up ( $192 \pm 49$  days) 10 hard events (5 cardiac death, 3 non-fatal myocardial infarctions, and 2 hospitalizations for congestive heart failure) were

**Table 3.** Significant predictors of LVEF selected by multivariate analysis from the variables that were significantly different between men and women

	<b>F value</b>	<b>P</b>
Infarct severity size	324	<.00001
Infarct size	28	<.00001
Gender	12	<.00001
Baseline ST elevation	9	<.005
Adjusted $R^2$ of the model = .470		



**Figure 1.** Scatter plot of infarct size vs. LVEF. Open circles indicate men, and closed circles women. The lines represent the slopes of linear regression for men (dashed line), and women (solid line).

**Table 4.** Significant predictors of LVEF selected by multivariate analysis from the variables that were significantly different between young and elderly patients

	<b>F value</b>	<b>P</b>
Infarct severity size	324	<.00001
Infarct size	28	<.00001
Killip class $> 1$	14	<.00001
Gender	16	<.00001
Adjusted $R^2$ of the model = .480		

registered. As expected because of the small number of events, there were no differences in the Kaplan-Meier survival curves when the patient population was divided according to gender or to age group. In the Cox proportional hazard model including age, gender, LVEF, infarct size, and infarct severity, LVEF was selected as the sole significant event predictor ( $\chi^2 = 11.9$ ,  $P < .001$ ).

## DISCUSSION

LVEF is certainly a major prognostic factor in acute myocardial infarction patients.<sup>31</sup> Infarct dimensions are major determinants of the functional impairment after acute myocardial infarction, as shown by their close (inverse) relationship with the post-infarction LVEF.<sup>31</sup> This relationship is certainly influenced by other

variables, as for instance infarct location.<sup>24</sup> If a parameter causes a more severe decrease in LVEF for the same degree of infarct size or infarct severity this could be a contributory mechanism for its adverse prognostic meaning. Both female sex and old age have been related to worse prognosis after acute myocardial infarction.<sup>1-14</sup> As regards gender, various data suggest that it is not an independent adverse prognosticator, but that it is frequently related to high-risk profile and worse coronary angiographic pattern.<sup>13,14</sup> On the other hand, the reasons why elderly patients have a worse prognosis even after successful reperfusion are not completely clear, and apparently neither larger infarct size nor lower LVEF are involved as causative mechanisms.<sup>11,12</sup> On these premises, we tried to verify whether gender and older age influence the relationship between infarct dimensions and LVEF.

Our results confirm that in patients successfully reperfused with primary PCI advanced age is not related to differences in infarct size, infarct severity, and LVEF. Moreover, there are no differences in the relationships between indicators of infarct dimensions and LVEF based on age as a continuous variable or on advanced age as a dichotomous parameter.

In the same clinical setting, women as a group are confirmed to have significantly smaller and less severe infarctions and higher LVEF than men. However, in our series gender emerges as a significant predictor of LVEF even after correcting for infarct size, infarct severity and the other variables that are different between women and men. In particular, gender modulates the relationship between infarct size (and to a more limited degree, infarct severity) and LVEF. Apparently, females have a steeper decrease of LVEF with increasing infarct size. In part, this can be explained by the high LVEF values registered in women with negligible or small infarctions, a circumstance possibly related also to gated SPECT overestimation of LVEF in small hearts.<sup>32</sup> However, for infarcts of moderate to large extent (as shown in Figure 1, infarct size > approximately 20%) in women there is a trend to a more severe impairment of LVEF than in men. Because of the essential prognostic role of LVEF in acute myocardial infarction patients, which is confirmed also in our small cohort, this could be a contributing factor for explaining the worse prognosis of women after acute myocardial infarction. Naturally, studies on much larger patient populations are needed to confirm this hypothetic connection among gender, infarct size, LVEF, and prognosis.

The results of the present study must be evaluated taking into account its limitations. Our patient population was selected because included only patients with successful early primary PCI. Therefore, different results could be possible in patients submitted to less

effective reperfusion strategies. Furthermore, the very low event rate obtained because of the aggressive treatment, and the short-term follow up preclude a reliable analysis of the prognostic factors. The lack of follow up data with regard to ventricular volumes and function is another major limitation. Certainly the demonstration of more frequent and extensive left ventricular remodeling in women would add a most important link between gender and adverse prognosis.

## CONCLUSION

Our data suggest that age has no influence on the relationship between post-infarction myocardial damage and left ventricular function. Conversely, this relationship is influenced by gender, with women showing the trend to a worse functional response with increasing infarct size.

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