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Influence of Cardiovascular Risk Factors on the Prevalence of Coronary Atherosclerosis in Patients with Angiographically Normal Coronary Arteries

Daniel O. Bittner, MD^{a,b,*}, Lutz Klinghammer, MD^a, Mohamed Marwan, MD^a, Jasmin Schmid, MD^a, Christian Layritz, MD^a, Udo Hoffmann, MD, MPH^b, Stephan Achenbach, MD^a, and Tobias Pflederer, MD^a

^aFriedrich-Alexander University Erlangen-Nürnberg (FAU), Department of Cardiology, University Hospital Erlangen, Germany

^bCardiac MR PET CT Program, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Abstract

Rationale and Objectives—Cardiovascular (CV) disease is predominately influenced by CV risk factors and coronary CT angiography (CTA) is capable to detect early stage coronary artery disease (CAD). We sought to determine the influence of CV risk factors on the prevalence of nonobstructive atherosclerosis in patients with normal appearing coronary arteries in invasive coronary angiography (ICA).

Materials and Methods—In this retrospective analysis, we included 60 consecutive symptomatic patients, having undergone ICA and coronary CTA. Coronary dual source CT (DSCT) angiography was performed using ECG-triggered retrospective gated image acquisition at 40–70% of RR-interval (tube voltage 100–120 kV, tube current time product 320–440 mAs, 60 mL contrast, flow rate 6 mL/s).

Results—Out of 60 patients (32 men, mean age 61±11 years) with a normal coronary artery appearance in ICA, 45 (75%) patients showed atherosclerotic plaque in CTA. Plaque was present in 14/60 (23%) left main, 41/60 (68%) left anterior descending, 21/60 (35%) circumflex coronary arteries and 24/60 (40%) right coronary arteries. More than 15% of all coronary artery segments showed detectable plaques. Interobserver agreement ranged from good to very good on a per patient, per vessel and per segment level. Patients with presence of plaque were significantly older ($p=0.005$) and showed higher incidence of arterial hypertension ($p=0.019$) as compared to individuals without coronary plaque in DSCT.

Conclusion—The prevalence of coronary atherosclerosis by CTA is substantial in symptomatic patients with normal invasive coronary angiogram. Hypertension and older age significantly

*Corresponding author: Daniel Bittner, MD; Massachusetts General Hospital, Harvard Medical School and Department of Cardiology, University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nürnberg (FAU), Germany; Phone: +49-9131-85-35301; Fax: +49-9131-85-35303; daniel.bittner@uk-erlangen.de.

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influence the prevalence of atherosclerotic plaque and highlights the importance of risk modifying therapy.

Keywords

Cardiovascular risk factors; Coronary artery disease; Coronary plaque; Invasive coronary angiography; Computed Tomography

Introduction

Cardiovascular risk factors are widely used for risk assessment and direction of medical management in patients with suspected coronary heart disease (CHD). In patients with known coronary artery disease (CAD), strict risk factor control is crucial [1, 2].

Coronary CT angiography (CTA) can detect coronary artery stenosis non-invasively with excellent diagnostic accuracy [3–5] and hence is successfully used to predict prognosis [6–8]. Importantly, not only obstructive CAD increases the risk of all-cause mortality. There is substantial data consistently demonstrating a significant increase in risk for major adverse cardiac events (MACE) with increasing burden of atherosclerotic disease in CT-angiography [9–12]. Clinical relevance to detect even small amounts of coronary artery calcium (CAC) for instance has been demonstrated by the Multi-Ethnic Study of Atherosclerosis (MESA), as these individuals had significantly (3-fold) increased risk for future cardiac events [13]. It is also known that CAC has not only strong incremental value to predict cardiac events but also provides independent information in addition to traditional risk factors [14, 15]. The identification of nonobstructive non-calcified lesions by CT has also been shown to be of prognostic value [6, 9, 16]. In 10,418 patients undergoing CTA, the international multicentre registry CONFIRM found a 6% higher risk of mortality for each additional segment with nonobstructive atherosclerotic plaque ($p=0.021$). Moreover, in patients with nonobstructive CAD, baseline statin use was associated with a 56% decreased mortality risk (HR 0.44) compared to patients without statin therapy. Statin use at baseline did not decrease the risk in patients without plaque in CTA [17].

Invasive coronary angiography (ICA), while clinical “gold standard” to detect obstructive coronary disease, has limited ability to identify nonobstructive coronary plaque. Thus, symptomatic patients with “normal coronary arteries” based on invasive angiography only, could potentially be misclassified as low-risk patient population despite the presence of CV risk factors. To adequately tailor optimal therapy, precise identification of atherosclerotic disease is necessary. Therefore, we sought to determine the association of cardiovascular risk factors to the prevalence of nonobstructive CAD as assessed by coronary CTA in symptomatic patients with normal appearance of the coronary arteries in invasive catheterization

Material and Methods

Study design and patient population

This is a retrospective analysis of 60 consecutive patients with symptoms suggestive of coronary artery disease and low-to-intermediate pretest likelihood according to clinical

parameters. All individuals were hospitalized for diagnostic workup, underwent invasive catheterization for clinical reasons and coronary DSCT angiography per research protocol within 24 hours before the scheduled coronary angiogram. The CT results did not influence the decision for or against invasive angiography. All patients showed normal results in invasive angiography. “Normal” coronary arteries by invasive angiography were defined as entirely normal and smooth angiographic appearance without any sign of atherosclerotic disease or wall irregularities. The invasive coronary angiograms were performed and evaluated in clinical routine by experienced interventional cardiologists. The DSCT examination for this patient population was approved by the local ethics committee and the German radiation protection agency.

DSCT data acquisition and image analysis

For coronary CTA, we used a second generation DSCT (Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany) with retrospectively ECG-triggered spiral scan mode (at 40–70% of the RR-interval) and body-weight adapted tube energy modulation (100–120 kV, 320–440 mAs, 60ml of contrast agent). Two independent and experienced cardiac CT observers evaluated all data sets with respect to the presence or absence of coronary calcified and non-calcified atherosclerotic plaque on a per-segment basis using the SCCT 18-segment model of the coronary artery system [18]. We examined all data sets using transaxial cross-sections as well as interactively manipulated multiplanar reconstructions in various planes to achieve longitudinal and orthogonal visualization of the coronary arteries (Figure 1).

Analysis of coronary atherosclerosis

Each coronary segment was allocated by the two independent observers to one of the following diagnostic categories: (1) no atherosclerotic plaque detectable (no plaque), (2) presence of exclusively non-calcified plaque (NCP), (3) presence of exclusively calcified plaque (CP) or (4) presence of mixed plaque (mixed). A segment was classified as “mixed”, if a single plaque was partly calcified and partly non-calcified or if the analysed segment showed both purely calcified as well as purely non-calcified coronary plaques. To reflect the number of affected segments per patient, three different patient groups were defined: The first patient group showed no single diseased segment, the second group one to five affected segments and the last group more than five segments with coronary plaque (Table 2).

Likewise, vessels were classified as having calcified, non-calcified or “mixed” plaque or as being free of atherosclerosis (Table 3). Patients were classified in a similar way and in addition, patients with any detectable coronary plaque in coronary DSCT angiography were further divided in patient groups showing one-, two- or three-vessel coronary artery disease. Left main coronary atherosclerosis was per se regarded as at least two-vessel disease (Table 4).

Statistical analyses

Continuous data are presented as mean $\pm$ standard deviation (SD). Categorical variables are shown in proportions. Interobserver reliability was quantified by Cohen’s kappa with its 95% confidence interval. A kappa between 0.61–0.80 between two observers suggested a

“good”, a kappa greater than 0.80 a “very good” interobserver agreement in accordance to DG Altman.[19]

A univariable comparison across patient groups (Supplemental Table) was performed by t-test or by Chi-square test. The influence of selected parameters of patient characteristics, cardiovascular risk factors and scan characteristics on the plaque burden was visualized by odds ratios with their 95%CI in a multivariable model of logistic regression. Segment-based results were grouped to vessel and patient based results by Microsoft® (Redmond) Excel® (version 14.0). All statistical analyses were performed using IBM® (New York) SPSS® Statistics (version 21.0) or (4.02) of Graph Pad® (San Diego) Prism® (version 4.02 and Quickcalcs 2014).

Results

Patient and DSCT scan characteristics

Patient and scan features are displayed in Table 1. The study population showed the following characteristics: Of all 60 symptomatic patients, 28 (47%) were female. Mean age was 61 ± 11 years and mean BMI was 28.0 ± 4.4 kg/m². Patients showed an intermediate cardiovascular risk profile, consisting of hypertensive patients [39 (65.0%)], diabetics [3 (5.0%)], current or prior smokers [28 (46.7%)], and patients with a family history for cardiac events [17 (28.3%)] and hyperlipidemia [39 (65.0%)]. This resulted in an average of 2.1 ± 1.0 risk factors per patient.

CT angiography was performed with the following scan parameters: in 39 patients with a tube voltage of 100 kV (65%) and in 21 patients with 120kV (35%). The mean tube current time product was 371.0 ± 60.0 mAs, resulting in a mean estimated effective radiation dose of 6.3 ± 3.9 mSv.

Interobserver differences for plaque detection

Interobserver reliability was calculated using a binary classification (plaque vs. no plaque) for a segment-, a modified segment-, a vessel- and a patient level.

For the segment-based identification of coronary plaques, interobserver reliability was good (kappa = 0.72). Table 2 shows the modified segment level in groups, reflecting the number of affected segments per patient. Within 94 diseased segments from 35 patients in group 2, there was an interobserver difference in 2 segments. In 10 patients with more than 5 atherosclerotic segments per patient and a total number of 64 affected segments (group 3), observers differed in 10 segments (kappa=0.86).

Interobserver differences on a vessel level is displayed in Table 3 and reveals disagreement in 2 out of 240 vessels, resulting in a kappa of 0.98.

On a per-patient basis, every patient with presence of atherosclerotic disease was identified correctly by both observers, resulting in a 100% reliability (kappa 1.0).

Overall the suggested strength of agreement ranged from “good” to “very good”.[19]

Segment based analysis

For a segment-based analysis, the SCCT 18-segment model was used. [18] Out of a total of 1080 segments, 917 (84.9%) segments showed no atherosclerotic plaque and were regarded as “disease-free” in accordance with the result of invasive catheterization. In contrast, 163 (15.1%) segments did show coronary atherosclerotic plaque. Out of this group, 73 (44.8%) segments showed exclusively non-calcified plaque, 32 (19.6%) segments showed exclusively calcified plaque and 58 (35.6%) segments displayed mixed plaques resulting in a total of 90 (55.2%) segments being at least partly calcified.

Vessel based analysis

Out of a total of 240 vessels, 100 (41.7%) showed coronary atherosclerosis. 14 of 60 (23.3%) left main coronary arteries, 41 of 60 LADs (68.3%), 21 of 60 LCXs (35.0%) and 24 of 60 RCAs (40.0%) showed atherosclerotic plaques with regard to the DSCT angiography data sets. Among 100 diseased vessels, 13 (13.0%) showed purely calcified plaques, 43 (43.0%) purely non-calcified plaques, whereas 44 vessels (44.0%) showed mixed atherosclerotic plaques. 23.8% of all diseased vessels were at least partly calcified. Differences in plaque composition between the four major coronary arteries (LM, LAD, LCX and RCA) are displayed in Table 3.

Patient based analysis

Of a total of 60 patients, 45 (75%) showed CT-angiographically nonobstructive coronary atherosclerosis as demonstrated in Table 4a. Out of all patients with disease, in 16 (35.6%) individuals exclusively non-calcified lesions were detected and 29 (64.4%) patients showed both calcified and non-calcified plaque. No patient showed purely calcified plaque.

With regard to the number of affected vessels, in 15 (25.0%) patients no vessel was affected. 16 (26.7%) patients showed single vessel disease, 9 (15.0%) patients 2-vessel disease and 18 (30.0%) patients 3-vessel disease, respectively (Table 4b).

Influence of cardiovascular risk factors

Detailed differences in cardiovascular risk profile are displayed in the Supplemental Table 1 and visualized in Figure 2, using a multivariable model of selected parameters.

We compared 15 patients with entirely normal coronary arteries in CT angiography to 45 patients with the presence of any plaque, irrespective of the composition. Patients without coronary plaques in CTA were significantly younger (53.7 ± 9.8 and 62.9 ± 11.0 years of age respectively; $p=0.005$) and had less frequently arterial hypertension (6 [40.0%] and 33 [73.3%]; $p=0.019$). All other conventional risk factors did not show significant differences. Of note, in 14 out of 45 patients with plaque (31.1%) atherosclerotic lesions were present in the left main coronary artery and in 18 (40.0%) patients 3 vessels were affected.

When 31 patients without plaque or with exclusively noncalcified plaque were compared to 29 patients with presence of calcification, patients with calcification were significantly older (57.4 ± 10.9 and 64.0 ± 11.0 years of age respectively; $p=0.015$). No difference was seen for other risk factors. A slightly higher number of traditional risk factors >1 was observed in the

patient group with coronary calcification (86.2% (25) and 64.5% (20) respectively), however this was not statistically significant ($p=0.053$).

Discussion

In the underlying analysis, coronary CTA revealed a high prevalence of early stage coronary atherosclerosis in symptomatic patients with normal invasive coronary angiograms. In addition, this study could demonstrate the significant influence of risk factors such as hypertension and age on the prevalence of atherosclerotic plaque.

Although invasive coronary angiography did not reveal any sign of coronary atherosclerosis in our patient cohort, 29 (48%) individuals showed coronary artery calcification. As already mentioned in the beginning, Budoff et al. pointed out that even small amounts of coronary artery calcium detected by CT are a marker of increased risk for developing cardiovascular events when compared to a CAC value of zero [13]. In 18 (30%) patients of our study, atherosclerotic lesions in 3 vessels could be identified. According to Ostrom et al., a 3-vessel nonobstructive CAD carries a 1.7-fold increased risk for death, demonstrated in over 2500 patients, referred for evaluation of suspected CAD by CT [6]. From a segment perspective, 10 (17%) individuals of our population showed atherosclerotic disease in more than 5 segments. The prognostic impact of nonobstructive CAD in at least five coronary segments was demonstrated in a cohort study with 1,127 patients. Compared to patients with less than five involved segments, the risk for mortality was significantly higher ($p<0.001$) [9]. Another large cohort demonstrated that each additional segment with nonobstructive atherosclerotic plaque carries a 6% higher risk of mortality ($p=0.021$) [17].

In line with this, the absence of coronary atherosclerotic plaque in CT angiography is again of high prognostic value. In a smaller trial, it was shown to be associated with a zero% cardiac event rate [20]. Consistently, the negative predictive likelihood ratio of a normal CTA was found to be 0.008 for MACE ($p<0.001$), demonstrated by a pooled meta-analysis from 2011 with over 9500 patients [21]. With over 10,000 individuals the so far probably largest cohort looking at patients without evidence of CAD by CT is a multicentre registry, confirming a very low mean annualized rate of death (0.28%) [12]. Even in an acute setting, the absence of CAD on CT provides a 2-year MACE-free warranty period in a symptomatic patient population presenting to the ED [22].

Overall, the present study showed a high prevalence of coronary atherosclerosis in symptomatic patients with an entirely normal and smooth angiographic appearance in ICA. 75% (45) of all patients and 42% (100) of all examined coronary arteries showed nonobstructive CAD in CTA. This finding is supported by published data from Kim et al. performing intravascular ultrasound (IVUS) in 198 donor hearts 4 weeks after transplantation. 177 hearts showed a completely normal angiographic appearance. However, in 48.5% (96) of the donor organs atherosclerotic lesions were detected by IVUS [23]. Similar findings were shown by Tuzcu et al. also examining donor hearts after transplantation. In 241 of 262 patients (92%) coronary angiograms were completely normal, whereas 136 (51.9%) showed at least one atherosclerotic lesion in IVUS [24]. Discrepancies in the detection and discrimination of coronary plaque between IVUS and angiography were

also seen in the prospective natural history study of atherosclerosis [25]. This landmark trial demonstrated the substantial risk for future events from initially mild non-culprit atherosclerotic lesions and revealed that about 30% of non-culprit coronary plaque visualized by IVUS were inconspicuous in invasive coronary angiography [25]. This emphasizes even more the importance to adequately visualize also nonobstructive CAD. Still, the prevalence of nonobstructive CAD diagnosed by CTA in the our analysis was substantially higher compared to the first two IVUS studies mentioned above. The difference in diagnostic methods alone will most likely not explain this deviation, as, compared to IVUS, the detection of coronary plaques by CTA was shown to have an excellent diagnostic accuracy in a comprehensive meta-analysis. In detail, the detection and characterization of coronary plaque was similar between CTA and IVUS concerning plaque area, luminal area, percentage of area stenosis and plaque volume [26, 27]. In case a difference attributable to methods had occurred, a higher prevalence of plaque would have been expected in patients examined by IVUS, not by CTA. However, both IVUS studies examined only asymptomatic patients with a mean age of 31 years and a low cardiovascular risk profile. In contrast, the present study included a symptomatic patient population with a mean age of 61 years. The difference in age could potentially explain the higher extent of plaque seen in our analysis, as age is a well-known risk factor for CAD [12]. Consistently, comparing patients with and without plaque within our patient cohort, age showed a significant positive association with the presence of plaque. Moreover, a substantial number of atherosclerotic risk factors were present in our population and might have intensified this affect. Even in our small cohort, hypertension seems to be a substantial risk factor. The impact of risk profile on outcome in patients with typical angina or angina-like chest pain and normal coronary angiographic findings was already demonstrated in a report dating back to 1995 by Lichtlen et al., focusing on long-term prognosis. A significantly higher incidence of coronary events in patients with an increased number of risk factors ($p < 0.01$) was demonstrated [28]. Now, having methods available to identify coronary atherosclerosis with higher sensitivity, atherosclerotic findings can and need to be translated into clinical practice. With statin therapy at baseline for instance, a substantial decrease in mortality risk was seen in patients with nonobstructive CAD (HR 0.44), compared to no statin therapy, as shown in the CONFIRM registry. Of note, this beneficial effect was not seen in the absence of plaque [17].

Limitations

Some limitations of our study need to be mentioned. First, it is a retrospective analysis. Second, the patient population of the presented study consists of a rather small number of patients, potentially causing underestimation of the effect of other CV risk factors. Third, only symptomatic patients were included. Therefore, differences in the prevalence of coronary artery disease might significantly vary, if also asymptomatic patients would have been considered.

Conclusion

In symptomatic patients with normal coronary arteries in invasive angiography, the prevalence of early stage coronary atherosclerosis is substantial as identified by CTA,

highlighting the value of accurate non-invasive diagnostic imaging techniques. As the prevalence of coronary plaque seems to be significantly influenced by hypertension and older age, this data suggests strict risk factor control in symptomatic patients even with normal coronary arteries in invasive coronary angiography.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

95%CI	95% confidence interval
CAC	Coronary artery calcification
CAD	Coronary artery disease
CP	Calcified plaque
(C)CTA	(Coronary) CT Angiography
CTDI	Computed tomography dose index (mGy)
CV	Cardiovascular
DLP	Dose length product (mGy cm)
DSCT	Dual source computed tomography
ICA	Invasive coronary angiography
LAD	Left anterior descending coronary artery
LCX	Left circumflex coronary artery
LM	Left main coronary artery
NCP	Noncalcified plaque
OR	Odds ratio
RCA	Right coronary artery

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Figure 1. shows a coronary CT angiography of the right coronary artery (RCA) in maximum-intensity-projection (A) and on axial view (B) with coronary plaques (indicated by arrows); below, corresponding invasive angiography in different RCA-projections (C, D) without detectable plaques and “normal” appearance

Figure 2.

shows a logistic regression multivariable comparison of patient groups defined by plaque detection. A) Patients without plaque (n=15) were compared to patients with plaque (n=45), with odds ratios and p values for age, obesity, number of risk factors and effective dose. B) Patients without calcification (n=31) were compared to patients with calcified plaque (n=29), again with odds ratios and p values for the same variables.

Table 1

Patient and scan characteristics

Patients characteristics	mean±SD or n (%)
Age (years)	61±11
Male gender	32 (53)
Weight (kg)	80±14
Height (m)	1.7±0.1
BMI (kg/m ²)	28.0±4.4
Obesity	15 (25)
Cardiovascular risk factors	
1. Hypertension	39 (65)
2. Diabetes mellitus	3 (5)
3. Smoker current or prior	28 (47)
4. Familial history	17 (28)
5. Hyperlipidemia	39 (65)
Number of risk factors	2.1±1.0
Scan parameters	
Tube voltage (100 kV)	39 (65)
Tube voltage (120 kV)	21 (35)
Tube current time product (mAs)	371±60
CDTI (mGy)	37.4±46.0
DLP (mGy·cm)	450±282
Effective dose (mSv)	6.3±3.9

Table 2

Segment based analysis

Group	Number of diseased segments per patient	Number of patients	Number of segments	
			with plaque	interobserver differences
1	0	15		0
2	1–5	35	94	2
3	>5	10	69	10
Total		60	163	12

Number of C'T-angiographically detected segments with any plaque

Table 3

Vessel based analysis

	O1	No Plaque	NCP	CP	Mixed
	O2				
Coronary arteries					
LM (PdV: 23.3%; PcV: 15.0%; κ : 0.83 (CI 0.67–0.99))					
No Plaque		46	0	0	0
NCP		0	5	0	0
CP		0	0	2	3
Mixed		0	0	1	3
LAD (PdV: 68.3%; PcV: 41.7%; κ : 0.93 (CI 0.84–1.00))					
No Plaque		19	0	0	0
NCP		0	16	0	0
CP		0	0	0	3
Mixed		0	0	0	22
LCX (PdV: 35.0%; PcV: 18.3%; κ : 0.97 (CI 0.91–1.00))					
No Plaque		38	1	0	0
NCP		0	10	0	0
CP		0	0	2	0
Mixed		0	0	0	9
RCA (PdV: 40.0%; PcV: 20.0%; κ : 0.91 (CI 0.82–1.00))					
No Plaque		35	1	0	0
NCP		0	12	0	0
CP		0	0	1	2
Mixed		0	0	0	9
Total					
ALL (PdV: 41.7%; PcV: 23.8%; κ : 0.92 (CI 0.87–0.97))					
		No Plaque	NCP	CP	Mixed
		Sum			
No Plaque	138	2	0	0	140
NCP	0	43	0	0	43

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O1	O2			
	No Plaque	NCP	CP	Mixed
CP	0	0	5	8
Mixed	0	0	1	43
Sum	138	45	6	51

O1: Observer 1 (columns); O2: Observer 2 (rows); No Plaque: disease free condition, NCP: the presence of exclusively non calcified plaque, CP: exclusively calcified plaque, Mixed: mixed plaque; PdV: percentage of diseased vessels, PcV: percentage of exclusively or partly calcified vessels

Table 4

Patient based analysis with regard to (a) plaque composition and (b) number of affected vessels

a) Plaque composition

<u>O1</u>				
O2	No Plaque	NCP	CP	Mixed
No Plaque	15	0	0	0
NCP	0	16	0	0
CP	0	0	0	0
Mixed	0	0	0	29

b) Number of affected vessels per patient

<u>O1</u>				
O2	0	1	2	3
0	15	0	0	0
1	0	16	2	0
2	0	0	9	0
3	0	0	0	18

O1: Observer 1 (columns); O2: Observer 2 (rows); values in diagonals represent number of patients without differences between both observers. No Plaque: disease free condition, NCP: the presence of exclusively non calcified plaque, CP: exclusively calcified plaque, Mixed: mixed plaque;