Imaging of coronary atherosclerosis with multi-slice computed tomography

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Chapter 12

Gender-Specific Differences in Extent and Composition of Coronary Atherosclerotic Plaques in Relation to Age: Non-invasive Assessment With Multi-Slice Computed Tomography and Invasive Evaluation With Gray-Scale and Virtual Histology Intravascular Ultrasound

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Submitted

Abstract

Aims: We evaluated coronary plaque patterns in men and women in relation to age using multi-slice computed tomography (MSCT). The findings were compared with observations on gray-scale and Virtual Histology (VH) intravascular ultrasound (IVUS).

Methods: 93 patients (59 men, 34 women) underwent 64-slice MSCT followed by conventional coronary angiography with IVUS. Plaque extent and composition were assessed on MSCT, gray-scale and VH IVUS. Coronary plaque patterns were compared between men and women in 2 age groups (<65 and ≥65 years old).

Results: More plaques were observed on MSCT in younger men (6±4 versus 2±2 in women, $p<0.001$). A larger plaque burden was observed on gray-scale IVUS (45.7±11.4% versus 36.3±11.6%, $p<0.001$). Similarly, more mixed plaques were observed in younger men (3±3 versus 1±1, $p=0.003$), whereas a larger arc of calcium was detected on gray-scale IVUS (91.7±93.5 versus 25.7±51.0 degrees, $p<0.001$). On VH IVUS, the prevalence of thin cap fibroatheroma was higher in younger men (31% versus 0%). No differences in plaque patterns were observed in older patients.

Conclusions: More extensive atherosclerosis and more calcified lesions were observed in men as compared with women. Moreover, these differences were predominantly present in younger patients and were lost in older patients.

Introduction

Coronary artery disease (CAD) is the leading cause of mortality not only for men but also for women. Moreover, although cardiovascular mortality has declined in the male population over the years, no substantial decrease has been observed in women.[1-3]

Accordingly, timely assessment of CAD in women is currently being increasingly recognized as a clinically relevant issue. Nevertheless, the diagnosis of CAD appears to be more complicated in women. First, gender differences in clinical presentation of CAD have been observed.[4] The initial presentation of CAD in women is frequently rather atypical, whereas men relatively more often present with more typical symptoms of CAD. Second, the traditional diagnostic evaluation strategies have been validated in men and may be less suited for women.[4] Indeed, recent investigations have increased our awareness that gender-specific differences may exist in the pathophysiology of CAD.[5] In general, premenopausal women tend to have lower prevalences of obstructive CAD as compared with age-matched men. In fact, a ~10 year lag in the development of clinically overt CAD has been reported in women, although this difference tends to diminish in the seventh decade.[6] However, despite the absence of evident obstructive culprit lesions in women, their prognosis may not be considered benign with regard to symptoms and future events.[7-10]

Accordingly, direct visualization of coronary atherosclerosis rather than testing for obstructive CAD may be more appropriate for the initial assessment of CAD in women. While plaque burden is traditionally evaluated invasively using intravascular ultrasound (IVUS),[11,12] also non-invasive imaging methods have become available for this purpose. In previous studies, coronary calcium scoring has been used to evaluate age and gender differences in the extent of coronary calcium.[13,14] More detailed information, including stenosis severity and plaque composition, can be derived using Multi-Slice Computed Tomography (MSCT).[15-17] Possibly, MSCT coronary angiography may become a useful technique for the initial evaluation of CAD in women. However, data evaluating gender-specific differences in plaque observations on MSCT are scarce, but highly needed to understand the potential value of MSCT in this population. In addition, as the extent of these gender-specific differences may be highly influenced by age, it is important to establish whether these observations hold true for both younger and older patients.

Thus, the purpose of the study was to evaluate gender-specific differences in coronary plaque extent and composition in relation to age using non-invasive MSCT. Coronary plaque patterns were compared between men and women with further division into younger (<65 years old) and older (≥65 years old) patients. The findings were compared with invasive coronary plaque observations obtained with gray-scale and Virtual Histology (VH) IVUS.

Methods

Patient population and study protocol

A total of 93 patients were included in the study. All patients presented with chest pain suggestive of CAD. Patients underwent 64-slice MSCT coronary angiography, followed within a month by conventional coronary angiography in combination with gray-scale and VH IVUS of 1 to 3 vessels. The clinical history of the patients was evaluated prior to conventional coronary angiography to ensure that neither acute coronary events nor worsening of angina occurred between the examinations.

Patients were excluded from the study if contraindications for MSCT were present.[18] IVUS examination was not performed if severe vessel tortuousness, severe luminal narrowing precluding the insertion of the IVUS catheter or vessel occlusion were present. Informed consent was obtained from all patients.

For comparisons, the patient population was first divided based on gender (men versus women) and secondly based on age (younger (<65 years old) patients versus older (≥65 years old) patients).

MSCT

Image acquisition

MSCT coronary angiography was performed using a 64-slice Toshiba Aquilion (Toshiba Medical Systems, Tokyo, Japan) scanner. A helical scan protocol with electrocardiographic gating was applied as described previously.[19]

Image analysis

Images were evaluated on a remote workstation with dedicated software (Vitrea 2, Vital Images, Minnetonka, Minnesota, USA and Advantage, GE Healthcare, Boston, Massachusetts, USA). First, coronary Agatston calcium score was obtained from image dataset without contrast enhancement. Subsequently, 2 experienced observers evaluated the non-invasive coronary angiograms side-by-side in consensus. The presence of coronary plaques was visually assessed while scrolling through axial images and inspecting curved multiplanar reconstructions.[20] First, plaques were visually classified as obstructive or not using a threshold of 50% luminal narrowing. Second, the plaques were classified into 3 types: non-calcified (plaques having lower density as compared with the contrast-enhanced vessel lumen), mixed (plaques with non-calcified and calcified elements within the same plaque) and calcified (plaques having predominantly high density). The images were evaluated on a patient level. The mean number of any, non-obstructive and obstructive plaques was determined per patient. Likewise, the mean number of non-calcified, mixed and calcified plaques was determined per patient.

Gray-scale and VH IVUS

Image acquisition

IVUS examinations were performed with a 20 MHz, 2.9 F phased-array IVUS catheter (Eagle Eye, Volcano Corporation, Rancho Cordova, California, USA). After intracoronary administration of nitrates, the catheter was introduced to the distal coronary artery and withdrawn at a continuous speed of 0.5 mm/s to the coronary ostium using automated pullback device. To define the starting position of the IVUS catheter, cine runs before and during contrast injection were performed. The images were stored for off-line analysis.

Image analysis, gray-scale IVUS

To evaluate geometrical plaque characteristics, gray-scale IVUS datasets were evaluated by an experienced observer, using dedicated software (QCU CMS 4.0 Medis Medical imaging systems, Leiden, The Netherlands). Cross-sectional images spaced 0.5 mm apart in the pullback were analyzed within the full length of the examined vessel. The contours of the external elastic membrane (EEM) were identified and the mean EEM area was calculated in the examined vessel. Subsequently, lumen-intima interface was identified and mean lumen area was calculated. Plaque area was enclosed by the contours of EEM and lumen. Plaque burden was calculated as the percentage of EEM occupied by plaque: [Plaque burden (%)=$\Sigma(EEM_{area}\text{-}lumen_{area})/\Sigma EEM_{area}$ x 100]. Plaque burden was identified per vessel. Plaque volume was determined in 10 mm of the vessel containing most and least plaque. Percent of abnormal images (having a maximal plaque thickness >0.5 mm) was calculated in each examined vessel.[21] Remodeling index was calculated by dividing the EEM area at the site with most plaque by the EEM area at proximal reference site. The latter was defined as the frame with largest lumen area located within 10 mm from the most diseased frame with no major intervening side branches.[22,23] Positive remodeling was considered as the remodeling index of ≥1.05. Finally, the largest arc of calcium in each examined vessel was obtained.

Image analysis, VH IVUS

An experienced observer performed quantitative VH IVUS image analysis on a plaque level using dedicated software (pcVH 2.1, Volcano Corporation, Rancho Cordova, California, USA). Qualitative VH IVUS analysis was performed side-by-side in consensus by 2 experienced observers. First, 4 tissues were differentiated and labeled with different colours (fibrotic, fibro-fatty tissues, necrotic core and dense calcium), as described and validated previously.[24,25] The mean percentage of each plaque component was obtained in

the full length of plaques observed on MSCT. In addition, plaques were visually assessed in 3 consecutive frames within 10 mm from the minimal lumen area site and were classified into 4 types based on geometrical and compositional parameters as well as the location of specific components in the plaque: (1) Pathological intimal thickening, 2) Fibroatheroma, 3) Thin cap fibroatheroma, and 4) Fibrocalcific plaque.[26-28] Plaques were matched between MSCT and VH IVUS as previously described.[29]

Statistical analysis

For comparisons, the patient population was divided based on gender (men versus women) and age (younger (<65 years old) patients versus older (≥65 years old) patients).

First, gender-specific characteristics of coronary atherosclerosis were evaluated in the entire patient population by comparing observations between all men and women. Secondly, age-related differences between men and women were evaluated. For this purpose, the 2 patient populations (men versus women) were further divided into younger (<65 years old) and older (≥65 years old) patients.

Categorical variables are expressed as numbers (percentages) and compared between groups with Chi-square test or Fisher's exact test. When normally distributed, continuous variables are expressed as means (standard deviation) and compared with t-test for independent samples. When not normally distributed, continuous variables are expressed as medians (interquartile range) and compared with the non-parametric Mann-Whitney test. All analyses were 2-tailed.

To minimize the effects of baseline patient characteristics, the correlation between the characteristics of coronary atherosclerosis and patient age and gender was evaluated by multivariable linear regression analysis. The analysis was performed in the 2 age groups. To determine the variables for inclusion in the final multivariable model, unpaired t-test was performed for each of the variables. Variables showing a difference in relation to the dependent variable (number of plaques per patient on MSCT, calcium score on MSCT, plaque burden on gray-scale IVUS and the arc of calcium on gray-scale IVUS) at the significance level of $p \leq 0.2$ were included in the final model.

P-values <0.05 were considered as statistically significant. Statistical analyses were performed using SPSS software (version 14.0, SPSS Inc, Chicago, Ill, USA).

Results

Baseline clinical characteristics of the entire patient population are provided in Table 1. Of 93 patients, 59 (63%) were men and 34 (37%) were women.

IVUS examination was available in 208 (71%) of 279 vessels of 93 patients (129 (62%) vessels in men and 79 (38%) vessels in women). VH IVUS examination was available in a subpopulation of 43 (46%) patients (23 (54%) men and 20 (46%) women). The characteristics of this study subpopulation (patients with VH IVUS) were identical to the general patient population, whereas no differences in CAD risk factors and use of cardiovascular medication were observed between men and women. In total, 70 vessels were available for VH IVUS analysis (37 (53%) vessels in men and 33 (47%) vessels in women).

Table 1. Patient characteristics

Patient characteristic	Men (n=59)	Women (n=34)	P-value
Age	61±9	64±8	0.2
Body mass index	27±4	26±4	0.3
CAD risk factors			
Obesity	18 (31%)	8 (24%)	0.6
Hypercholesterolemia	46 (78%)	26 (77%)	0.9
Hypertension	30 (51%)	24 (71%)	0.06
Diabetes	11 (19%)	4 (12%)	0.4
Family history of CAD	23 (39%)	20 (59%)	0.07
Smoking	27 (46%)	17 (50%)	0.7
Previous CAD			
Previous MI	10 (17%)	5 (15%)	0.8
Previous PCI	12 (20%)	8 (24%)	0.7
Medications			
Aspirin	34 (58%)	21 (62%)	0.7
Statins	38 (64%)	24 (71%)	0.5

Data are mean±SD or n (%).

CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Gender-specific differences in coronary atherosclerosis in the entire patient population

Geometrical characteristics (plaque extent)

MSCT. MSCT coronary angiograms were of diagnostic quality in all patients.

Coronary plaques were more prevalent in men (6.7±3.8 versus 4.0±3.0 in women, p=0.001). This observation was related to a higher prevalence of obstructive plaques (2.0±2.2 in men versus 0.7±1.1 in women, p=0.002), as well as non-obstructive plaques (4.7±3.1 in men versus 3.4±2.8 in women, p=0.04).

Gray scale IVUS. A larger plaque burden was observed in men (45.7±11.4% versus 36.3±11.6% in women, p<0.001). The percentage of IVUS frames with plaque was also higher in men (87.8±19.9% versus 70.2±28.3% in women, p<0.001). In addition, a higher mean remodeling index was observed in men (1.04±0.1 versus 0.99±0.1 in women, p=0.01). Consequently, positive remodeling was more prevalent in men as compared with women (40 (31%) versus 12 (15%) respectively, p=0.02).

Compositional characteristics

MSCT. The median coronary calcium score in men was 256.0 (interquartile range 43.5-706.5) versus 72.0 (interquartile range 2.3-155.8) in women (p=0.003). In line with this observation, the number of calcified plaques on MSCT coronary angiography tended to be higher in men although no statistical significance was reached (2.7±3.5 in men versus 1.7±1.9 in women, p=0.1). Nevertheless, men had significantly more mixed plaques (2.8±3.1) as compared with women (1.3±1.5), p=0.01). Interestingly, the number of non-calcified plaques was identical in men and women (1.3±1.8 versus 1.0±1.3 respectively, p=0.5).

Gray-scale and VH IVUS. The arc of coronary calcium on gray-scale IVUS was larger in men (94.4±88.5 degrees versus 63.6±68.1 degrees in women, p=0.02).

On VH IVUS, the amount of fibrotic tissue was less in the plaques of men (53.6±7.4% versus 57.5±8.0% in the plaques of women, p=0.008). No differences were observed in the amount of fibro-fatty tissue (28.5±12.2% in men versus 25.5±10.4% in women, p=0.2), necrotic core (11.1±6.2% in men versus 10.7±5.9% in women, p=0.7) and dense calcium (6.9±6.3% in men versus 6.3±4.8% in women, p=0.6).

Likewise, no differences were observed in the prevalence of plaque types as determined on visual assessment: pathological intimal thickening was observed in 10 (16%) plaques in men versus 9 (18%) plaques in women (p=0.7), fibroatheroma was observed in 27 (42%) plaques in men versus 20 (40%) plaques in women (p=0.8), thin cap fibroatheroma was observed in 13 (20%) plaques in men versus 6 (12%) in women (p=0.2) and fibrocalcific plaque was observed in 14 (22%) plaques in men versus 15 (30%) plaques in women (p=0.3).

Gender-specific differences in coronary atherosclerosis in younger (<65 years old) patients

In total, 55 (59% of the total population) patients were <65 years old (39 (71%) men and 16 (29%) women). The mean age was 56±5 years in men and 57±5 years in women (p=0.4). No differences in the distribution of CAD risk factors, history of CAD and use of cardiovascular medication were observed between men and women.

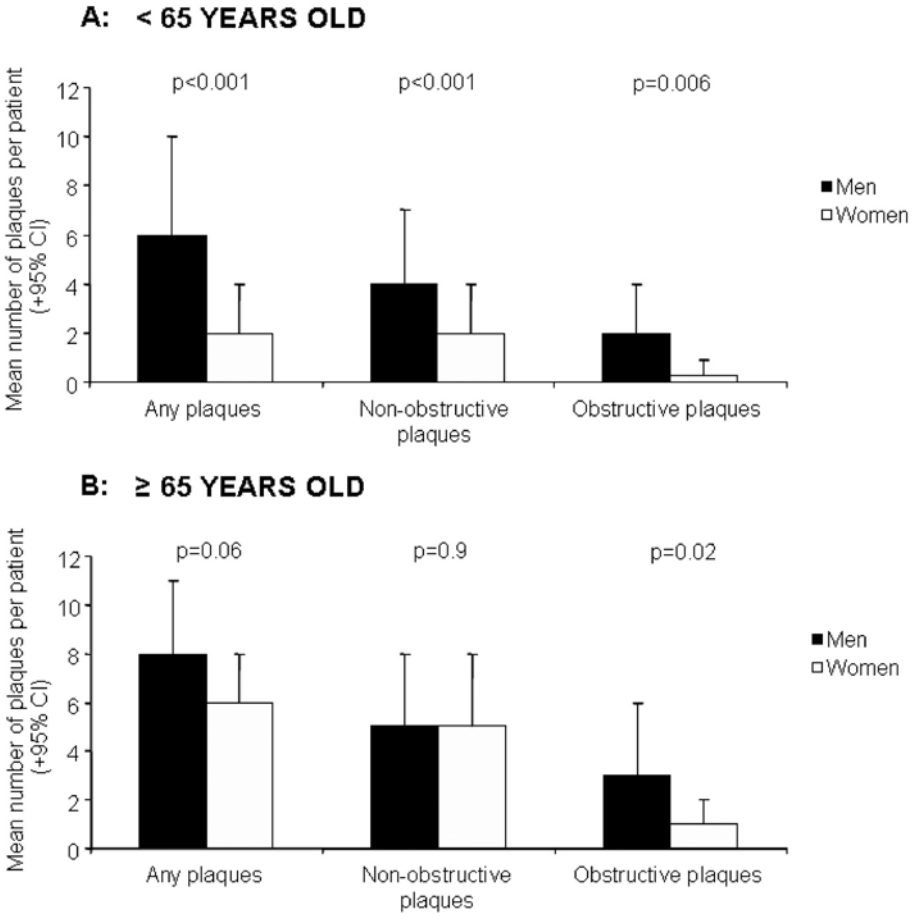

Figure 1. Coronary plaque extent on MSCT versus age and gender.
(A) Younger (<65 years old) patients: a higher prevalence of both non-obstructive and obstructive plaques was observed in men as compared with women. (B) Older (≥65 years old) patients: the number of non-obstructive plaques was identical in both genders, whereas more obstructive plaques were observed in men.

Geometrical characteristics (plaque extent)

MSCT. Geometrical characteristics of coronary atherosclerosis on MSCT in younger patients are presented in Figure 1. The number of coronary plaques was higher in men as compared with women. Both the numbers of non-obstructive and obstructive plaques were higher in men.

Table 2. Geometrical and compositional characteristics of coronary atherosclerosis on gray-scale and VH IVUS in younger (<65 years old) patients

Characteristics	Men	Women	P-value
Plaque extent and composition, gray-scale IVUS	n=90 vessels	n=37 vessels	
Vessel length (cm)	7.0±5.5	7.4±3.8	0.7
EEM area (mm^2)	16.2±8.5	12.2±3.8	0.008
Lumen area (mm^2)	8.8±4.5	8.9±3.2	1.0
Plaque burden (%)	44.8±12.3	27.9±7.9	<0.001
% abnormal frames	85.9±21.4	53.0±26.8	<0.001
Plaque volume in most diseased 10 mm	100.0±41.9	54.9±24.3	<0.001
Plaque volume in least diseased 10 mm	42.1±29.1	18.9±13.2	<0.001
Remodeling index	1.03±0.1	0.99±0.1	0.06
Positive remodeling (n(%))	27 (31%)	6 (16%)	0.1
Largest arc of calcium (degrees)	91.7±93.5	25.7±51.0	<0.001
Plaque composition, VH IVUS			
Lesion length (mm)	24.6±16.8	30.9±17.5	0.3
% fibrotic	51.1±5.1	59.1±8.7	0.001
% fibro-fatty	27.0±11.5	26.7±10.2	0.9
% necrotic core	12.8±6.8	8.5±4.1	0.04
% dense calcium	9.1±7.8	5.7±3.7	0.1
Pathologic intimal thickening	2 (7%)	3 (23%)	0.2
Fibroatheroma	8 (28%)	5 (39%)	0.5
Thin cap fibroatheroma	9 (31%)	0 (0%)	0.04
Fibrocalcific	10 (34%)	5 (38%)	1.0

Data are mean±SD or n (%).

EEM, external elastic membrane; IVUS, intravascular ultrasound; VH IVUS, virtual histology intravascular ultrasound.

Gray-scale IVUS. In total, 127 vessels were available for analysis (90 vessels in men and 37 vessels in women).

Geometrical characteristics of coronary atherosclerosis on gray-scale IVUS in younger patients are presented in Table 2. Coronary artery diameter was larger in men as compared with women. In addition, coronary plaque burden was larger in men in the entire vessel as well as in both the most and the least diseased coronary artery segments. A trend towards a higher prevalence of positive remodeling was observed in men.

Compositional plaque characteristics

MSCT. The median coronary calcium score in men was 216.0 (interquartile range 4.0-714.0) versus 3.5 (interquartile range 0-109.0) in women (p=0.003). Compositional characteristics of coronary atherosclerosis on MSCT in younger patients are presented in Figure 2. A higher number of mixed plaques was observed in men as compared with women. In addition, a trend towards a higher number of calcified plaques was observed in men.

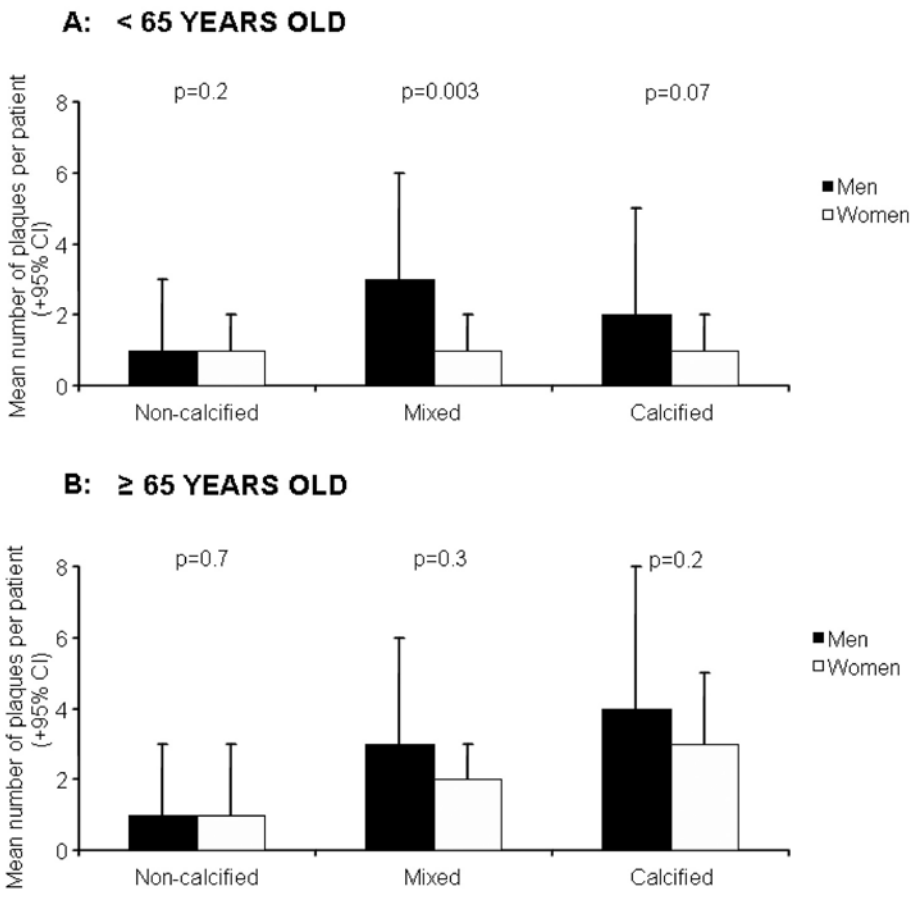

Figure 2 Coronary plaque composition on MSCT versus age and gender.
(A) Younger (<65 years old) patients: more mixed plaques and a trend towards more calcified plaques were observed in men as compared with women. (B) Older (≥65 years old) patients: no differences in coronary plaque composition were observed between men and women.

Gray-scale and VH IVUS. The arc of coronary calcium was larger in men as compared with women (Table 2).

VH IVUS was available in 32 vessels of 21 patients (21 vessels in men and 11 vessels in women). Compositional characteristics of coronary atherosclerosis on VH IVUS in younger patients are presented in Table 2. The plaques in the female population contained more fibrotic tissue, whereas more necrotic core was observed in the plaques of male patients. Thin cap fibroatheroma were observed exclusively in plaques of male patients.

Gender-specific differences in coronary atherosclerosis in older (≥65 years old) patients

In total, 38 (41% of the total population) patients were ≥65 years old (20 (53%) men and 18 (47%) women). The mean age was 72±4 years in men and 70±4 years in women (p=0.2). No differences in the distribution of CAD risk factors, history of CAD and use of cardiovascular medication were observed between men and women.

Geometrical characteristics (plaque extent)

MSCT. Geometrical characteristics of coronary atherosclerosis on MSCT in older patients are presented in Figure 1. No gender based differences were observed in the prevalence of any and non-obstructive plaques. Nevertheless, obstructive plaques were still more frequently present in the male population.

Gray-scale IVUS. In total, 81 vessels were available for analysis (39 vessels in men and 42 vessels in women).

Geometrical characteristics of coronary atherosclerosis on gray-scale IVUS in older patients are presented in Table 3. Similar to younger patients (<65 years old), coronary artery diameter remained larger in men as compared with women. Nevertheless, diffuse coronary atherosclerosis was observed in both men and women, resulting in the absence of differences of plaque burden and percentage of IVUS frames with plaque. In addition, no differences in the measures of coronary artery remodeling were observed. However, more plaque was observed in the most diseased 10 mm of the vessel in men as compared with women.

Table 3. Geometrical and compositional characteristics of coronary atherosclerosis on gray-scale and VH IVUS in older (≥65 years old) patients

Characteristics	Men	Women	P-value
Plaque extent and composition, gray-scale IVUS	n=39 vessels	n=42 vessels	
Vessel length (cm)	7.8±3.5	9.8±10.6	0.3
EEM area (mm^2)	15.3±4.8	12.6±4.6	0.009
Lumen area (mm^2)	7.9±2.6	6.9±2.2	0.07
Plaque burden (%)	47.6±9.1	43.8±8.9	0.06
% abnormal frames	92.1±15.4	85.3±19.8	0.09
Plaque volume in most diseased 10 mm	103.4±41.8	85.4±34.3	0.04
Plaque volume in least diseased 10 mm	39.7±23.1	35.6±27.9	0.5
Remodeling index	1.05±0.2	0.99±0.1	0.1
Positive remodeling (n(%))	12 (31%)	4(14%)	0.2
Largest arc of calcium (degrees)	100.1±77.7	104.1±60.8	0.8
Plaque composition, VH IVUS			
Lesion length (mm)	26.6±18.3	27.4±14.1	0.8
% fibrotic	55.7±8.3	57.0±7.8	0.5
% fibro-fatty	29.7±12.9	25.0±10.6	0.1
% necrotic core	9.6±5.3	11.4±6.2	0.2
% dense calcium	5.0±4.0	6.6±5.2	0.2
Pathologic intimal thickening	8 (23%)	6 (16%)	0.5
Fibroatheroma	19 (54%)	15 (41%)	0.2
Thin cap fibroatheroma	4 (11%)	6 (16%)	0.7
Fibrocalcific	4 (11%)	10 (27%)	0.1

Data are mean±SD or n (%).

EEM, external elastic membrane; IVUS, intravascular ultrasound; VH IVUS, virtual histology intravascular ultrasound.

Compositional plaque characteristics

MSCT. The average coronary calcium score in older men was 387.0 (interquartile range 29.0-704.0) versus 114.5 (interquartile range 36.0-363.25) in older women (p=0.03). Compositional characteristics of coronary atherosclerosis on MSCT in older patients are presented in Figure 2. No differences in plaque composition were observed between men and women.

Gray-scale and VH IVUS. The arc of calcium as measured on gray-scale IVUS was identical in the plaques of both genders (Table 3).

VH IVUS was available in 38 vessels (16 vessels in men and 22 vessels in women). Compositional characteristics of coronary atherosclerosis on VH IVUS in older patients are presented in Table 3. No differences in plaque composition were observed between 2 genders.

Progression of coronary calcification in relation to age and gender

The development of coronary calcification with increasing age is depicted in Figure 3. As can be derived from Figure 3, more extensive calcification was observed in men. However, progression of coronary calcification, as reflected by the coronary calcium score as well as the arc of calcium, was substantially more pronounced after the age of 65 years old in women as compared with men.

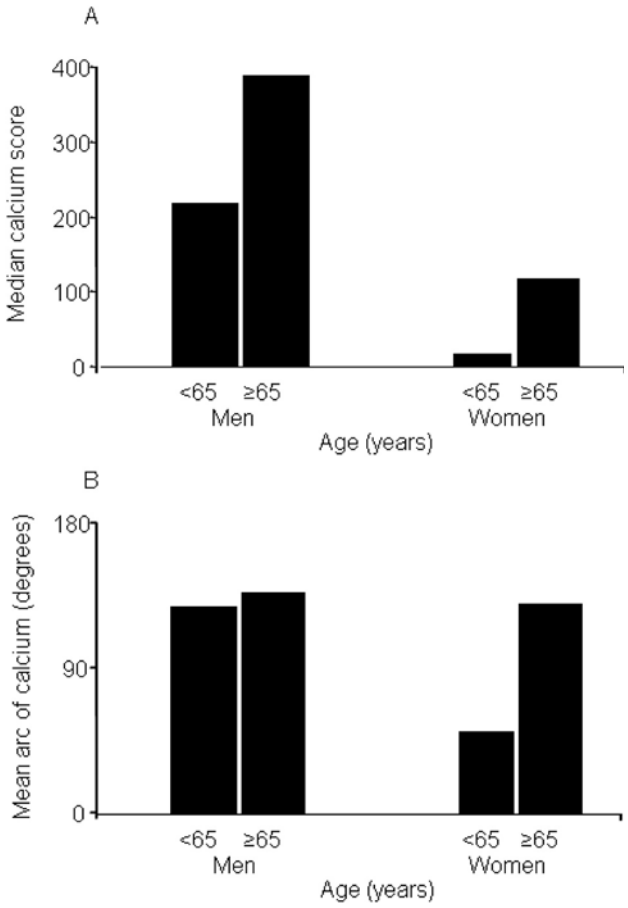

Figure 3. The progression of coronary calcification in relation to age and gender.
(A) Coronary calcium score on MSCT: a higher calcium score was observed in men. The progression of coronary calcification was more prominent after the age of 65 years old in women as compared with men. (B) The arc of calcium on gray-scale IVUS: similar pattern of progression of coronary calcification was observed on gray-scale IVUS.

Correlation between characteristics of coronary atherosclerosis, age and gender

Finally, the results of multivariable regression analysis evaluating the correlation between variables of coronary atherosclerosis and baseline patient characteristics are presented in Tables 4 and 5. As can be derived from Table 4, male gender was correlated with the measures of coronary plaque extent both on MSCT and on gray-scale IVUS in younger (<65 years old) patients. Nevertheless, this relationship was lost when the analysis was performed in the older (≥65 years old) patient group.

Table 4. Correlation between the geometrical characteristics of coronary atherosclerosis and baseline patient characteristics: multivariable regression analysis

Predictors	β coefficient (95% CI)	P-value
Nr of plaques per patient on MSCT, younger (<65 years old) patients		
Male gender	3.7 (1.7-5.7)	<0.001
Previous CAD	2.7 (0.5-4.9)	0.02
Hypercholesterolemia	-0.2 (-2.5-2.0)	0.8
Statins	1.1 (-0.9-3.1)	0.3
Nr of plaques per patient on MSCT, older (≥65 years old) patients		
Male gender	1.9 (-0.2-4.0)	0.08
Diabetes	2.4 (-0.9-5.8)	0.1
Hypertension	-0.2 (-2.5-2.1)	0.9
Plaque burden on gray-scale IVUS, younger (<65 years old) patients		
Male gender	15.0 (8.7-21.3)	<0.001
Previous CAD	2.7 (-4.3-9.7)	0.4
Smoking	-3.9 (-9.6-1.9)	0.2
Statins	3.9 (-2.2-10.0)	0.2
Plaque burden on gray-scale IVUS, older (≥65 years old) patients		
Male gender	3.0 (-2.8-8.9)	0.3
Hypercholesterolemia	-2.9 (-10.6-4.7)	0.4
Hypertension	-4.2 (-10.8-2.3)	0.2

CAD, coronary artery disease; CI, confidence intervals; IVUS, intravascular ultrasound; MSCT, multi-slice computed tomography.

Similar observations were obtained with regard to plaque composition. The coronary calcium score on MSCT and the arc of calcium on gray-scale IVUS were correlated with male gender in younger patients. No correlation between calcified lesions and gender was observed in older patients (Table 5).

Table 5. Correlation between compositional characteristics of coronary atherosclerosis and baseline patient characteristics: multivariable regression analysis

Predictors	β coefficient (95% CI)	P-value
Total calcium score on MSCT*, younger (<65 years old) patients		
Male gender	0.9 (0.2-1.6)	0.009
Smoking	-0.4 (-1.1-0.2)	0.2
Total calcium score on MSCT*, older (≥65 years old) patients		
Male gender	0.3 (-0.2-0.8)	0.3
Obesity	0.4 (-0.1-0.9)	0.1
Hypertension	-0.3 (-0.9-0.2)	0.2
Statins	-0.2 (-0.8-0.4)	0.5
The arc of calcium on gray-scale IVUS, younger (<65 years old) patients		
Male gender	66.8 (1.3-132.2)	0.04
Obesity	28.4 (-40.2-97.0)	0.4
Hypertension	44.2 (-14.5-102.9)	0.1
Smoking	-44.6 (-102.5-13.3)	0.1
The arc of calcium on gray-scale IVUS, older (≥65 years old) patients		
Male gender	26.8 (-9.4-63.0)	0.1
Diabetes	136.9 (74.1-199.6)	<0.001
Hypercholesterolemia	75.0 (12.5-137.4)	0.02
Statins	1.6 (-52.7-55.8)	1.0

* log10 transformation of the total calcium score.

CAD, coronary artery disease; CI, confidence intervals; IVUS, intravascular ultrasound; MSCT, multi-slice computed tomography.

Discussion

The findings of the study can be summarized as follows. More extensive atherosclerosis and more advanced calcified lesions were observed in men on MSCT as compared with women. Conversely, in women atherosclerosis tended to be non-obstructive with a relatively larger contribution of non-calcified plaque. The findings were confirmed on invasive gray-scale and VH IVUS. Comparison of the observations with regard to age revealed that the differences of coronary plaque observations were predominantly present in younger patients. The differences in coronary plaque extent and composition were lost or minimal between the 2 genders in older patients.

Plaque extent and severity

In the present study, less coronary plaques were observed in younger (<65 year old) women as compared with younger men both on MSCT and on gray-scale IVUS. This observation is in-line with previous IVUS studies.[12] Indeed, in a recent investigation by Nicholls et al (including 251 female patients, mean age <65 years),[12] coronary plaque burden was significantly lower in women (33.9% versus 37.8% in men, $P < 0.001$). Similarly, a pathologic study of victims of accidents revealed a lower prevalence of atherosclerotic plaque with ≥40% stenosis in young women as compared with men.[30] In contrast, Kornowski et al,[31] who performed preinterventional IVUS in slightly older women (average age 66 years) and compared findings to significantly younger male population (average age 60 years), failed to show any differences in plaque burden). Similarly, the difference in plaque extent was also lost in our study when comparing patients older than 65 years. To a large extent, these observations indicate a delay in the development of CAD in premenopausal women. Nevertheless, diffuse (non-obstructive) coronary atherosclerosis was observed in women across all ages both on MSCT and on gray-scale IVUS. Moreover, whereas CAD progression in men was related with an increase in both non-obstructive and obstructive lesions coronary atherosclerosis in women progressed with age mainly due to an increase in non-obstructive plaques. In line with this observation, plaque volume in the most diseased 10 mm remained significantly higher in older men as compared with older women, whereas no differences were observed in measures reflecting the total extent of atherosclerosis, including percentage of abnormal frames. Possibly, the presence of non-obstructive atherosclerosis in the absence of evident obstructive lesions may reflect a different manifestation of CAD and should not necessarily be considered benign. Indeed, 4 years of follow-up in the Women's Ischemia Syndrome Evaluation study revealed that women with no or minimal stenoses on invasive coronary angiography still had a 9.4% risk of death or myocardial infarction.[4] It has been hypothesized that the occurrence of chest pain in women may be related to vasculopathy in the absence of obstructive CAD.[32] Importantly, the traditional diagnostic work-up based on luminography may result in under-appreciation of CAD in women and atherosclerosis imaging may be preferable. Future research is necessary to investigate possible relationship between the presence of diffuse atherosclerosis on MSCT and coronary artery dysfunction in women.

Plaque composition

In the present study, lesions in men tended to be more calcified whereas the relative contribution of non-calcified plaques to the total plaque burden was higher in women. In younger women, smaller numbers of mixed plaques and a trend for less calcified plaques were observed on MSCT as compared with men. This observation is in line with observations by Burke et al [33] who investigated the hearts of victims of sudden death. The mean calcification load was lower in women of less than 60 years old as compared with men. Similar observations were reported on calcium scoring with electron beam computed tomography.[13] Indeed, calcium is often associated with more advanced atherosclerotic lesions.[33,34] As a result, the smaller amount of calcium in younger women may reflect less progressed atherosclerosis. Indeed, in the current study more fibrotic tissue and a trend towards a higher proportion of pathological intimal thickening were observed in the plaques of younger women on VH IVUS. In contrast, in patients <65 years old thin cap fibroatheromas were exclusively observed in men while also percentage of necrotic core was significantly higher. This is in line with observations in sudden death post-mortem studies. In men as well as older women, ruptured lesions with typically a large necrotic core and disrupted fibrous cap infiltrated by macrophages and lymphocytes were frequently observed.[35] In younger women, however, a greater tendency towards erosion of lesions that are rich in fibrotic tissue but contain limited calcium has been observed.[26,33] As a result, the differences in coronary plaque calcification in younger patients may reveal particular patterns of plaque progression in 2 genders.

Of interest, coronary calcium score as detected on MSCT was still lower in older women as compared with men, whereas the number of calcium containing lesions was the same between the 2 genders. Indeed, in line with our observations a smaller coronary artery calcium load has been observed in women of all ages in previous studies with electron beam computed tomography.[13] Nevertheless, it has also been demonstrated that similar calcium load in men and women was related with worse prognosis in women.[36] The possible explanation for this phenomenon may be two-fold. First, calcium scoring does not take coronary artery size into account. A similar calcium score may actually imply a higher percentage atheroma volume in women due to smaller vessel caliber (as also observed in the present study). Secondly, the relative contribution of non-calcified atherosclerosis to total plaque burden may be higher in women.[26,33] Accordingly, non-invasive coronary angiography with MSCT may be superior to calcium scoring as it also allows detection of non-calcified plaque and thus may provide a more reliable estimate of total plaque burden.

Interestingly, as compared with men, a more pronounced increase in coronary calcifications was observed in women over the age of 65 years old both on MSCT and on gray-scale IVUS. Indeed, also pathology and other non-invasive imaging studies have shown that an initial ~10 year lag in the development of calcifications exists. However, this phenomenon disappears during the sixth and seventh decade in women.[4,13,33] As a result, initial differences between men and women in coronary plaque composition appear to converge in older patients, as also observed in the present study.

Limitations

Observations of the current study were obtained in a relatively small patient population. In general, MSCT is still associated with an elevated radiation exposure, although radiation doses are rapidly decreasing with newer acquisition protocols. Also, no dedicated algorithms that allow quantification of plaque stenosis or volume are available for MSCT at present. An important limitation of VH IVUS is the fact that the technique is relatively new and not widely available. Moreover, the current observations need confirmation in future studies including higher patient numbers.

Conclusions

Using both non-invasive and invasive plaque imaging modalities, more extensive atherosclerosis and more advanced calcified lesions were observed in men as compared with women. Comparison of the observations with regard to age revealed that these differences were predominantly present in younger patients and were lost or minimal in older patients.

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