Sex Differences in Myocardial Salvage and Clinical Outcome in Patients With Acute Reperfused ST-Elevation Myocardial Infarction

Advances in Cardiovascular Imaging

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Background—There is conflicting evidence regarding sex-based differences in myocardial salvage and clinical outcome in patients after ST-elevation myocardial infarction (STEMI). The aim of this study was to investigate whether there are sex-associated differences in infarct characteristics (myocardial salvage, infarct size, microvascular obstruction) and clinical outcome in STEMI patients who are reperfused by primary angioplasty.

Methods and Results—In this study, we included 96 women and 239 men with STEMI undergoing primary angioplasty <12 hours after symptom onset. T2-weighted and contrast-enhanced cardiac MRI was used to assess myocardial salvage, infarct size, and microvascular obstruction. The primary clinical end point was mortality within 6 months after the index event. The amount of myocardium at risk and final infarct size did not differ significantly between women and men. Consequently, myocardial salvage was similar between groups (P=0.36). Women had a higher in-hospital (3% versus 10%; P=0.03) and 30-day (5% versus 11%; P=0.05) mortality rate than did men. Six months after infarction, no significant sex differences in survival were obvious (11% versus 7%; P=0.21). After adjustment for baseline differences (age, diabetes, hypertension), female sex was not an independent predictor of mortality and major adverse cardiac events.

Conclusions—The efficacy of primary percutaneous coronary intervention (myocardial salvage) in patients with STEMI is not sex dependent. Although women STEMI patients had worse unadjusted in-hospital and 30-day clinical outcomes than did men, multivariate analysis revealed that the observed sex-based differences in early death after STEMI were likely related to differences in baseline risk and clinical characteristics. (Circ Cardiovasc Imaging. 2012;5:119-126.)

Key Words: myocardial salvage ■ myocardial infarction ■ sex differences ■ MRI

It is unclear whether mortality after acute myocardial infarction is higher among women than in men.1 As a consequence, considerable interest has been focused on the study of sex-based differences in the outcome of myocardial infarction. Numerous studies reported increased mortality rates after ST-elevation myocardial infarction (STEMI) in women, whereas others found no sex differences in mortality, especially after adjustment for differences in age and other prognostic factors.2-17

Clinical Perspective on p 126

Recently, a study demonstrated greater myocardial salvage assessed with single-photon emission computed tomography (SPECT) imaging in women as compared with men.18 The results of this trial have important clinical implications, indicating that the efficacy of primary percutaneous coronary intervention (PCI) in patients with STEMI appears to be sex-dependent. However, SPECT imaging has several limitations, including its low spatial resolution, particularly of subendocardial infarcts; as a result, cardiac MRI (CMR) has emerged as the reference method to assess myocardial salvage.19-21 Furthermore, CMR can visualize additional cardiac markers relevant to primary PCI outcomes (eg, infarct size and microvascular obstruction [MO]).22 To date, no studies have addressed whether there are sex-related differences in the amount of the salvaged area at risk and in other infarct characteristics using CMR.

The aim of this study was therefore to investigate whether there are differences between women and men in the amount of myocardial salvage and myocardial damage (myocardium at risk, infarct size, MO) as assessed by CMR. A secondary objective was to evaluate sex differences in mortality and major adverse cardiac events (MACE) in consecutive STEMI patients who are reperfused by primary PCI.

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Methods
This study was conducted at a single tertiary care center. The local ethics committee approved the study protocol, and all patients gave written informed consent. Patients with STEMI undergoing primary PCI were eligible if onset of symptoms was <12 hours before PCI and if they had ST-segment elevation of at least 0.1 mV in ≥2 extremity leads or at least 0.2 mV in ≥2 precordial leads.

Exclusion criteria were previous fibrinolysis and contraindications to CMR at study entry, such as implanted pacemakers, defibrillators, claustrophobia, or metallic intracranial implants.

Primary PCI and Subsequent Treatment
Primary PCI was performed according to standard clinical practice. The decision to use bare-metal or drug-eluting stents was left to the discretion of the interventional cardiologist.

Additional use of intra-aortic balloon counterpulsation or thrombectomy was performed, depending on the hemodynamic instability and thrombus in the infarct-related artery. All patients received 500 mg of aspirin and heparin (60 U/kg body weight) intravenously before PCI. Clopidogrel (600 mg orally during PCI, if not administered before, followed by 75 mg/d for at least 12 months) was mandatory. Aspirin was given indefinitely at a dose of 100 mg/d. The use of glycoprotein IIb/IIIa inhibitors, angiotensin-converting enzyme inhibitors, β-blockers, and statins was strongly recommended, according to guidelines.23

Angiographic and Enzymatic Analysis
Coronary angiography of the target lesion was performed before and after PCI with the same projections. The angiographic projections used were those that allowed optimal evaluation of the thrombolysis in myocardial infarction (TIMI) flow of the infarct-related artery or of the myocardium supplied by it. Angiographic analysis included initial and final flow of the culprit vessel. Visual assessments were performed offline in the angiographic core laboratory by double-blinded observers.

Plasma samples for creatine kinase (CK) and the CK myocardial band (CK-MB) fraction were collected on admission and subsequently during hospitalization every 6 hours for 2 days.

Cardiovascular Magnetic Resonance Imaging
All CMR examinations were performed on a 1.5 Tesla scanner (Intera CV, Philips Medical Systems) with a dedicated 5-channel, phased-array surface coil in supine position. A cine steady-state-free-precession (SSFP) sequence in a short-axis-orientation (TR, 3.2 ms; TE, 1.2 ms; flip angle, 60°; typical voxel size, 1.7×1.7×8 mm; gap, 0 mm) was acquired for volumetric and functional imaging. For area at risk determination, short-axis slices covering the whole ventricle using a T2-weighted, fat-suppressed, triple inversion recovery breath-hold pulse sequence (TR, 2× RR-interval; TE, 80 ms; flip angle, 180°; typical voxel size, 1.5×1.8×8 mm; gap, 0 mm) were obtained using a body coil. Late gadolinium enhancement imaging (LGE), covering the whole ventricle in a short-axis orientation, was acquired approximately 10 to 15 minutes after intravenous application of 0.15 mmol/kg body weight of gadobutrol (Gadovist) for quantification of scar tissue and late MO. A 3D inversion recovery turbo gradient echo sequence (TR, 2.8 ms; TE, 1.1 ms; flip angle, 15°; typical voxel size, 1.8×1.8×5 mm; gap, 0 mm) was used for image acquisition. Inversion times were individually adjusted to optimize nulling of apparently normal myocardium (typical values, 200–300 ms).

Image Analysis
For all quantitative analyses, certified CMR evaluation software was used (cmr®; Circle Cardiovascular Imaging, Inc.). Offline image analysis was performed by fully blinded observers. Semiautomated, computer-aided threshold detection was used to identify regions of edema, infarcted myocardium, and MO. A myocardial region was regarded as affected if at least 10 adjacent myocardial pixels revealed a signal intensity of >2SD of remote myocardium for edema and >5 SD in LGE images (Figure 1). Infarct size, area at risk, and MO were expressed as percentage of left ventricular (LV) mass, given by the sum of the volume of edema, LGE, and MO regions for all slices divided by the sum of the LV myocardial cross-sectional volumes. In patients with MO, these dark areas were included for infarct size analysis, and the area of MO was assessed separately. Salvaged myocardium was quantified as the difference between the volume of increased T2-signal (area at risk) and the volume of LGE (infarct size) as previously described (Figure 1).24,25 The CMR core laboratory has excellent reproducibility and low inter- and intraobserver variability for infarct size and myocardial salvage assessment.24,25
occurred simultaneously, the most severe event was chosen (death >myocardial reinfarction >congestive heart failure).

Safety
Major safety endpoints were severe or life-threatening or moderate or minor bleeding according to the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) criteria, and the occurrence of any ischemic stroke.

Statistical Analysis
Each categorical variable is expressed as the number and percentage of patients. Most continuous variables had non-normal distribution and are therefore presented as medians together with the interquartile range. Differences between groups were assessed by the Fisher exact or the \( \chi^2 \) test for categorical variables, and by the Student t test for continuous data with normal distribution. Otherwise, the nonparametric Wilcoxon rank-sum test was used. Univariate and multivariate linear regression analyses were performed to characterize predictors of myocardial salvage. For univariate analyses, all variables of Table 1 were tested. All variables showing a significant association (\( P<0.05 \)) with the myocardial salvage index (MSI) at univariate analysis were included in the multivariate model. For the clinical endpoint, the Kaplan-Meier method was applied, and differences were assessed by the log-rank test. Univariate Cox regression analysis was used to identify predictors of mortality and MACE during 6 months after infarction. Significant variables (\( P<0.05 \)) were then tested in a multivariate Cox regression analysis. We performed 3 separate Cox regression models for time to in-hospital death, time to death through 30 days, and time to death through 6 months. All significant predictors of our Cox regression analysis were assessed for possible interaction. \( P \) values for possible interactions were computed with likelihood ratio tests, and models with and without the interaction term were compared. No statistically significant interactions were found. Hazard ratios (HR) with their corresponding 95% CI are reported.

All statistical tests were performed with SPSS software, version 17.0 (SPSS, Inc.). A 2-tailed probability value \( <0.05 \) was considered statistically significant.

Results
Of 345 eligible STEMI patients, this study included 335 patients (Figure 2). Results of CMR imaging were available in 297 patients (89%). Reasons for not undergoing CMR are listed in Figure 2.

Patient Characteristics
Demographic and clinical characteristics are shown in Table 1. Women were older, had significantly higher incidence of diabetes, and presented later in the hospital after symptom onset as compared with men. No other significant differences were observed between the sexes with regard to angiographic or procedural characteristics. Almost all patients received glycoprotein IIb/IIIa-inhibitors after PCI (92%). There were no significant baseline differences (age, cardiovascular risk factors, reperfusion times, angiographic characteristics) in patients undergoing and those not undergoing CMR.

Sex and Infarct Characteristics
Median time between the index event and CMR was 3 days (interquartile range, 2–4) for both groups. The myocardium at risk and infarct size did not differ significantly between women and men (Figure 3). Consequently, no differences in myocardial salvage could be observed. The occurrence and extent of MO were similar between women and men, despite longer ischemic time and an increased cardiovascular risk profile in women. No sex disparities in LV ejection fraction were detected (Table 2).

Predictors of Myocardial Salvage
Female sex was not a significant predictor of myocardial salvage in our linear regression analysis (\( P=0.63 \)). In a multivariate regression model adjusted for significant variables in univariate regression analysis using myocardial salvage index as the dependent variable, anterior myocardial infarction (\( P<0.001 \)), Killip class on admission (\( P<0.001 \)), time from symptom onset to reperfusion (\( P=0.01 \)), and TIMI flow grade before PCI (\( P=0.008 \)) were the most statistically significant predictors of myocardial salvage.

Sex and Clinical Outcome
Eighteen patients (5%) died in the hospital. Women had a significantly higher in-hospital mortality as compared with men (10 deaths [10%] versus 8 deaths [3%]; HR, 2.81 [CI, 1.09–7.30; \( P=0.03 \))]. Thirty days after infarction, 11 women (11%) versus 13 men (5%) died (HR, 6.21 [CI, 1.00–4.86; \( P=0.05 \)); Figure 4). After multivariate adjustment for clinical characteristics, sex was not a significant predictor of in-hospital mortality (HR, 1.93 [CI, 0.72–5.30; \( P=0.20 \)]) or 30-day mortality (HR, 1.29; [CI, 0.52–3.22; \( P=0.59 \)]. Likewise, after 6 months, no significant sex differences in survival were obvious (11 deaths [11%] versus 17 deaths [7%]; unadjusted HR, 1.61 [CI, 0.76–3.45]; \( P=0.21 \)). Kaplan-Meier plots of survival according to sex are shown in Figure 5.

The causes of death of the men were as follows: cardiogenic shock (n=4), recurrent infarction (n=4), stroke (n=3), sudden cardiac death (n=2), ventricular septal defect (n=1), pulmonary embolism (n=1), cancer (n=1), and unknown (n=1). Women died because of the following causes: cardiogenic shock (n=3), sudden cardiac death (n=2), recurrent infarction (n=2), ventricular septal defect (n=1), LV free wall rupture (n=1), stroke (n=1), and cancer (n=1).

Nonfatal reinfarctions (2 [2%] versus 10 [4%]; \( P=0.35 \)) and congestive heart failure (4 [4%] versus 9 [5%]; \( P=0.54 \)) were similar between men and women, respectively. Consequently, at 6 months follow-up, no sex disparities in MACE were observed (36 events [15%] versus 17 events [18%] in men and women, respectively; \( P=0.16 \)).

The relationships between sex and age as well as sex and diabetes were evaluated to assess whether a different mortality risk existed in women compared with men. Overall, no significant interaction was detected between sex and age (\( P=0.59 \)), whereas diabetic women had a significantly higher mortality 6 months after infarction as compared with diabetic men (\( P=0.03 \)). The prevalence of diabetes was 83% in women who died within 6 months after the index event.

Safety
There were no differences in bleeding according to the GUSTO severity criteria in women versus men (severe/life-threatening: 1% versus 1%, respectively; \( P=0.96 \); moderate: 3% versus 4%, respectively; \( P=0.58 \); mild: 6% versus 6%, respectively; \( P=0.96 \)). In addition, there was 1 ischemic stroke (1%) in the women and 3 ischemic strokes (1%) in the men (\( P=0.98 \)).
Discussion

In this study, we analyzed the relationship between sex and outcomes as well as sex and myocardial salvage in an unselected and consecutive population of patients with STEMI exclusively reperfused by primary PCI. The main finding of our study is that the efficacy of primary PCI (myocardial salvage) in patients with STEMI is not sex-dependent. Second, although women STEMI patients had higher unadjusted in-hospital and 30-day mortality rates than did men, multivariate analysis revealed that these differences were likely because of disparities in baseline risk.

Sex and Outcome

Although several studies have shown an improvement of prognosis in women with coronary artery disease and myocardial infarction, overall outcomes remain worse for women
compared with men. Studies have highlighted important sex differences in the pathophysiology, presentation, treatment, and ultimately outcome of ischemic heart disease. However, in high-risk patients with STEMI, there is much controversy and conflicting evidence in the literature, with some studies demonstrating better and others worse survival rates in women. Whether sex disparities in clinical care and death after STEMI are still present in the current PCI era remains a matter of constant debate and has important clinical implications.

Consistent with previous reports, we found that women had a higher baseline risk profile than did men. Women as a group were older with more comorbidities than men, including hypertension and particularly diabetes. Of note, women had also significantly longer pain-to-balloon times as compared with men. This is in line with previous studies that have identified sex, age, and socioeconomic status as factors associated with a delay in presentation in STEMI patients. Such evidence of delayed reperfusion among women compared with men highlights the need to improve awareness of risk for ischemic heart disease and provision of healthcare among women.

Women hospitalized for STEMI have also been shown to receive less aggressive medical and invasive treatments. These gaps may in part derive from bleeding concerns among women. Although some have found that the treatment differences are small and do not affect mortality, others have attributed the sex disparities in death after STEMI to these treatment differences. Thus, the extent to which mortality differences between men and women are related to dis-

Table 2. Cardiovascular Magnetic Resonance Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Male</th>
<th>Female</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>219</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Area at risk/edema, % LV</td>
<td>33.7 (26.5–42.5)</td>
<td>35.8 (28.0–45.5)</td>
<td>0.28</td>
</tr>
<tr>
<td>Infarct size, % LV</td>
<td>16.6 (8.3–25.7)</td>
<td>13.7 (9.6–26.9)</td>
<td>0.89</td>
</tr>
<tr>
<td>Presence of late microvascular obstruction</td>
<td>161 (74)</td>
<td>55 (71)</td>
<td>0.54</td>
</tr>
<tr>
<td>Late microvascular obstruction, % LV</td>
<td>0.8 (0.1–2.9)</td>
<td>0.6 (0.0–1.2)</td>
<td>0.07</td>
</tr>
<tr>
<td>Myocardial salvage, % LV</td>
<td>14.6 (8.8–25.1)</td>
<td>17.7 (8.9–25.0)</td>
<td>0.36</td>
</tr>
<tr>
<td>Myocardial salvage index</td>
<td>46.8 (28.6–70.5)</td>
<td>48.0 (30.9–73.5)</td>
<td>0.72</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>52.8 (43.3–61.8)</td>
<td>52.6 (42.7–60.5)</td>
<td>0.41</td>
</tr>
<tr>
<td>LV enddiastolic volume index, mL/m²</td>
<td>70.2 (59.2–82.4)</td>
<td>67.4 (57.6–78.7)</td>
<td>0.16</td>
</tr>
<tr>
<td>LV endystolic volume index, mL/m²</td>
<td>33.4 (23.7–44.3)</td>
<td>30.9 (23.2–41.0)</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Data are presented as median and interquartile range.
LV indicates left ventricle.
*LV enddiastolic volume and LV endystolic volume indexed by body surface area.
crepancies in baseline risk versus treatment bias remains unknown.

In our study, men and women were treated identically with primary PCI and with large use of glycoprotein IIb/IIIa inhibitors. There were no in-hospital treatment delays, as reflected by an excellent door-to-balloon time in both women and men patients. The efficacy of primary PCI (myocardial salvage and other infarct characteristics) was not sex-dependent and, importantly, no safety concerns were observed; 96% of the women received aggressive antiplatelet therapy with glycoprotein IIb/IIIa inhibitors as an adjunct to PCI. To the best of our knowledge, this data set included a higher use of glycoprotein IIb/IIIa inhibitors than in any sex-specific data previously reported. Our data support a recent joint statement of the American Heart Association and the American College of Cardiology on PCI and adjunctive pharmacotherapy in women, suggesting the same procedures and adjunctive therapies in women that have been shown to be beneficial in men.30 Moreover, our data highlight that once women are referred for cardiac catheterization, revascularization practices, success, and complications are similar to those in men.

In the present study, we observed a higher unadjusted in-hospital and 30-day mortality rate for women than for men; however, much of this difference was attenuated following adjustment for baseline differences at the time of presentation. Six months after infarction, sex differences were no longer observed between women and men. Multiple studies have shown the increased death among women to be related to their higher baseline risk.9,12–16 These results lend support to the notion that sex by itself, in the current PCI era, does not independently predict death after STEMI. Regardless, women presenting with STEMI appear to be at high risk of death in the initial 30 days and they represent a subgroup of patients in whom prompt and aggressive therapies are warranted. In line with other studies,21,32 we confirmed that diabetes is associated with a greater mortality risk in women than in men. Thus, diabetic women may represent a distinct high-risk group. Additional prospective studies are needed to ascertain conclusively this observation.

Sex and Infarct Characteristics

It has been speculated that the efficacy of primary PCI in patients with STEMI appears to be sex-dependent.18 This may improve the chances of survival of women, despite their more adverse cardiovascular profile. Fundamental sex-specific differences exist in endothelial vascular function, arterial compliance, microvascular function, insulin resistance, lipid metabolism, and inflammation.33,34 Also, sex-specific differences exist in the way the LV remodels in response to cardiac stress and infarction.35 These differences could translate into sex-specific PCI outcomes in acute reperfused STEMI. In our study, no sex-associated differences in myocardial salvage and reperfusion injury could be observed. Our study is the first using CMR for assessment of sex-specific reperfusion therapy efficacy. CMR can provide a wide range of prognostic information in acute STEMI by detecting the area at risk, infarct size, MO, and myocardial salvage, and is thus ideally suited to assess differences in infarct characteristics in women versus men.20–22 Notably, because of its higher resolution, CMR detects subendocardial infarcts that are missed by SPECT.19 In contrast to a recent SPECT study,18 our data clearly underline that PCI is similarly effective in women and men and that women should receive the same aggressive treatment for STEMI as do men.

Limitations

Some limitations need attention. This study represents a single-center experience with a limited number of patients. Some patients had to be excluded from CMR myocardial salvage assessment. Because the baseline characteristics of patients undergoing and those not undergoing CMR were similar, a potential selection bias is limited. Furthermore, these patients were included in the analysis of clinical adverse events. Infarct size, myocardial edema, MO, and myocardial salvage are dynamic processes after acute infarction. Imaging time after reperfusion is thus an important determinant for the presence and extent of MO, as well as is infarct size. As in our study, both groups underwent CMR after a similar time delay; therefore, a potential bias is unlikely.

Conclusions

The efficacy of primary PCI (myocardial salvage) in patients with STEMI is not sex-dependent. Although women STEMI patients had worse unadjusted in-hospital and 30-day clinical outcomes than did men, multivariate analysis revealed that the observed sex-based differences in early death after STEMI were likely related to differences in baseline risk and clinical characteristics.
Disclosures

None.

References


CLINICAL PERSPECTIVE

Studies have highlighted important sex differences in the pathophysiology, presentation, treatment, and outcome of ischemic heart disease. It has been also speculated that the efficacy (myocardial salvage) of primary percutaneous coronary intervention (PCI) in high-risk patients with ST-elevation myocardial infarction (STEMI) appears to be sex-dependent. Whether sex disparities in clinical care and death after STEMI are still present in the current PCI era remains a matter of constant debate and has important clinical implications. In this study, we analyzed the relationship between sex and outcomes as well as sex and myocardial salvage in an unselected and consecutive population of patients with STEMI exclusively reperfused by primary PCI. Our study is the first using cardiac MRI for assessment of sex-specific reperfusion therapy efficacy. We observed no sex-associated differences in myocardial salvage and reperfusion injury. Although women STEMI patients had higher unadjusted in-hospital and 30-day mortality rates than did men, multivariate analysis revealed that these differences were likely because of disparities in baseline risk. Thus, our data highlight that sex by itself, in the current PCI era, does not independently predict death after STEMI and that once women are referred for cardiac catheterization, revascularization practices, success, and complications are similar to those in men.
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