JACC: CARDIOVASCULAR IMAGING
VOL. 9, NO. 4, 2016

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcmg.2016.02.007

Multimodality Intravascular Imaging to Evaluate Sex Differences in Plaque Morphology in Stable CAD

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate sex differences in plaque morphology in stable coronary artery disease (CAD) patients using a multimodality intravascular imaging approach.

BACKGROUND Differences in atherosclerotic burden and plaque morphology between men and women is a focus of treatment and preventative measures.

METHODS We retrospectively analyzed data from 383 patients with stable CAD who were referred for angiography and underwent optical coherence tomography. Among them, 128 also underwent intravascular ultrasound (IVUS)/near infrared spectroscopy.

RESULTS Of the 383 patients included in the study, 268 were men and 115 were women. Women tended to be older (66 ± 10 years of age vs. 62 ± 11 years of age; p = 0.002) and have more comorbidities including hypertension (97% vs. 90%; p = 0.031), diabetes with insulin use (18% vs. 10%; p = 0.043), obesity (body mass index 30 kg/m^2 vs. 28 kg/m^2; p = 0.022), and lower estimated glomerular filtration rate (88 ml/min/1.73m^2 vs. 98 ml/min/1.73m^2; p = 0.001). Optical coherence tomography data demonstrated that there was no sex difference in plaque morphology as characterized by maximum lipid arc, lipid length, lipid volume index, minimum cap thickness, incidence of thin cap fibroatheroma, microvessels, macrophages, and calcification. There was also no difference in maximal lipid core burden index at the 4-mm maximal segment as seen on near infrared spectroscopy. Plaque characteristics by IVUS were similar between men and women except for an increase in plaque burden in men compared to women in the reference segment (44.4 vs. 39.3; p = 0.031). After adjusting for age, body mass index, percutaneous coronary intervention history, and clinical risk factors, sex was not found to be an independent predictor of severe plaque burden by IVUS.

CONCLUSION Among men and women with stable CAD referred for coronary angiography, there was no difference in plaque characteristics as assessed by multimodality imaging. These findings, which are hypothesis generating, suggest that equally aggressive primary and secondary preventive efforts irrespective of sex must be undertaken. (J Am Coll Cardiol Img 2016;9:400–7) © 2016 by the American College of Cardiology Foundation.

Coronary artery disease (CAD) is the leading cause of death in both men and women. Data from the INTERHEART global case-control study, which included more than 27,000 men and women from 52 countries, showed that women experience their first acute myocardial infraction (MI) on average 9 years later than men (1). However, a growing body of evidence suggests that during the last 2 decades the prevalence of CAD has increased among middle-aged women, whereas the

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Manuscript received December 28, 2015; revised manuscript received February 12, 2016, accepted February 17, 2016.

prevalence among similarly aged men decreased (2). Although the risk of future cardiovascular events remains higher in middle-aged men compared with middle-aged women, the gap has narrowed in recent years (2–4).

The role of traditional risk factors such as hypertension, diabetes mellitus, smoking, dietary patterns, and family history in the progression of CAD in both sexes is well established (1,3,4). The INTERHEART study attributed the difference in age of first MI largely to the higher risk factor levels at younger ages in men compared to women (1). Some researchers have suggested that women who are "relatively protected" against CAD require a greater risk factor burden before developing overt disease as a result of which women with significant CAD represent a high-risk group (5,6).

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At a histopathological level, there are limited data from post-mortem studies to evaluate the differences in plaque morphology between men and women (7,8). Recently there has been growing interest in using in vivo intravascular imaging for characterization of plaque morphology (9–16). We sought to evaluate the differences in plaque morphology between men and women with stable CAD using a multimodality approach with intravascular ultrasound (IVUS), near infrared spectroscopy (NIRS), and optical coherence tomography (OCT) techniques.

METHODS

STUDY POPULATION. This was a retrospective analysis of prospectively collected data from the institutional review board-approved clinical and multimodality imaging database. All procedures were performed in the Mount Sinai Cardiac Catheterization Lab. Our cath lab database was used to obtain the baseline demographic, clinical, procedural, and in-hospital outcomes data and imaging characteristics. As shown in **Figure 1**, our study group consisted of 420 consecutive patients with stable CAD who were referred for cardiac catheterization on whom OCT was performed. The lesion to image was based on the operator's discretion and lesions represented de novo atherosclerosis. Of these 420 patients, 37 were excluded because OCT image quality was not deemed to be optimum. The remaining 383 patients were analyzed. Of the total number, a sub-group of patients (n = 133) also underwent IVUS/NIRS imaging and 5 were excluded because of suboptimal image quality. One hundred twenty-eight patients included in the study also formed a part of the COLOR (Chemometric Observation of Lipid Core Plaques of Interest in Native Coronary Arteries) registry enrolled only from our center. Patients with renal failure (creatinine >1.5 mg/dl), contrast allergy, hemodynamic compromise, and aorto-ostial coronary artery lesions were excluded from the study.

OCT IMAGE ACQUISITION AND ANALYSIS. OCT image acquisition was performed with a commercially available C7-XR OCT Intravascular Imaging System (OCT C7 Dragonfly, St. Jude Medical, St. Paul, Minnesota). The OCT catheter was advanced at least 10 mm distal to the imaging target lesion. OCT image acquisition was then performed with automatic pullback (20 mm per second) and continuous intracoronary contrast injection (iodixanol) (total volume 12 to 16 ml injected at 3 to 4 ml/s). Each OCT catheter pullback imaged a total of 54 mm of the vessel.

OCT images were analyzed using the St. Jude Medical Offline Review Workstation at 1-mm intervals according to previously validated criteria (17,18) and as we described previously (19–22). The smallest cross-sectional area (CSA), reference CSA, and percent lumen area stenosis ([reference lumen CSA − minimum lesion lumen CSA]/reference lumen CSA × 100) were calculated for each lesion. The thinnest part of the fibrous cap was measured 3 times, and its average was reported as minimum cap thickness. In addition, OCT-dependent lipid arc was also measured at 1-mm intervals through the entire length of the lesion, and expressed in degrees. Lipid length was measured on longitudinal view (using frame analysis). Lipid volume index was calculated as the averaged lipid arc multiplied by lipid length (23). Thin cap fibroatheroma (TCFA) was defined as a plaque with lipid arc >90° and fibrous cap thickness <65 μm. Calcified plaques were defined as areas with well-delineated borders and the degree of circumferential extent of calcification was quantified at 1-mm intervals (24). A microvessel was defined as a black hole or tubular structure within a plaque, which was not connected to the vessel lumen and was clearly visible in at least 3 consecutive cross-sectional OCT images (25). Macrophages accumulation was defined as confluent or punctate highly backscattering focal regions in the artery wall. Thrombi were identified as masses protruding into the vessel lumen discontinuous from the surface of the vessel wall. Plaque rupture was detected by OCT as a ruptured fibrous cap that connects the lumen with the lipid pool, which may occur with or without a superimposed thrombus. To evaluate the interobserver variability, 2

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CAD = coronary artery disease

CSA = cross sectional area

IVUS = intravascular ultrasound

maxLCBI$_{4mm}$ = maximal lipid core burden index at the 4-mm segment

MI = myocardial infarction

MLA = minimum luminal area

NIRS = near infrared spectroscopy

OCT = optical coherence tomography

TCFA = thin cap fibroatheroma