Impact of gender differences on myocardial salvage and post-ischaemic left ventricular remodelling after primary coronary angioplasty: new insights from cardiovascular magnetic resonance

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Received 10 February 2012; accepted after revision 29 March 2012; online publish-ahead-of-print 24 April 2012

Aims
There is conflicting evidence on the impact of gender on reperfusion after primary coronary angioplasty (PPCI), and on left ventricular (LV) remodelling (LVR). In a cohort of patients with reperfused ST elevation myocardial infarction (STEMI), gender-related differences on myocardial reperfusion, and sex-related differences on LVR were assessed by using a comprehensive cardiac magnetic resonance (CMR) approach.

Methods and results
In four tertiary referral centres, 283 (238 males and 45 females) consecutive STEMI patients, treated with PPCI within 12 h from symptoms onset underwent CMR 3±2 days after STEMI and at 4-month follow-up. By CMR, the area at risk, infarct size (IS), microvascular obstruction (MVO), and myocardial salvage index (MSI) were assessed. Women were older than men \((P = 0.014)\), more hypertensive \((P < 0.001)\) and more frequently presented with pre-infarct angina \((P = 0.018)\). An MSI extent was significantly higher \((P = 0.013)\), IS was significantly smaller at both time points \((P < 0.001)\), follow-up \((P < 0.001)\), and the MVO extent was significantly smaller \((P < 0.001)\) in women. At multivariate analysis, Killip class and female sex were independently associated with a higher MSI \((P = 0.02, P = 0.05, \text{ respectively})\). A similar incidence of LVR in both sexes was observed at follow-up \((P = 0.808)\).

Conclusions
The better reperfusion pattern observed in women by CMR in our population of reperfused STEMI suggests sex-based differences exist. No gender differences were observed with respect to incidence of LV remodelling at the follow-up mainly occurring in the subset of patients with a larger IS.

Keywords
Acute myocardial infarction • Myocardial perfusion • Gender difference

Introduction
Contemporary evidence on the clinical outcome by gender following primary percutaneous coronary intervention (PPCI) for acute ST elevation myocardial infarction (STEMI) is lacking. In particular, it is still unclear whether sex differences can modulate the response to reperfusion treatment after PPCI and then outcome. Although the remodelling process appears to be more favourable in women than men,1 females are known to have a higher incidence of adverse outcomes after STEMI.2–4 The increased mortality after
myocardial infarction in women was explained by their older age and more associated risk factors at hospital presentation. However, recent studies demonstrated that after adjustment for baseline clinical characteristics, sex-based differences in early death after acute coronary syndrome remained evident in STEMI population. Whether the increased mortality in women is due to the frequent co-existence of adverse co-morbid features or to other unidentified risk factors remains unsettled.

Since the outcome after acute myocardial infarction is closely related to the tissue level perfusion after revascularization and to the infarct size (IS), possible interactions between gender, myocardial salvage, IS, and post-infarction left ventricular (LV) remodelling (LVR) should be investigated.

Cardiovascular magnetic resonance (CMR) allows an accurate and reproducible determination of acute and chronic IS and microvascular obstruction (MVO) by the late gadolinium enhancement (LGE) technique. Additionally, early post-infarction T2-weighted CMR enables to quantify the area at risk (AAR) and the amount of salvaged myocardium by combining T2-weighted and LGE imaging.

The aim of this study was to evaluate possible gender-related differences in myocardial salvage after reperfusion and in post-ischaemic LVR by studying a cohort of patients with reperfused STEMI by using a comprehensive CMR approach.

Methods

Study population

Between May 2006 and April 2009, 283 consecutive STEMI patients were prospectively studied by CMR 3 ± 2 days after STEMI and at 4-month follow-up in four tertiary referral centres [UZ Leuven, Leuven-Belgium (centre A), Sapienza University Hospital, Rome, Italy (centre B), Fondazione G.Monasterio, Pisa, Italy (centre C), and Bristol Heart Institute (centre D)].

Inclusion criteria were: (i) typical chest pain lasting >30 min and unresolved by nitro-glycerine, (ii) ST segment elevation >0.2 mV in at least two contiguous leads in the initial electrocardiogram, (iii) elevated markers of myocardial necrosis, (iv) treatment with PPCI within 12 h from symptoms onset.

Exclusion criteria were: (i) cardiogenic shock or clinical instability (Killip class IV); (ii) previous myocardial infarction or coronary artery by-pass graft; (iii) contraindications to perform CMR; (iv) rescue or facilitated PCI. The Ethical Committee of the Institutions involved approved the study and all patients gave informed consent to participate.

Baseline clinical characteristics of patients were collected and the study population was divided into males and females.

CMR protocol

The CMR studies were performed at centre A and D with 1.5 T unit (Intera-CV, Philips, Best-The Netherlands), at centre B with 1.5 T unit (Avanto-Siemens, Erlangen-Germany), and at centre C with 1.5 T unit (CVi-GE Healthcare, Milwaukee, WI, USA). All studies were performed using dedicated cardiac software, phased-array surface receiver coil, and electrocardiograph triggering. A similar CMR study protocol was followed in all centres as previously described.

In brief, all patients were imaged in supine position. After determination of cardiac axes with localizers, breath-hold steady-state free-precession cine CMR was performed in cardiac vertical and horizontal long-axis, and in short-axis orientation. In cardiac short-axis, both ventricles were completely encompassed by a stack of contiguous slices. Next, AAR was determined using breath-hold black-blood T2-weighted short inversion-time inversion-recovery fast spin-echo sequence in cardiac short-axis. Post-contrast breath-hold T1-weighted two-dimensional (Avanto-Siemens/CVi, GE Healthcare) or three-dimensional (Intera-CV, Philips) inversion-recovery segmented gradient-echo sequence was used to detect MVO and IS. An i.v. contrast agent dose of 0.1–0.2 mmol/kg Gadolinium-BOPTA (Multihance, Bracco, Milan, Italy) or Gadolinium-DOTA (Dotarem, Guerbet-France) was used. Early and late post-contrast imaging were performed immediately after 10–20 min following contrast administration to assess the presence of MVO and IS, respectively. The inversion time was individually adapted to nullify the signal of remote myocardium. At 4-month follow-up, the same CMR protocol was used with exception for T2-weighted imaging.

Image analysis

CMR images were analysed as used previously described. In brief, all studies were analysed offline using the cardiac vendor independent software (CardioViewer) by consensus of two experienced observers. Both operators were unaware of clinical and angiographic data. Analysis was started by scoring T2-weighted imaging quality using a 4-grade score: (1) poor, (2) moderate, (3) good, and (4) excellent. Only exams scored >1 were considered for further analysis. Myocardial oedema was considered present when signal intensity (SI) was >2 SD above the mean SI of the remote myocardium. The extent of AAR was obtained by manually drawing the region of interest, and expressed as LV percentage. Myocardial regions were considered infarcted if the SI was >5 SDs above the remote myocardium. MVO was defined as hypo-enhanced region within the hyperintense myocardium. IS and MVO were manually traced and calculated from the LGE short-axis images and expressed as percentage of LV mass. The myocardial salvage index (MSI) was defined as the difference between the AAR extent and the baseline IS divided by the AAR. The left ventricle was segmented based on 17-segment model according to AHA recommendation. Cine CMR was used to derive the LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), LV ejection fraction (LVEF), and LV mass. LV volumes and mass were normalized for the body surface area. Follow-up variation (Δ) of the LVEDV was determined as the difference between the LV end-diastolic BSA-indexed volume (LVEDVi) at the follow-up and the LVEDVi at baseline divided by the LVEDVi at baseline, and expressed in percentages. A ΔLVEDVi >20% was considered to represent adverse LV remodeling.

Percutaneous coronary intervention and medications

PPCI and stenting of the infarct-related artery was performed in all patients as previously described. The decision whether to use glycoprotein IIb/IIIa inhibitors, angiotensin-converting enzyme inhibitors or angiotensin-II-receptor antagonists, beta-blockers, and statins was left at the discretion of each centre. TIMI grade was semi-quantitatively scored as previously described. A successful angioplasty was defined by the combination of post-procedural TIMI flow grade 3 and residual stenosis <30%. Time-to-reperfusion was defined as the interval from symptoms onset to the first balloon inflation.

Statistical analysis

Statistical analysis was performed with the use of the SPSS software package for Windows v. 16.0 (SPSS, Inc., Chicago IL, USA). All
categorical variables are expressed as percentages and all continuous variables as mean ± SD. Differences between means were calculated using an unpaired t-test or Mann–Whitney test if variables were not normally distributed, whereas differences between categorical variables were analysed by Pearson’s χ² test.

Univariate and multivariate linear regression analyses were used to assess the independent impact of gender on myocardial salvage, while adjusting for other variables by using the stepwise method. The following parameters were entered into the model: age, diabetes, hypertension, dyslipidaemia, smoking, Killip class, anterior infarction, time-to-admission interval, initial TIMI flow grade, and pre-infarct angina. Only variables with a P-value < 0.25 at univariate analysis were entered into the multivariable model as covariates. A two-tailed P < 0.05 was considered statistically significant.

Results

Of the 283 patients enrolled in the study, 45 were females (16%) and 238 (84%) males. Clinical and angiographic characteristics at presentation are shown in Table 1. Females were older (P = 0.014), more frequently hypertensive (P < 0.001) and experienced more often pre-infarct angina than men (P = 0.02). Peak troponin release was significantly lower in females (P = 0.019). No significant differences were found for the other clinical variables; in particular, time-to-treatment and anterior location were similar. A statistically significant in-hospital underuse of statins (P = 0.001) and β-blockers (P = 0.001) in women was observed. Also a trend towards less antiplatelets use in women was detected (75 vs. 84%, P = 0.144) (Table 2).

LV end-systolic BSA-indexed volume (LVESVi) and LVEDVi were significantly smaller in women than in men, both in the acute phase and at the follow-up (LVESVi: P = 0.001 and P = 0.008, and LVEDVi: P = 0.001 and P = 0.002, respectively) (Table 3). At the follow-up a similar slight increase in the LVEDVi was observed in both sexes (+5.5% in females and +4.8% in males); the LVEF was higher in females (acute: P = 0.01; follow-up, P = 0.005). Also, the reperfusion pattern was better in females (Table 3); despite a similar AAR (P = 0.856), M0% was significantly greater in women (P = 0.013) reflecting smaller IS in the acute phase (P < 0.001) and at the follow-up (P < 0.001) and less MVO (P < 0.001). At univariate analysis, a significant association between female gender and myocardial salvage was detected. After adjustment in the multivariate model, female gender remained an independent factor associated with higher myocardial salvage after reperfusion together with Killip class (Table 4).

LVR occurred at the follow-up in 46 of 238 (19%) male and in 8 of 45 (18%) female patients without statistical difference (P = 0.808) (ΔLVEDV 23% in males, ΔLVESD 17% in females, P = 0.748) (Table 3). IS was significantly greater in remodelling patients (LVR-IS acute = 25 ± 19 vs. 16 ± 11%, in patients without LVR, P = 0.001), and, M0% was significantly lower in patients with LVR (0.44 ± 0.2 in LVR patients vs. 0.53 ± 0.2 in non-LVR patients, P = 0.032). No gender difference was observed in the remodelling cohort for both parameters (LVR-IS acute, 29 ± 23% in males vs. 21 ± 13% in females, P = 0.327 and LVR-M0%, 0.39 ± 0.2 in males vs. 0.49 ± 0.2 in females, P = 0.295).

### Table 1 Study population: clinical and angiographic characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Male (n = 238)</th>
<th>Female (n = 45)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>57 ± 10</td>
<td>62 ± 11</td>
<td>0.014</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>82 (34)</td>
<td>29 (64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>136 (57)</td>
<td>25 (55)</td>
<td>0.843</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>29 (12)</td>
<td>6 (13)</td>
<td>0.830</td>
</tr>
<tr>
<td>Dyslipidaemia (%)</td>
<td>122 (51)</td>
<td>26 (57)</td>
<td>0.442</td>
</tr>
<tr>
<td>Family history CAD (%)</td>
<td>96 (40)</td>
<td>19 (42)</td>
<td>0.813</td>
</tr>
<tr>
<td>Pre-infarct angina (%)</td>
<td>27 (11)</td>
<td>11 (24)</td>
<td>0.018</td>
</tr>
<tr>
<td>BSA</td>
<td>2.06 ± 1.1</td>
<td>1.71 ± 0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Killip class (%)</td>
<td>1.3 ± 0.6</td>
<td>1.4 ± 0.6</td>
<td>0.318</td>
</tr>
<tr>
<td>I (%)</td>
<td>158 (66)</td>
<td>28 (63)</td>
<td>0.589</td>
</tr>
<tr>
<td>II (%)</td>
<td>55 (23)</td>
<td>12 (26)</td>
<td>0.606</td>
</tr>
<tr>
<td>III (%)</td>
<td>25 (11)</td>
<td>5 (11)</td>
<td>0.768</td>
</tr>
<tr>
<td>Time to reperfusion (min)</td>
<td>260 ± 15</td>
<td>264 ± 160</td>
<td>0.864</td>
</tr>
<tr>
<td>Maximum serum troponin I (ng/mL)</td>
<td>103 ± 112</td>
<td>65 ± 91</td>
<td>0.019</td>
</tr>
<tr>
<td>CK-MB, peak (ng/mL)</td>
<td>274 ± 158</td>
<td>217 ± 180</td>
<td>0.215</td>
</tr>
<tr>
<td>STEMI location (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior 0–1 (%)</td>
<td>118 (49)</td>
<td>27 (60)</td>
<td>0.199</td>
</tr>
<tr>
<td>Non-anterior 0–1 (%)</td>
<td>120 (50)</td>
<td>18 (40)</td>
<td>0.336</td>
</tr>
<tr>
<td>Angiographic data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infarct-related artery (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>114 (47)</td>
<td>26 (57)</td>
<td>0.224</td>
</tr>
<tr>
<td>LCX</td>
<td>29 (12)</td>
<td>2 (4.6)</td>
<td>0.127</td>
</tr>
<tr>
<td>RCA</td>
<td>95 (39)</td>
<td>17 (37)</td>
<td>0.787</td>
</tr>
<tr>
<td>TIMI flow pre (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>168 (70)</td>
<td>29 (64)</td>
<td>0.411</td>
</tr>
<tr>
<td>2–3</td>
<td>70 (29)</td>
<td>16 (35)</td>
<td>0.626</td>
</tr>
<tr>
<td>TIMI flow post (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>8 (3)</td>
<td>3 (6)</td>
<td>0.501</td>
</tr>
<tr>
<td>2–3</td>
<td>230 (96)</td>
<td>42 (93)</td>
<td>0.946</td>
</tr>
</tbody>
</table>

LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery. Continuous variables are expressed as mean ± SD. Categorical variables are expressed as frequency with percentage.

### Table 2 In-hospital medications

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Male (n = 238)</th>
<th>Female (n = 45)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-I or ARBs, n (%)</td>
<td>210 (88)</td>
<td>37 (82)</td>
<td>0.266</td>
</tr>
<tr>
<td>β-Blockers, n (%)</td>
<td>214 (89)</td>
<td>31 (68)</td>
<td>0.001</td>
</tr>
<tr>
<td>Aspirin, n (%)</td>
<td>232 (97)</td>
<td>42 (93)</td>
<td>0.146</td>
</tr>
<tr>
<td>Statins, n (%)</td>
<td>222 (93)</td>
<td>35 (77)</td>
<td>0.001</td>
</tr>
<tr>
<td>Glycoprotein inhibitor IIb/IIIa, n (%)</td>
<td>201 (84)</td>
<td>34 (75)</td>
<td>0.144</td>
</tr>
</tbody>
</table>
In our STEMI population, we observed higher myocardial salvage, smaller IS, and microvascular damage in women after PPCI showing sex-based differences in the acute phase after reperfusion. Female gender per se had an independent impact on myocardial salvage. The favourable myocardial indices after reperfusion in women compared with men occurred despite their older age and increased prevalence of hypertension at presentation, suggesting that gender may account for the differences in the response to ischaemic injury.

At 4-month follow-up a similar incidence of LVR was detected. However, adverse remodelling was detected only in the subset of patients with a larger IS and lower MSI without any gender difference, further demonstrating the key role of these two parameters in LVR occurrence.

**Gender, ischaemic damage, myocardial reperfusion, and salvaged myocardium**

Different response to ischaemic injury in the two sexes has been investigated for long time. Pioneering studies reported greater sensitivity to aggregating stimuli and greater benefit from effective antiplatelet inhibition in women. Moreover, it has been observed that women more frequently present with pre-infarct angina, as in our series of patients, and as a consequence of ischaemic preconditioning, may have enhanced spontaneous thrombolysis and better cellular hypoxic tolerance. All these factors may contribute to the more favourable myocardial reperfusion pattern observed in our female STEMI population.

By using SPECT imaging, Mehilli et al. previously observed a greater myocardial salvage after primary PCI in women. However, patients included in the Mehilli et al. study were derived from three randomized trials (STOPAMI-1,-2,-3) comparing different reperfusion strategies. By using CMR, a more robust imaging technique for detection of myocardial necrosis, our study confirms and extends this previous observation in a more uniform population, all treated with primary PCI. We report greater myocardial salvage in women, smaller IS in the acute phase and at the follow-up and smaller microvascular damage than men, despite less favourable clinical characteristics at presentation. Consistent with previous reports showing a higher cardiovascular risk profile in women at hospital admission, our female STEMI population was older and more hypertensive. Thus, the better reperfusion pattern in women is probably attributable to gender-related differences in response to ischaemic injury and ischaemic preconditioning.

The ‘ischaemic time’ was similar in our two groups of patients. Previous studies evaluated the influence of time-to-reperfusion on salvaged myocardium. Despite conflicting results, experimental and clinical trials using CMR the duration of ischaemia is one of the major determinants of myocardial salvage and consequently of definitive IS and MVO. Since time from symptom onset-to-balloon was similar between men and women, other factors account for the greater myocardial salvage observed in women, in particular the incidence of pre-infarct angina, a key protector against ischaemia/reperfusion damage. In a recent study by Eitel et al. using CMR, no gender differences were observed in terms of IS and myocardial salvage after coronary reperfusion in a large STEMI population. However, differently from our study, time-to-reperfusion was significantly longer (180 vs. 250 min in females, $P = 0.004$) and anterior infarct location was more common in females (44 vs. 58% in females, $P = 0.01$). These two important factor may strongly contributed to mask the improved time-to-reperfusion.
The efficacy of primary PCI in women previously observed by Mehilli et al.24 and confirmed by our data.

**Gender and left ventricular remodelling**

Conflicting data exist on the impact of gender on LVR. Experimental studies suggest the presence of important differences in cardiac remodelling between females and men.1 The remodelling process appears to be more favourable in women than in men. Post-ischaemic LVR is a complex multifactorial process in which myocardial hypertrophy, fibrosis, ventricular dilation, but also apoptosis and autophagy at the cellular level, play a complex role.34 Post-mortem data suggest that males and females may have a different modulation of the apoptotic pathway in the peri-infarct region.1,35 Females appear to be, at least partially, protected from ischaemia-induced activation of the apoptotic cascade.3,35 Further, microvascular perfusion plays an important role in protecting against adverse remodelling processes.11,12,36 Despite the advantageous reperfusion pattern in females, and the biological advantages described before, the incidence of LVR, in our series of STEMI patients, was similar. These data are in agreement with our previous multicentre study investigating the determinants of adverse remodelling where no correlation was found between gender and LVR.17 However, adverse remodelling occurred only in women with a larger IS and a lower MSI without any gender difference, further demonstrating the key role of these two parameters in favouring LVR.

In the present study, women were significantly older than men. The well-known harmful impact of ageing37 on post-infarction LVR could probably also play a role. Furthermore, it has been demonstrated that loss of oestrogen protection enhances LVR in rats subjected to chronic volume or pressure overload18,39 and also increases fibrosis development after myocardial infarction by interfering with matrix metalloproteinase-2 transcription.40 The mean female age in our study population was 62 ± 11 years, thus the majority of women were post-menopausal without oestrogen protection.

It is also important to underline the impact of medical therapy to prevent adverse LVR. A statistically significant in-hospital underuse of statins and β-blockers in women was observed in our study. A recent meta-analysis41 and also other cohort studies8–10 confirm that women with acute coronary syndrome are less likely to receive aspirin, β-blockers or glycoprotein IIb/IIIa inhibitors. Moreover, it has been reported that the impact of glycoprotein IIb/IIIa inhibitors on major adverse coronary events at 30 days after PPCI is age dependent42 underlyng again the tight relation between age and response to pharmacological therapy. These findings could further contribute to the similar incidence of LVR observed in our study.

In conclusion, coronary reperfusion seems more effective in women. Application of guideline-indicated therapy after acute coronary syndromes is strongly recommended in women in order to protect their higher amount of salvaged myocardium in the acute phase.

**Study limitations**

The study population shows a numeric disparity between men and women but this difference is in line with other clinical studies, clearly showing the lower incidence of STEMI in women.1–10,24,30 However, we cannot exclude that our results may be partially influenced by this sex disparity. Further larger studies are needed to confirm our data. Only consecutive STEMI patients successfully and timely reperfused with PPCI and studied by CMR were selected for this study. Therefore, the impact of gender difference on myocardial salvage and LVR in a general population with acute myocardial infarction and in particular in high-risk STEMI patients suboptimally treated cannot be derived. The conclusion of our study may not be applied to sicker patients, with a greater degree of LV dysfunction. However, the multicentre design of the study adds strength to the results, and the data set collected allows drawing conclusions with sufficient statistical power. Finally, our study is not powered to evaluate the impact of gender difference on major adverse coronary events and long terms mortality. In line with previous reports,2,6–10 also our female STEMI population was older and more hypertensive at hospital admission. Larger studies are needed to assess if the better reperfusion pattern observed in women may counterbalance, at long term, the higher risk profile.

**Conclusion**

By using a comprehensive CMR approach, our multicentre study shows a greater myocardial salvage in women, a smaller IS in the acute phase and at 4-month follow-up, and less microvascular damage than in men. Thus, women, if adequately and timely treated, show a better myocardial reperfusion pattern despite an adverse cardiovascular profile at presentation. The higher incidence of pre-infarct angina in women and otherwise-unidentified biological factors could play a key role in mediating a gender-based difference after reperfusion, and protecting against myocardial ischaemia/reperfusion damage.

No gender differences were observed with respect to incidence of LVR at the follow-up mainly occurring in the subset of patients with a larger IS. The harmful impact of ageing and the in-hospital under-treatment in women may also contribute to the similar incidence of post-infarction LVR. Larger clinical trials are needed to better understand biological or clinical factors involved in enhanced reperfusion pattern observed in women, whereas greater attention should be paid to reduce gender disparity in the treatment of acute myocardial infarction.

**Conflict of interest:** None declared.

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Gender and myocardial salvage


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