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Research paper

Sex differences in coronary atherosclerosis progression and major adverse cardiac events in patients with suspected coronary artery disease

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ABSTRACT

Background: Little is known about the influence of coronary atherosclerosis progression on the risk of major adverse cardiac events (MACE). Similarly, differences between men and women regarding atherosclerosis progression are poorly understood. The purpose of this study was to investigate the progression of coronary atherosclerosis by coronary CT angiography (coronary CTA) in men and women, and to evaluate its prognostic value regarding MACE.

Methods: This study included 1046 patients with suspected coronary artery disease (CAD) who underwent serial coronary CTA because of new or worsening symptoms or because follow-up coronary CTA had been recommended by attending physicians. Coronary atherosclerosis was semi-quantitatively assessed as follows: three-vessel plaque score (TVPS), severe proximal plaque score (SPPS), segment stenosis score (SSS), segment involvement score (SIS), and coronary artery calcium score (CACs). Patients were followed-up regarding the occurrence of MACE, defined as cardiac death, coronary revascularization, nonfatal myocardial infarction and hospitalization due to unstable angina. Follow-up information was gathered by clinical visits or telephone contacts.

Results: Follow-up was achieved in 953 (91.1%) patients (63.8% male; mean age, 53.9 ± 9.7 years) with a mean interval of 4.9 ± 1.1 years. MACE occurred in 132 (13.9%) patients. The average interscan time was 2.1 years. Compared with women, men had significantly higher progression of SPPS, SSS and SIS (6.6% vs. 3.5%, 28.0% vs. 18.3%, 26.6% vs. 16.8%, respectively, all $P < 0.005$). There was a strong association between the progression of SPPS as well as SSS and MACE, both for men (SPPS, HR:2.17, $P < 0.001$; SSS, HR:1.28, $P = 0.023$) and women (SPPS, HR:2.75, $P < 0.001$; SSS, HR:1.19, $P = 0.027$).

Conclusions: Progression of coronary atherosclerosis as determined by coronary CTA is higher in men than women, it is associated with the risk of future MACE.

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1. Introduction

Sex differences regarding the prognosis of coronary artery disease (CAD) are well documented,^{1,2} and women both with symptoms and with nonobstructive CAD were found more likely to

experience major adverse cardiac events (MACE).³ The occurrence of MACE may be associated with the progression of coronary atherosclerosis.⁴ Intravascular ultrasound and optical coherence tomography can be used to evaluate coronary atherosclerosis progression, but both are invasive, costly and not free from complications. Coronary CT angiography (coronary CTA) is a high-resolution cardiovascular imaging technology that permits the evaluation of luminal stenosis, coronary plaque amount and distribution, as well as plaque progression. Previous studies have demonstrated that plaque progression detected by serial coronary CTA was an

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Abbreviations

CACS	coronary artery calcium score
CAD	coronary artery disease
CTA	CT angiography
MACE	major adverse cardiac events
SIS	segment involvement score
SPPS	severe proximal plaque score
SSS	segment stenosis score
TVPS	three vessel plaque score

independent predictor of acute coronary syndromes.⁵ However, sex differences in coronary atherosclerosis progression and their association with cardiac events in patients with suspected CAD are still unclear. In our study, we investigated sex differences in coronary atherosclerosis progression as determined by coronary CTA and we analyzed the association between the atherosclerosis progression and MACE stratified by sex.

2. Methods

2.1. Patients

The study was approved by the local institutional review board, and the requirement to obtain informed consent was waived. We retrospectively enrolled 1046 patients with suspected CAD who underwent serial coronary CTA because of new or worsening symptoms or because follow-up coronary CTA had been recommended by attending physicians from September 2009 to January 2015. Exclusion criteria included the following: 1) patients who underwent coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) between the two CT scans ($n = 176$); 2) patients in which at least one coronary CTA data set was unevaluable because of motion artifact ($n = 27$). 3) patients in which MACE occurred within less than 30 days following the second coronary CTA scan ($n = 11$). Cardiovascular risk factors and medical treatment were obtained from electronic databases.

2.2. Coronary CTA protocol

All examinations were performed with a dual-source CT scanner (SOMATOM Definition or SOMATOM Definition Flash, Siemens Healthcare, Forchheim, Germany). Oral beta-blocker (Metoprolol; Betaloc, AstraZeneca, Cambridge, England) was administered if patients presented with a resting heart rate > 90 beats per minute. After non-enhanced CT, contrast enhanced coronary CTA was performed using prospectively ECG-triggered axial acquisition. Following parameters were used: slice collimation $2 \times 64 \times 0.6$ mm by using z-flying focal spot; gantry rotation time 0.28 s; tube voltage 120 kV or 100 kV (100 kV tube potential was used for patients with a body mass index (BMI) < 30 kg/m², 120 kV for BMI > 30 kg/m²); tube current 400–500 mAs; field of view 200–250 mm. Contrast medium (Iohexol Omnipaque 350 mg/ml, GE Healthcare, USA or Ultravist 370 mg/ml, Bayers-Schering Pharma, Germany) was injected via a 20-gauge trocar in the antecubital vein using a power injector (Stellant; Medrad, Indianola, Pennsylvania) at a rate of 4–5 ml/s. A triple phase contrast material injection protocol was used as follows: iodinated contrast, followed by a mixture of 30% iodinated contrast and 70% saline, followed by a saline flush. Coronary CTA images were reconstructed with a slice

thickness of 0.625 mm.⁶

2.3. Coronary CTA image analysis

All coronary CTA images were interpreted by two experienced radiologists blinded to clinical parameters and coronary CTA findings in any scans. Coronary atherosclerotic lesions were evaluated by visual estimation. The coronary artery tree was divided into 16 separate segments.⁷ Coronary stenosis severity was classified using 4 categories: none or minimal ($< 30\%$ estimated narrowing of the coronary luminal diameter, score 0), mild (30%–49% estimated luminal diameter obstruction, score 1), moderate (50%–69% luminal diameter obstruction, score 2), or severe ($\geq 70\%$ coronary luminal diameter narrowing, score 3).⁸

Semi-quantitative parameters of coronary atherosclerosis were defined according to previous studies⁸ as follows: 1) three vessel plaque score (TVPS); 2) severe proximal plaque score (SPPS); 3) segment stenosis score (SSS); 4) segment involvement score (SIS); 5) coronary artery calcium score (CACS). TVPS was 0 or 1 based on coexisting presence of plaque in the left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA). Because it was just one vessel with severe proximal plaque at baseline as well as at follow up CCTA in all individuals, SPPS was 0 or 1 based on the presence of severely stenotic plaque ($\geq 70\%$ luminal stenosis) in the proximal portion of the LAD, LCX, or RCA in this study. SSS (0–48) was defined as the total numbers of involved segments (0–16) multiplied by the degree of segment stenosis (0–3). SIS (0–16) was defined as the total number of segments (0–16) exhibiting plaque with any degree of luminal stenosis.⁷

Analysis of follow up coronary CTA was performed by operators who were blinded to the baseline CT data, and all analyses were performed in an identical fashion to the baseline data set. Progression of the TVPS was defined as $TVPS_{\text{follow-up}} = 1$, $TVPS_{\text{baseline}} = 0$; Progression of the SPPS was defined as $SPPS_{\text{follow-up}} = 1$, $SPPS_{\text{baseline}} = 0$ and proximal luminal stenosis $< 50\%$ at baseline; Progression of the SSS was defined as $SSS_{\text{follow-up}} - SSS_{\text{baseline}} > 0$; Progression of the SIS was defined as $SIS_{\text{follow-up}} - SIS_{\text{baseline}} > 0$, and progression of CACS was defined as $(CACS_{\text{follow-up}} - CACS_{\text{baseline}}) / CACS_{\text{baseline}} > 15\%$.⁹ The progression of any single of these parameters progression was considered as atherosclerosis plaque progression.

2.4. Follow-up

The follow-up period started with the second scan to the final follow-up. Follow-up information was gathered by clinical visits or telephone contacts. We verified all reported events by hospital records or contacts with the attending physicians. The end point of the study was the occurrence of cardiac events defined as cardiac death (including any death without definitive non-cardiac cause), nonfatal myocardial infarction, hospitalization due to unstable angina, and coronary revascularization. Nonfatal myocardial infarction was defined based on the criteria of typical acute chest pain and persistent ST-segment elevation or positive cardiac enzymes.

2.5. Statistical analysis

Statistical analyses were performed using SPSS software package (version 17.0, SPSS, Chicago, IL, USA). The Kolmogorov Smirnov analysis was used for assessing normality of data distribution. For descriptive statistics, continuous variables were expressed as mean \pm standard deviation or median (interquartile range) and categorical variables as percentages. Differences between groups were analyzed by the chi-square test for comparison of categorical

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