Original article

**Gender differences in coronary plaque components in patients with acute coronary syndrome: Virtual histology-intravascular ultrasound analysis**

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**KEYWORDS**

Coronary disease; Gender; Plaque; Ultrasonics

**Summary**

**Background:** The aim of this study was to evaluate the gender differences in plaque components in acute coronary syndrome (ACS) patients.

**Methods:** We used virtual histology-intravascular ultrasound to evaluate the plaque components in culprit lesions in 362 ACS patients (254 men, 108 women).

**Results:** Women were more likely to be diabetic (34% vs 23%, *p* = 0.030), had greater percentage necrotic core (%NC) volume (19.0 ± 12.7% vs 16.8 ± 11.9%, *p* = 0.040), and had trends toward higher high-sensitivity C-reactive protein (hs-CRP) (0.85 ± 1.28 mg/dl vs 0.53 ± 0.48 mg/dl, *p* = 0.063), and higher incidence of thin-cap fibroatheroma (TCFA) (62% vs 52%, *p* = 0.078) compared with men. %NC volume was significantly greater in diabetic patients compared with nondiabetic patients (20.4 ± 10.2% vs 16.0 ± 8.9%, *p* < 0.001) and was significantly greater in patients with elevated hs-CRP (>0.2 mg/dl) compared with those with normal hs-CRP (<0.2 mg/dl) (18.8 ± 8.9% vs 16.6 ± 9.7%, *p* = 0.021). However, there were no differences in plaque components between diabetic women and men, and between women and men with elevated hs-CRP levels. Diabetes [odds ratio (OR): 2.44, 95% confidence interval (CI): 1.35–3.82, *p* = 0.003] and hs-CRP (OR: 1.54, 95% CI: 1.08–2.65, *p* = 0.032), but not female gender, were the independent predictors of TCFA.

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Conclusions: Although it seems likely that female ACS patients have more vulnerable plaque components compared with male ACS patients, these findings may result not from true gender differences in plaque components but higher prevalence of diabetes and hs-CRP elevation in women.

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Introduction

Coronary artery disease is the most frequent cause of mortality among women [1,2]. Previous studies fully addressed gender-related extent and localization of coronary artery disease [3–5]. Several studies have reported gender differences in the diagnosis and medical treatment of cardiovascular disease, to the detriment of women [6–9]. On the other hand, some other studies showed no differences in the extent and localization of coronary artery disease [3,10,11].

Women develop coronary artery disease later in life than men. This difference has been attributed to the loss of female sex hormones at the time of menopause, but the biological explanations for gender differences in cardiovascular diseases are more complex [12]. Mechanisms for cardiovascular gender differences have not yet been proved, and it is not well known about the gender differences in plaque components. Therefore, the aim of the present study was to evaluate whether there would be gender-related differences in terms of the composition of coronary artery plaques in patients with acute coronary syndrome (ACS) using virtual histology-intravascular ultrasound (VH-IVUS).

Methods

Study population

This study was a retrospective, single-center study. A total of 2580 patients with ACS were admitted to our institute from February 2007 to January 2009. We excluded patients with stent thrombosis, restenosis after stenting, coronary artery bypass graft failure, severe heart failure or cardiogenic shock, important systemic disease, serum creatinine ≥2.5 mg/dl, any concomitant infection which could falsely increase high-sensitivity C-reactive protein (hs-CRP), and patients in whom adequate IVUS images could not be obtained. Finally, we identified 362 consecutive ACS patients who underwent pre-intervention VH-IVUS within 24 h of symptom onset. The presence of unstable angina was determined by chest pain within the preceding 72 h with or without ST-T wave changes or positive cardiac biochemical markers (creatine kinase-MB or cardiac-specific troponin-I). The presence of ST-segment elevation myocardial infarction was determined by >30 min of continuous chest pain, a new ST-segment elevation ≥2 mm on at least two contiguous electrocardiographic leads, and creatinine kinase-MB >3 times normal. The presence of non-ST-segment elevation myocardial infarction was diagnosed by chest pain and positive cardiac biochemical markers (creatine kinase-MB or cardiac-specific troponin-I) without new ST-segment elevation. The protocol was approved by the institutional review board. Hospital records of patients were reviewed to obtain information on clinical demographics.

Laboratory analysis

Peripheral blood samples were obtained before coronary angiography using direct venipuncture. The blood samples were centrifuged, and serum was removed and stored at –70°C until the assay could be performed. Absolute creatine kinase-MB levels were determined by radioimmunoassay (Dade Behring Inc., Miami, FL, USA). Cardiac-specific troponin-I levels were measured by a paramagnetic particle, chemiluminescent immunoenzymatic assay (Beckman, Coulter Inc., Fullerton, CA, USA). The serum levels of total cholesterol, triglyceride, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol were measured by standard enzymatic methods. hs-CRP was analyzed turbidimetrically with sheep antibodies against human CRP; this has been validated against the Dade Behring method [13].

Quantitative coronary angiography analysis

Coronary angiogram was analyzed with a validated quantitative coronary angiography (QCA) system (Philips H5000 or Allura DCI program, Philips Medical Systems, Eindhoven, The Netherlands). With the outer diameter of the contrast-filled catheter as the calibration standard, the minimal lumen diameter and reference diameter were measured in diastolic frames from orthogonal projections.

Gray-scale and VH-IVUS imaging and analysis

All pre-intervention gray-scale and VH-IVUS examinations were performed after intracoronary administration of 300 μg nitroglycerin. A 20-MHz, 2.9F IVUS imaging catheter (Eagle Eye, Volcano Corp., Rancho Cordova, CA, USA) was advanced >10 mm beyond the lesion; and automated pullback was performed to a point >10 mm proximal to the lesion at a speed of 0.5 mm/s. In patients with Thrombolysis In Myocardial Infarction (TIMI) 0 or 1 flow, we performed thrombus aspiration or percutaneous transluminal coronary angioplasty with small-sized balloon at low pressure first before IVUS examination.

Gray-scale IVUS and VH-IVUS data were analyzed by two independent observers (H.Y.J. and C.Y.H.). The levels of reproducibility for external elastic membrane (EEM), lumen, and plaque plus media (P&M), and cross-sectional areas (CSAs) using the Spearman rank-order correlation coefficients were 0.96, 0.97, and 0.97, respectively. Similarly, for plaque components by VH-IVUS, reproducibility for the fibrous (FT), fibro-fatty (FF), dense calcium (DC), and necrotic core (NC) volume measurements using the Spearman rank-order correlation coefficients were 0.93, 0.94, 0.93, and 0.93, respectively.
Quantitative volumetric gray-scale and VH-IVUS analyses were performed across the entire lesion segment, and cross-sectional analyses were performed at the minimum lumen sites and at the largest NC sites. Conventional quantitative volumetric gray-scale IVUS analysis was performed according to the American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies [14]. Measurements were made at every 1-mm interval for the region of interest, which was defined as the segment between distal to proximal reference sites that were the most normal looking within 5 mm proximal and distal to the lesion. Volumetric data were generated by the software using Simpson’s method. EEM and lumen CSAs were measured. P&M CSA was calculated as EEM minus lumen CSA; and plaque burden was calculated as P&M divided by EEM CSA. VH-IVUS analysis classified the color-coded tissue into four major components: green (FT); yellow–green (FF); white (DC); and red (NC) [15–18]. Thin-cap fibroatheroma (TCFA) was defined as focal, NC-rich (≥10% of the CSA) plaques being in contact with the lumen in a plaque burden ≥40% [16]. VH-IVUS analysis was reported as a percentage of plaque area or volume.

### Statistical analysis
The Statistical Package for Social Sciences (SPSS) for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA) was used.
for all analyses. Continuous variables were presented as the mean value \( \pm 1 \) SD; comparisons were conducted by student’s t-test or the Wilcoxon rank-sum test if normality assumption was violated. Discrete variables were presented as percentages and frequencies; comparisons were conducted by \( \chi^2 \) statistics or Fisher’s exact test as appropriate. A multivariable logistic regression analysis was performed to identify the independent predictors of culprit lesion TCFA. A \( p \) value <0.05 was considered statistically significant.

**Results**

**Baseline characteristics**

The baseline characteristics are summarized in Table 1. Women were older, had more hypertension and diabetes, and were less likely to be smokers compared with men. Hemoglobin and creatinine levels were significantly lower, and there was a trend toward higher hs-CRP level in women compared with men.

**Angiographic results**

Angiographic findings are summarized in Table 2. There were no significant differences in culprit vessel, lesion location, TIMI flow grade, and angiographic lesion length. However, multivessel disease was more common and there were trends toward smaller angiographic reference diameter and minimal lumen diameter in women compared with men.

**Gray-scale IVUS results**

Gray-scale IVUS findings are summarized in Table 3. EEM and lumen CSAs were significantly smaller in women compared with men. At the minimum lumen sites, EEM and P&M CSAs were significantly smaller, and there was a trend toward smaller lumen CSA in women compared with men. At the largest NC sites, EEM, lumen, and P&M CSAs were significantly smaller in women compared with men. By volumetric analysis, EEM, lumen, and P&M volumes were significantly smaller in women compared with men.

**VH-IVUS results**

At the proximal reference sites, there were trends toward greater \%DC (10.9 \( \pm \) 9.0% vs 9.3 \( \pm \) 7.6%, \( p = 0.13 \)) and \%NC areas (13.1 \( \pm \) 9.9% vs 11.0 \( \pm \) 9.2%, \( p = 0.083 \)) and smaller \%FF area (15.9 \( \pm \) 13.9% vs 19.3 \( \pm \) 15.8%, \( p = 0.062 \)) in women compared with men. At the distal reference sites, there were trends toward greater \%DC (11.2 \( \pm \) 9.0% vs 8.9 \( \pm \) 7.6%, \( p = 0.064 \)) and \%NC areas (13.8 \( \pm \) 9.9% vs 11.0 \( \pm \) 9.2%, \( p = 0.14 \)) and smaller \%FF area (15.2 \( \pm \) 13.9% vs 18.6 \( \pm \) 15.8%, \( p = 0.078 \)) in women compared with men.

At the minimum lumen sites, \%DC and \%NC areas were significantly greater in women compared with men; conversely, \%FT area was significantly smaller in women compared with men (Fig. 1A). At the largest NC sites, \%NC area was significantly greater (27.2 \( \pm \) 11.7% vs 24.6 \( \pm \) 11.3%, \( p = 0.050 \)) with the trend toward greater \%DC area (13.8 \( \pm \) 10.3% vs 11.9 \( \pm \) 9.0%, \( p = 0.082 \)) in women compared with men; conversely, \%FT area was significantly smaller (51.2 \( \pm \) 14.5% vs 54.6 \( \pm \) 13.4%, \( p = 0.030 \)) in women compared with men. By volumetric analysis, \%DC and \%NC volumes were significantly greater in women compared with men; conversely, there was a trend toward smaller \%FT volume in women compared with men (62% vs 52%, \( p = 0.078 \)).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Coronary angiographic findings.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men (n = 254)</strong></td>
<td><strong>Women (n = 108)</strong></td>
</tr>
<tr>
<td><strong>Culprit vessel</strong></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>152 (60)</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>41 (16)</td>
</tr>
<tr>
<td>Right</td>
<td>61 (24)</td>
</tr>
<tr>
<td><strong>Lesion location</strong></td>
<td></td>
</tr>
<tr>
<td>Ostium</td>
<td>12 (5)</td>
</tr>
<tr>
<td>Proximal</td>
<td>102 (40)</td>
</tr>
<tr>
<td>Middle</td>
<td>94 (37)</td>
</tr>
<tr>
<td>Distal</td>
<td>46 (18)</td>
</tr>
<tr>
<td><strong>Multivessel disease</strong></td>
<td>119 (47)</td>
</tr>
<tr>
<td><strong>TIMI flow grade</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>10 (4)</td>
</tr>
<tr>
<td>1</td>
<td>15 (6)</td>
</tr>
<tr>
<td>2</td>
<td>56 (22)</td>
</tr>
<tr>
<td>3</td>
<td>173 (68)</td>
</tr>
<tr>
<td><strong>Lesion length (mm)</strong></td>
<td>20 ( \pm ) 10</td>
</tr>
<tr>
<td><strong>Reference diameter (mm)</strong></td>
<td>3.24 ( \pm ) 0.54</td>
</tr>
<tr>
<td><strong>Pre-MLD (mm)</strong></td>
<td>0.95 ( \pm ) 0.56</td>
</tr>
</tbody>
</table>

Data are \( n \) (%), or mean \( \pm \) SD. TIMI, Thrombolysis In Myocardial Infarction; and MLD, minimal lumen diameter.
When we compared the plaque components between diabetic (n = 96) and nondiabetic patients (n = 266), %DC and %NC volumes were significantly greater in diabetic patients compared with nondiabetic patients; conversely, %FT and %FF volumes were significantly smaller in diabetic patients compared with nondiabetic patients (Fig. 2A). When we compared the relative volumetric plaque components between hypertensive men (n = 124) and women (n = 86), there were no significant differences in plaque components between both groups (%FT: 60.7 ± 10.7% vs 58.3 ± 11.2%, p = 0.11; %FF: 12.4 ± 7.9% vs 12.7 ± 8.6%, p = 0.8; %DC: 10.1 ± 6.4% vs 11.3 ± 8.3%, p = 0.2; %NC: 16.9 ± 8.6% vs 17.9 ± 9.8%, p = 0.5).

When we compared the plaque components between elderly (≥70 years, n = 83) and nonelderly (<70 years, n = 279) patients, there were no significant differences in plaque components between both groups (%FT: 60.7 ± 10.7% vs 59.8 ± 15.8%, p = 0.7; %FF: 12.5 ± 8.2% vs 13.2 ± 10.3%, p = 0.3; %DC: 10.6 ± 7.2% vs 9.7 ± 7.4%, p = 0.3; %NC: 16.3 ± 9.1% vs 17.3 ± 10.0%, p = 0.4). When we compared the relative volumetric plaque components between elderly men (n = 60) and elderly women (n = 23), there were...
The gender differences in the relative plaque components at the minimum lumen sites (A) and the volumetric (B) relative plaque components. FT, fibrous; FF, fibro-fatty; DC, dense calcium; and NC, necrotic core.

no significant differences in plaque components between both groups (%FT: 59.4 ± 10.4% vs 58.9 ± 11.4%, p = 0.9; %FF: 12.1 ± 7.0% vs 12.6 ± 8.5%, p = 0.8; %DC: 11.5 ± 7.5% vs 9.8 ± 6.9%, p = 0.3; %NC: 17.0 ± 8.4% vs 19.0 ± 10.1%, p = 0.4).

When we compared the plaque components between patients with elevated hs-CRP (≥0.2 mg/dl, n = 160) and those with normal hs-CRP levels (<0.2 mg/dl, n = 202), %DC and %NC volumes were significantly greater in patients with elevated hs-CRP compared with those with normal hs-CRP levels (Fig. 3A). When we compared the relative volumetric plaque components between men with elevated hs-CRP (n = 119) and women with elevated hs-CRP levels (n = 41), there were no significant differences in plaque components between both groups (Fig. 3B). Also, when we compared the relative volumetric plaque components between men with normal hs-CRP (n = 135) and women with normal hs-CRP levels (n = 67), there were no significant differences in plaque components between both groups.

Independent predictors of TCFA

We performed multivariable analysis to determine the independent predictors of culprit lesion TCFA. All the variables with p < 0.2 in univariable analysis (age, gender, ST-segment elevation myocardial infarction, diabetes, hs-CRP, and P&M volume) were tested for multivariable analysis. Diabetes [odds ratio (OR): 2.44, 95% confidence interval (CI): 1.35–3.82, p = 0.003] and hs-CRP (OR: 1.54, 95% CI = 1.08–2.65, p = 0.032), but not female gender, were the independent predictors of TCFA.

Discussion

The present VH-IVUS study demonstrated that (1) women had more risk factors such as old age, hypertension, and diabetes, (2) women had smaller vessel size with smaller plaque mass in culprit lesion than men, (3) minimum lumen site DC and NC areas were significantly greater in women compared with men, (4) although women had smaller plaque volume, they had greater DC and NC volumes compared with men, (5)
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Figure 3 The relative volumetric plaque components according to high-sensitivity C-reactive protein levels (A) and the gender differences in the relative volumetric plaque components in patients with elevated high-sensitivity C-reactive protein levels ($\geq 0.2\text{mg/dl}$) (B). FT, fibrous; FF, fibro-fatty; DC, dense calcium; and NC, necrotic core.

there was a trend toward higher incidence of TCFA in women compared with men, and (6) independent predictors of TCFA were diabetes and elevated hs-CRP, but not female gender.

Cardiovascular diseases are the major cause of morbidity and mortality for both men and women, which occur uncommonly in premenopausal women, but their incidence rises sharply after the menopausal transition. Cardiovascular gender differences are apparent long before cardiovascular diseases appear in men and women, and improved understanding of the biology underlying these differences has the potential to advance the diagnosis and treatment of cardiovascular diseases in both sexes [12].

Several studies reported that female gender itself was an independent predictor of increased major adverse cardiac event rate after percutaneous coronary intervention or coronary artery bypass graft [19,20], while others did not [21,22]. Women are affected with cardiovascular disease at an older age than men, and many risk factors for coronary heart disease have different distributions in men and women [23–25]. In the present study, women were older and had more hypertension and diabetes, which are consistent with the results of the previous studies, and women had more vulnerable plaque components than men. However, these gender differences in plaque composition disappeared in the same risk groups (diabetic patients, hypertensive patients, elderly patients, and patients with elevated hs-CRP). Because women had more risk factors, they had chances to have more vulnerable plaque components which can cause worse outcomes than men. Predictors relating to vulnerable plaque in the present study were diabetes and hs-CRP elevation, not female gender.

Morbidity and mortality in diabetic patients is markedly higher than nondiabetic patients [26,27]. Worse outcome in diabetic patients may be associated with endothelial dysfunction and abnormality of vascular smooth muscle cell function, in addition to a propensity to thrombosis, which contribute to atherosclerosis and its complications [28,29]. Previous studies showed diabetic patients had a larger content of lipid-rich plaque compared with nondiabetic patients [30], and inflammation and NC size play a greater role in the progression of atherosclerosis in diabetic patients in sudden coronary death [31]. A previous study [32] showed that the absolute NC and DC volumes and %NC and DC volumes were significantly greater in diabetic patients compared with nondiabetic patients; conversely, %FT and FF volumes were significantly smaller in diabetic patients compared with nondiabetic patients, and diabetes mellitus was the independent predictor of hs-CRP elevation and the presence of TCFA. An elevated CRP level is associated with an increased risk of future ischemic complications in ACS patients [33–35]. Another previous study demonstrated that CRP was associated with atherosclerosis in the arterial tree [36]. Several IVUS studies have demonstrated the association between CRP and vulnerable plaque in ACS patients [37,38]. Burke et al. [39] reported the correlation between CRP and the number of TCFA in patients who experienced a sudden death associated with severe coronary artery disease. Although it seems like that female ACS patients have more vulnerable plaque components compared with male ACS patients, it may result not from true gender differences in plaque components but higher prevalence of other risk factors such as diabetes and hs-CRP elevation in women than in men.

Study limitations

First, the present study is a retrospective single-center study, so, is subject to limitations inherent in this type of clinical investigation. Second, IVUS and VH-IVUS imaging were performed at the discretion of the individual operators leading to potential selection bias. Third, VH-IVUS is a weak tool to detect vulnerable plaque. The reason for that comes from the insufficient spatial resolution of commercially available VH-IVUS. Fourth, we did not perform three-vessel VH-IVUS. Therefore, we did not assess the frequency of non-culprit lesion TCFA. Fifth, we did not attempt to differentiate between atherosclerotic plaque and thrombus because VH-IVUS could not determine the presence of thrombus. This may obscure the identification of TCFA. Sixth, heavily calcified plaques may induce an artifact regarding the codification of plaques by VH-IVUS resulting in an increase in NC content. Seventh, this study population included patients with myocardial infarction. In these patients, the hs-CRP levels obtained before coronary
angiography may be influenced by myocardial tissue necrosis. Eighth, we excluded the patients with serious conditions such as severe heart failure, cardiogenic shock, important systemic disease, or severe renal dysfunction. Thus, the present study might not reflect the real incidences of TCFA and the percentage of NC burden in whole ACS populations.

Conclusions

Although it seems likely that female ACS patients had more vulnerable plaque components compared with male ACS patients, these findings might result from higher prevalence of diabetes and hs-CRP elevation in women.

Conflict of interest

There are no potential conflicts to declare.

Acknowledgment

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References

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