The International Journal of Cardiovascular Imaging (2019) 35:907–915
https://doi.org/10.1007/s10554-018-1512-0

ORIGINAL PAPER

Atherosclerotic plaque burden evaluated from neck to groin: effect of gender and cardiovascular risk factors

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Received: 15 August 2018 / Accepted: 2 December 2018 / Published online: 13 December 2018

Abstract

We explored the impact of gender and cardiovascular risk factors (RF) in the distribution and burden of coronary and extra-coronary atherosclerotic plaques among patients undergoing ECG-gated thoracoabdominal computed tomography angiography (CTA) from the supra-aortic trunks to the femoral arteries. We included a consecutive cohort of patients who underwent ECG-gated thoracoabdominal aortic CTA from the supra-aortic trunks to the pubic symphysis. We evaluated the number of coronary segments with plaques [segment-involvement score (SIS)]; and the extra-coronary atherosclerotic plaque burden, comprising the aorta and supra-aortic trunks, iliofemoral arteries, and visceral arteries (extra-coronary SS). A total of 3400 vascular segments were evaluated in 100 patients (mean age 67.0 ± 12.6 years, 66% male). Seventy-two (72%) patients had evidence of atherosclerosis in the coronary tree (coronary SIS ≥ 1), of which 32% was extensive (coronary SIS > 5). Males had a significantly higher prevalence of coronary SIS ≥ 1 [53 (80%), vs. 19 (56%), $p = 0.018$], and coronary SIS > 5 [24 (36%) vs. 8 (24%), $p = 0.035$] than females. Extra-coronary SS was similar between genders (males 10.2 ± 5.8 vs. females 9.7 ± 5.4, p = 0.70), irrespective of the location along the different vascular beds. The number of coronary RF was significantly related to the coronary SIS ($p = 0.038$), and hypertension and diabetes were consistently related to coronary and extra-coronary plaque burden. In the present study involving analysis of multiple vascular beds from the supra-aortic trunks to the femoral arteries, we identified significant sex-related differences in coronary plaque burden, whereas extra-coronary plaque burden was similar between genders irrespective of the vascular bed assessed.

Keywords Atherosclerosis · Computed tomography angiography · Sex-related · Vascular calcifications · Coronary

Introduction

Atherosclerosis is an inflammatory disease related to cardiovascular risk factors (RF) as well as to a number of genetic and environmental factors. Notwithstanding, rather than diffuse as it might be expected given the systemic influence of RF, atherosclerotic plaques develop and progress in a distinctive non-uniform manner. Indeed, the prevalence and extent of disease can differ along different vascular beds, although the underlying pathophysiological grounds remains unsettled [1]. Local hemodynamic flow patterns have a role in this regard since they have shown to promote or protect against plaque progression, leading to clustering of atherosclerotic lesions in certain regions [2–5]. In parallel, significant gender differences have been reported concerning the onset and extent of coronary atherosclerosis [6]. Previous epidemiological studies suggested that the higher estrogen levels might serve as a protective factor in pre-menopausal women, with the beneficial effect fading with aging [7]. However, a recent study has shown that gender differences in the coronary tree persist even among very elderly women, with males showing consistently higher calcification [8].

Overall, there is limited evidence exploring the effect of gender and cardiovascular RF on the extent and distribution of atherosclerosis in different vascular beds, and has been provided mainly by individual reports exploring the relationship between these variables and coronary or extra-coronary atherosclerosis. We therefore explored the impact of gender and cardiovascular RF in the distribution

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10554-018-1512-0) contains supplementary material, which is available to authorized users.

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and burden of coronary and extra-coronary atherosclerotic plaques among patients undergoing ECG-gated thoracoabdominal computed tomography angiography (CTA) from the supra-aortic trunks to the femoral arteries.

Methods

This was an investigator-driven observational study that included a consecutive cohort of patients who underwent ECG-gated thoracoabdominal CTA in our institution between January 2016 and November 2017. Thoracoabdominal aortic CTA were clinically indicated for various reasons comprising aortic dilatation, guidance of transcatheter aortic valve replacement, and atherosclerotic disease or suspicion of acute aortic syndrome among other. Patients with previous endovascular aortic repair (EVAR), aortic bifemoral bypass, aortic dissection, valve surgery, coronary artery bypass graft (CABG) surgery, and coronary stents were excluded. Among patients with repeated scans, only the first scan was included and those who refused to provide Habeas data were also excluded. A radiologist blinded to the CTA collected data regarding demographical characteristics and cardiovascular risk factors. Diagnosis of individual risk factors were established if documented in the clinical history or if the patient was under medical treatment for diabetes, hypercholesterolemia, or hypertension. Smoking was defined as current or previous smoking history. The protocol was approved by the institutional ethics committee and all studies have been performed in accordance with the ethical standards as laid down in the 1975 Declaration of Helsinki and its later amendments. Informed consent was obtained from all individual participants included in the study.

Image acquisition

In our institution, CTA scans comprising the thoracic aorta are acquired using ECG-gating with dose modulation in order to avoid motion artifacts and to enable more accurate measurements (16). Scans were acquired in three centers of the same institution using 64 (n = 27), 128 (n = 15), 256 (n = 41) slice CT scanners (Brilliance CT family; Philips Healthcare, Cleveland, USA) and a high definition CT (n = 17) scanner (Discovery HD 750, GE Medical Systems, Milwaukee, USA) with a single breath-hold from the supra-aortic trunks to the pubic symphysis. For CTA examinations acquired in the high-definition scanner, the thoracic CTA was acquired using ECG-gating and the abdominal CTA was performed non-gated immediately after. CTA were acquired as previously reported [9].

Image analysis

CTA images were transferred to a dedicated workstation (Brilliance Workspace, Philips Healthcare, Cleveland, Ohio, USA), and analyses were performed by an observer with more than 10 years of experience in cardiovascular imaging blinded to the clinical data. Gated systolic and mid-diastolic images were analyzed in the phase with the least motion artifacts. Axial planes and average multiplanar reconstructions and maximum intensity projections (1–5 mm thickness) were used to assess the presence and extent of coronary and extra-coronary atherosclerotic plaque burden. The number of coronary segments with mixed or calcified plaques (segment-involvement score, coronary SIS) was calculated as previously reported; irrespective of the degree of stenosis [10, 11]. Detailed methodological aspects regarding the assessment of coronary and extra-coronary plaque burden are provided in the (online) appendix. Briefly, the extra-coronary atherosclerotic plaque burden comprised the presence and extent of disease in the thoracoabdominal aorta (including supra-aortic trunks), iliofemoral arteries, and visceral arteries. Subsequently, we developed two scores according to the number of regions involved (extra-coronary SIS), and other score (extra-coronary SS) involving both the extra-coronary SIS and correction factors for extension and severity (longitudinal and axial extension, degree of stenosis, and presence of complex plaques) [12].

Statistical analysis

Discrete variables are presented as counts and percentages. Continuous variables are presented as means ± standard deviation, or median (interquartile range; IQR), as indicated. Comparisons between continuous variables were performed using independent samples t test and one-way analysis of variance tests, as indicated. Non-parametric comparisons were performed using Wilcoxon signed rank tests and Mann–Whitney U tests. Comparisons between categorical variables were performed using Chi square tests. We performed a logistic regression analysis to identify predictors of extensive coronary plaque burden (coronary SIS > 5), and of an extra-coronary SS > 13.1 (upper tertile) including the following variables in the model (Forward-Wald method): sex, age, BMI, hypercholesterolemia, hypertension, diabetes, smoking, and family history. In order to assess the interobserver agreement for the assessment coronary, and extra-coronary plaque burden, 20 cases were randomly selected and re-analyzed independently by two observers and analyzed using intraclass correlation coefficients (ICC; two-way random effect model,

absolute agreement, and average measurement) with 95% confidence intervals. A two-sided *p* value of less than 0.05 indicated statistical significance. Statistical analyses were performed using SPSS software, version 22.0 (IBM SPSS Statistics for Windows, Armonk, NY).

Results

One hundred and forty eight patients underwent thoracoabdominal ECG-gated aortic CTA in our institution between January 2016 and November 2017. Forty eight patients were excluded, 11 patients due to Habeas data refusal, 1 patient due to a repeated scan, 31 patients due to previous interventions (previous coronary revascularization, EVAR, aortic bifemoral bypass, or valve surgery), 5 due to aortic dissection, and 1 patient with poor image quality. Consequently, the study population comprised 100 patients, in whom a total of 3400 vascular segments were individually evaluated. The mean age was 67.0 ± 12.6 years, 66 (66%) were male and 18 (18%) had diabetes. Most (62%) scans were indicated in patients with suspicion or documentation of aortic dilatation, of which 33 (33%) were confirmed at CTA. Detailed demographical characteristics discriminated by sex are displayed in Table 1.

Seventy-two (72%) patients had evidence of atherosclerosis in the coronary tree (coronary SIS ≥ 1), of which 32% had extensive coronary atherosclerosis (coronary SIS > 5). The median coronary SIS was 3.0 (interquartile range 0.0–7.0). Only 10 (10%) patients had absence of thoracoabdominal extra-coronary atherosclerosis. The mean extra-coronary SIS and extra-coronary SS were 8.3 ± 4.2 and 10.0 ± 5.6, respectively [median of 9.0 (6.0; 12.0) and 10.7 (6.4; 14.5), respectively], with 144 complex (≥ 4 mm thick, ulcerated, or focally dissected) extra-coronary lesions identified in 52 (52%) patients. A good interobserver agreement was present regarding coronary SIS [ICC 0.97 (95% CI 0.93; 0.99)] and extra-coronary SS [ICC 0.96 (95% CI 0.89; 0.98)].

Table 1 Demographical characteristics

	Males (n = 66)	Females (n = 34)	*p* value
Age, years ± SD	66.6 ± 12.0	68.0 ± 13.8	0.62
Hypertension, n (%)	47 (71%)	23 (68%)	0.82
Hypercholesterolemia, n (%)	27 (41%)	9 (27%)	0.19
Smoking history, n (%)	39 (59%)	12 (35%)	0.03
Diabetes, n (%)	12 (18%)	6 (18%)	1.0
Family history of CHD, n (%)	4 (6%)	4 (12%)	0.43
Obesity, n (%)	23 (35%)	12 (36%)	1.0
Body mass index, kg/m^2 ± SD	29.7 ± 5.4	28.3 ± 7.5	0.30
Clinical presentation			0.07
Aortic dilatation	46 (70%)	16 (47%)	
Guidance of TAVR	9 (14%)	11 (32%)	
Atherosclerotic disease or suspicion of AAS	9 (14%)	4 (12%)	
Other	2 (3%)	3 (9%)	

CHD coronary heart disease, *TAVR* transcatheter aortic valve replacement, *AAS* acute aortic syndrome

Relationship between coronary and extra-coronary plaque burden, and effect of gender

Coronary and extra-coronary plaque burden were significantly related, and median extra-coronary SS was significantly higher among patients with increasing coronary plaque burden categories [coronary SIS 0, 2.0 (0.0; 7.0); coronary SIS 1–5, 9.0 (7.0; 11.0), coronary SIS > 5, 12.0 (10.0; 13.0), $p < 0.0001$]. Among patients with absence of plaques in the abdominal aorta, 88% had coronary SIS 0 and none exhibited coronary SIS > 5 (Fig. 1). However, patients with non-extensive coronary plaque burden (coronary SIS 1–5) showed a wide range of extra-coronary plaque prevalence, burden, and spatial distribution (minimum 2, maximum 13; Figs. 1, 2, 3).

We identified significant sex-related differences regarding the prevalence of any coronary plaque [males 53 (80%), vs. females 19 (56%), $p = 0.018$], with a significantly higher median coronary SIS in males [4.0 (1.0; 8.3) vs. 2.0 (0.0; 5.3), $p < 0.0001$]. The presence of extensive coronary atherosclerosis was also more prevalent in males [24 (36%) vs. 8 (24%), $p = 0.035$].

We found similar extra-coronary SIS [males 8.4 ± 4.2 vs. females 8.1 ± 4.2, $p = 0.68$] and extra-coronary SS [males 10.2 ± 5.8 vs. females 9.7 ± 5.4, $p = 0.70$] between genders. The same comparable prevalence of disease was noted irrespective of the location along the different vascular beds (Fig. 4). Likewise, males and females had a similar prevalence [males 37 (56%) vs. females 29 (44%), $p = 0.30$] and number [males 1.0 (0.0; 2.25) vs. females 0.0 (0.0; 2.0), $p = 0.20$] of extra-coronary complex lesions.

Relationship between coronary risk factors and plaque burden

The number of coronary RF was significantly related to the coronary SIS (0–1 RF 2.6 ± 2.7, 2 RF 5.0 ± 4.0, ≥ 3 RF 4.4 ± 4.4, $p = 0.038$), but we did not find a significant relationship with the extra-coronary SS (0–1 RF 8.4 ± 5.4, 2 RF 10.8 ± 6.2, ≥ 3 RF 10.7 ± 5.2, $p = 0.15$). A different contribution of individual RFs was observed. Of those, hypertension and diabetes were consistently related to coronary and extra-coronary plaque burden, whereas patients with a history of smoking showed only a trend towards larger extent of plaque

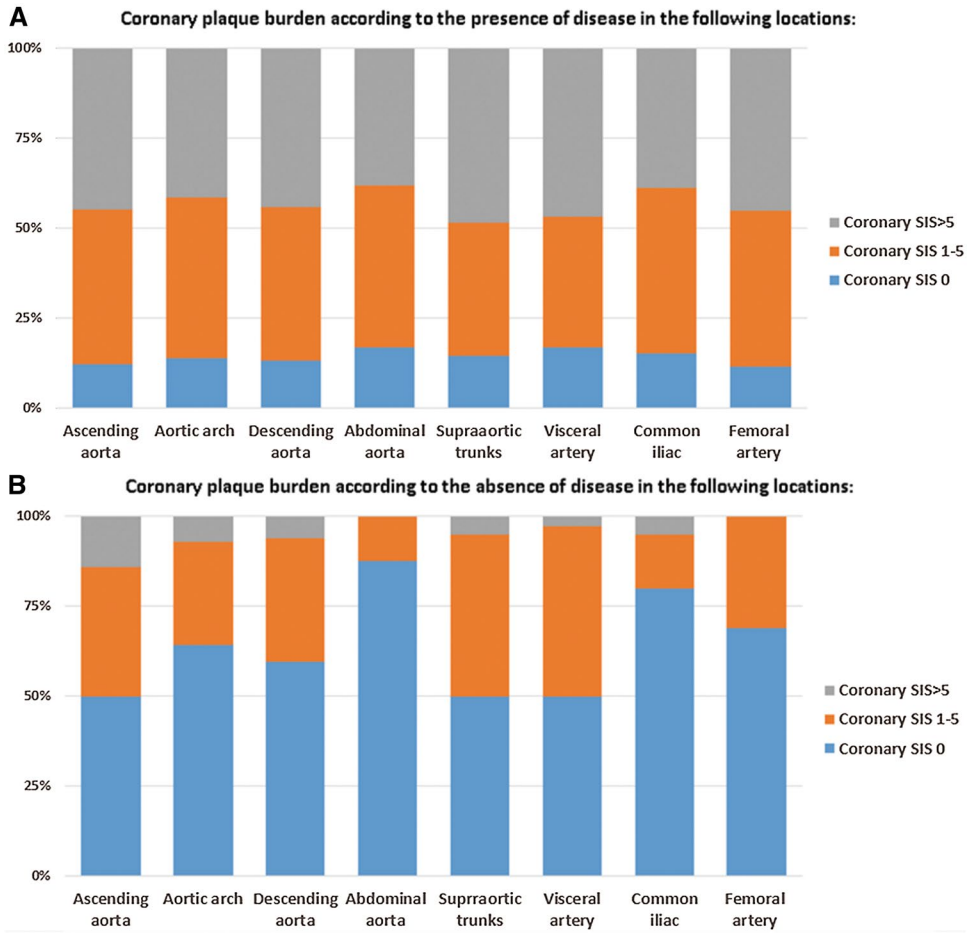

Fig. 1 Bar graphs displaying the extent of coronary plaque burden among patients with presence (**a**) or absence (**b**) of extra-coronary atherosclerotic disease at different vascular beds. Note the considerable percentage of patients with presence of coronary plaque despite absence of extra-coronary disease (**b**)

burden (Table 2). Obesity and hypercholesterolemia were not associated to coronary or extra-coronary plaque burden, whereas few subjects of our sample had family history of premature coronary heart disease. Table 2 displays these results in detail. At multivariate analysis, age was identified as the only independent predictor of extensive coronary [OR 1.07 (95% CI 1.03–1.12), $p=0.002$] and extra-coronary [OR 1.07 (95% CI 1.03–1.12), $p=0.001$] plaque burden.

Discussion

The main finding of our study, that involved gated CTA from the supra-aortic trunks to the femoral arteries, was the identification of significant sex-related differences in coronary plaque burden, whereas extra-coronary plaque burden was similar between genders irrespective of the vascular bed. Besides, patients with non-extensive atherosclerotic coronary disease showed a heterogeneous array of extra-coronary plaque prevalence, burden, and spatial distribution.

Few studies have evaluated the relationship between coronary and extra-coronary atherosclerosis. Importantly, most of them involved relatively young patients and did not use a single imaging modality to explore the atherosclerotic plaque burden. For instance, the Progression of Early Subclinical Atherosclerosis (PESA) study, that comprised an evaluation of coronary (by non-enhanced CT) and carotid, aortic, and iliofemoral (by ultrasound) territories in asymptomatic middle-aged (40–54 year-old) subjects, identified significant differences in the prevalence of plaque amongst vascular territories [13]. Also, in middle-aged men, Laclaustra et al. identified significantly higher prevalence of plaques in the femoral compared to the coronary territories [14]. In a more recent study including patients with normal myocardial perfusion imaging and whole body non-enhanced CT calcium scanning, Allam et al. reported significant differences between these. In particular, 53% of patients without coronary calcifications had evidence of extra-coronary calcifications [15].

In line with the above, though underscoring the inclusion of an older population and a more detailed analysis using ECG-gated CTA, we identified a variable extent of atherosclerotic disease between the different vascular territories. Particularly, patients with non-extensive coronary disease showed inconsistent extra-coronary plaque burden, ranging from almost none to severe.

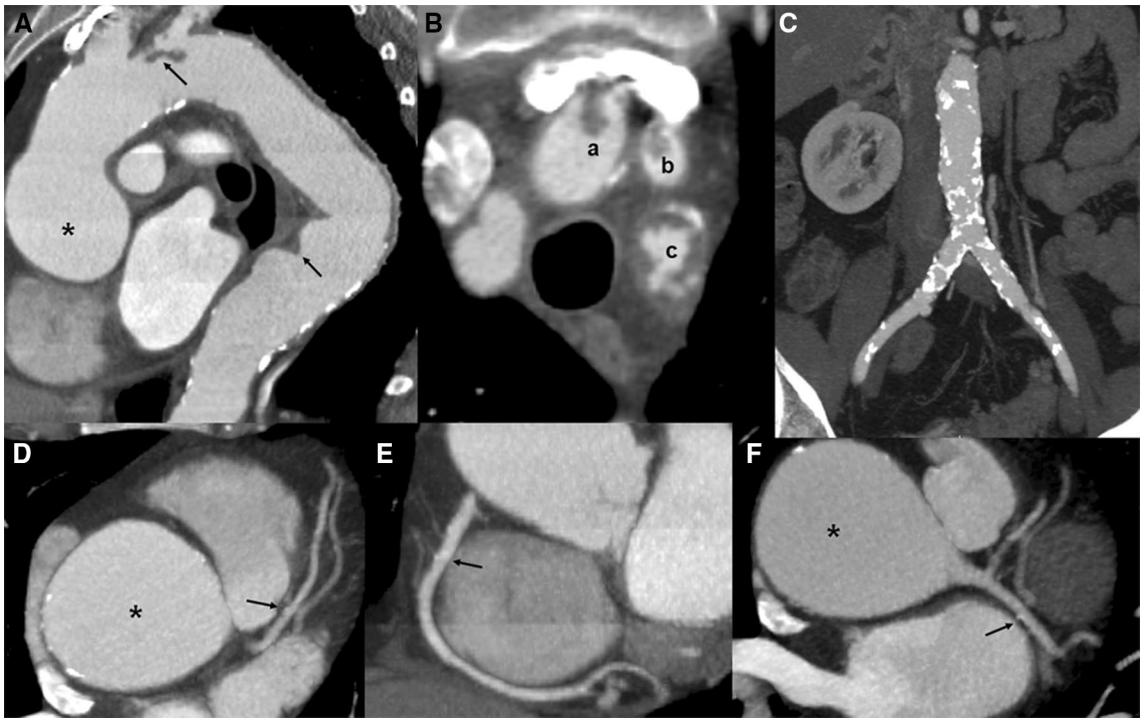

Fig. 2 Seventy-year-old female, with hypertension and smoking as risk factors, and a BMI of 33.1 kg/m^2. She underwent CTA due to an ascending aorta aneurysm (asterisk). She has diffuse complex disease of the thoracic aorta and supraaortic trunks, with multiple complex and fragmented thrombotic lesions in the aortic arch and descending aorta (arrows in **A**); innominate artery, common left carotid, and left subclavian artery (a, b, and c, in **B**). The abdominal aorta and iliofemoral tree are diffusely calcified (**C**). The coronary tree has only minimal calcifications (coronary SIS of 3; arrows in **D**–**F**)

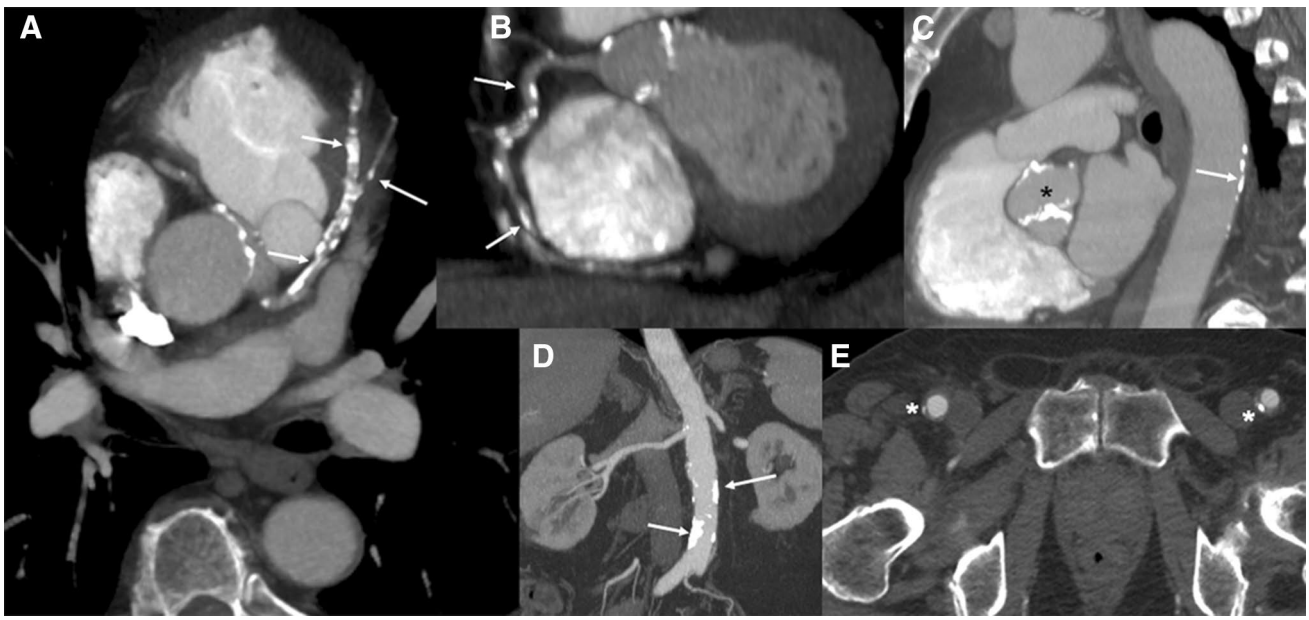

Fig. 3 Seventy-six year-old male, with hypercholesterolemia and hypertension as risk factors, and a BMI of 32.9 kg/m^2. Diffuse coronary atherosclerosis is clearly depicted (arrows **a, b**), with a coronary SIS of 12. The aortic valve is diffusely calcified (asterisk in **c**), and he has moderate extra-coronary atherosclerotic disease (arrows in **c, d**, extra-coronary SS 12.5) mostly within the abdominal aorta. Non-complex atherosclerotic lesions are observed at the femoral arteries (asterisk in **e**)

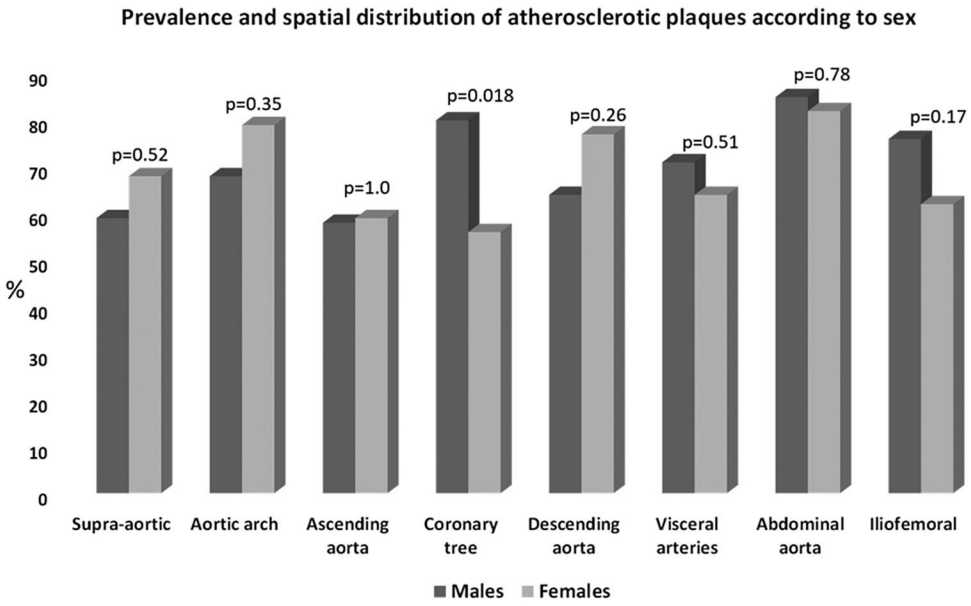

Fig. 4 Prevalence and spatial distribution of atherosclerotic plaques according to sex

Sex-related differences regarding the prevalence and severity of coronary atherosclerosis, previously deemed to fade away after menopause, have later shown to be unconnected to age [6, 8, 16]. As aforementioned, Liyanage et al. demonstrated enduring gender differences even among very elderly women, with males showing significantly higher coronary calcification prevalence and extension [8]. Likewise, in a sub-analysis of the multinational CONFIRM registry, Otaki et al. reported that among young (< 45 year-old) patients, males nearly doubled the prevalence of coronary plaques compared to females, independent of cardiovascular RF [6]. Our results, involving a relatively old population, are in keeping with the abovementioned studies showing a significantly larger coronary plaque burden among males. In contrast, and surprisingly, extra-coronary plaque burden was comparable between genders irrespective of the thoracoabdominal vascular bed assessed. The pathophysiological grounds for the discordant outcomes between coronary and extra-coronary territories remain elusive. Notwithstanding, a number of hypotheses can be drawn in this respect.

Firstly, coronary and extra-coronary artery disease have distinctive phenotypes. While coronary plaques typically show fibrous cap atheromas, necrotic cores, and dense underlying inflammation, aortic and peripheral atherosclerotic plaques are strongly influenced by the underlying coagulation state [17, 18]. Secondly, local hemodynamic forces (wall shear stress) and arterial elasticity, that have shown to have an impact in the development and composition of plaques, display different patterns in the coronary tree compared to the extra-coronary vascular beds [2, 19, 20]. Thirdly, genetic factors including the apoE genotype and single nucleotide polymorphisms have shown to elicit visible phenotype differences between the coronary tree and other territories [21, 22]. Finally, gender differences in regional fat depots, that have been reported to exert a distinct influence on coronary atherosclerosis by means of paracrine and vasocrine mechanisms, might have a role in this respect [23–25]. Indeed, we recently identified a relationship between the extent of pericardial fat and worsening survival in a cohort of 1250 patients who underwent conventional non-gated chest CT [26]. Sex-related differences in regional fat depots, with males showing higher pericardial and visceral fat (with similar embryological origin and associated to a pro-inflammatory state), and lower subcutaneous fat volume compared to females, might potentially explain such differences in plaque burden [27]. Furthermore, using CT coronary angiography in two large prospective cohorts, the recently published CRISP CT study validated the prognostic value perivascular fat attenuation as a predictor of all-cause and cardiac mortality, independent of demographics, epicardial fat volume, high-risk plaque features, and the extent of atherosclerosis [28]. Our investigation does not offer answers to the aforementioned assumptions. However, we provide intriguing data that reinforce the knowledge about the differences between the coronary tree and other vascular territories.

We identified a significant relationship between the increasing number of RFs and coronary plaque burden. Regarding the individual contribution of RF, hypertension and diabetes were consistently related to both coronary and extra-coronary plaque burden. It is noteworthy that obesity and hypercholesterolemia were not associated to coronary or extra-coronary plaque burden. The former adds to the puzzling evidence concerning the relationship between obesity and atherosclerosis, possibly linked to the fact that BMI is probably a poor marker of adiposity [9, 23, 29]. In

Table 2 Relationship between demographical characteristics and plaque burden

	Coronary plaque burden				Extra-coronary plaque burden	
	SIS 0	SIS 1–5	SIS > 5	SIS	SS	SIS
Age						
< 64 years-old (n = 33)	19 (58%)	4 (13%)	5 (14%)	1.8 ± 3.0	5.5 ± 5.6	4.6 ± 4.4
64–72 years-old (n = 32)	10 (30%)	16 (50%)	14 (40%)	5.1 ± 4.0	12.2 ± 4.3	9.8 ± 2.3
> 72 years old (n = 35)	4 (12%)	12 (38%)	16 (46%)	5.3 ± 3.7	12.3 ± 4.1	10.5 ± 2.9
p value	< 0.0001*			< 0.0001†	< 0.0001†	< 0.0001†
Sex						
Male (n = 66)	13 (20%)	29 (44%)	24 (36%)	4.8 ± 4.2	10.2 ± 5.8	8.4 ± 4.2
Female (n = 34)	15 (44%)	11 (32%)	8 (24%)	2.6 ± 2.8	9.7 ± 5.4	8.1 ± 4.2
p value	0.035*			0.006	0.70	0.68
Hypertension						
Yes (n = 70)	13 (19%)	30 (43%)	27 (39%)	4.9 ± 3.9	11.4 ± 4.5	9.5 ± 3.2
No (n = 30)	15 (50%)	10 (33%)	5 (17%)	2.2 ± 3.1	6.8 ± 6.6	5.5 ± 4.9
p value	0.004*			0.001	< 0.0001	< 0.0001
Hypercholesterolemia						
Yes (n = 36)	12 (33%)	12 (33%)	12 (33%)	4.1 ± 4.1	10.7 ± 5.2	8.9 ± 3.8
No (n = 64)	16 (25%)	28 (44%)	20 (31%)	4.0 ± 3.8	9.7 ± 5.9	8.0 ± 4.4
p value	0.54*			0.88	0.40	0.92
Smoking						
Yes (n = 51)	12 (24%)	20 (39%)	19 (37%)	4.7 ± 4.1	11.0 ± 5.8	8.8 ± 4.1
No (n = 49)	16 (33%)	20 (41%)	13 (27%)	3.4 ± 3.6	9.1 ± 5.3	7.8 ± 4.3
p value	0.44*			0.09	0.09	0.21
Diabetes						
Yes (n = 18)	4 (22%)	4 (22%)	10 (56%)	6.1 ± 4.3	12.0 ± 4.7	10.0 ± 3.3
No (n = 82)	24 (29%)	36 (44%)	22 (27%)	3.6 ± 3.7	9.6 ± 5.7	7.9 ± 4.3
p value	0.06*			0.03	0.08	0.03
Obesity						
Yes (n = 35)	10 (29%)	12 (34%)	13 (37%)	4.7 ± 4.5	10.1 ± 5.9	8.3 ± 4.4
No (n = 65)	18 (28%)	28 (43%)	19 (29%)	3.7 ± 3.5	10.0 ± 5.5	8.3 ± 4.1
p value	0.64*			0.28	0.95	0.98

SS severity score, *SIS* segment involvement score

*Chi square (across group)

†ANOVA

contrast, and unexpectedly, hypercholesterolemia was not related to coronary or extra-coronary plaque burden. Though not necessarily linked, the relatively old age of our cohort might have had influenced given the fact that several studies including a meta-analysis have shown an inverse relationship between LDL-cholesterol levels and mortality among patients older than 60 years [30]. Furthermore, since data regarding baseline medical therapy was not fully detailed, a possible influence of statins or other drugs known to promote plaque calcification and thus detectability, should not be overlooked [31, 32].

A number of study limitations should be acknowledged. The relatively small population included might lead to selection bias. Moreover, since CTA scans comprised from the supra-aortic trunks to the common femoral arteries, our results cannot be extrapolated to the cerebral, internal carotid, and/or lower limb circulation. Patients underwent thoracoabdominal aortic CTA for various clinical indications, and a larger proportion of males underwent CTA for aortic dilatation, thus possibly affecting vessels differently (indication bias). Nothwithstanding, we identified an intriguingly higher plaque burden among males only within the coronary tree, whereas similar plaque burden was found among all other vascular territories explored. Likewise, and as aforementioned, discriminated medical therapy, as well as lifestyle, renal function, and nutritional aspects that might have an effect on atherosclerosis were not fully detailed. Accordingly, the effect of diverse potential confounders as well as reverse causality bias cannot be disregarded. Since the presence and degree of coronary obstruction have not

been validated with aortic CTA studies, we only assessed the coronary SIS, previously established as a robust marker of events [33, 34]. Also, non-calcified coronary plaques were not computed, and the reason for this was two-fold. Firstly, these plaques are more prone to misclassification particularly in aortic CTA; and secondly, they have limited prognostic value compared to calcified and mixed plaques [11].

Conclusions

In the present observational study involving gated CTA from the supra-aortic trunks to the femoral arteries, we identified significant sex-related differences in coronary plaque burden, whereas extra-coronary plaque burden was similar between genders irrespective of the vascular bed. Our findings warrant further studies exploring the underlying pathophysiological mechanisms of the documented contrasts.

Compliance with ethical standards

Conflict of interest We declare that Dr. Patricia Carrascosa is consultant of GE Healthcare. There are no competing interests related to the manuscript for any of the other authors.

Ethical approval The protocol was approved by the institutional ethics committee and all studies have been performed in accordance with the ethical standards as laid down in the 1975 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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