Multimodality imaging in ischemic heart disease, from prevention to outcome

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Chapter 3

Long-term Prognosis of Patients with Intramural Course of Coronary Arteries Assessed with Computed Tomography Angiography

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Abstract

Objectives. The aim of the present study was to evaluated, in low-to-intermediate pre-test probability patients who were referred for coronary computed tomography angiography (CTA) and did not show obstructive coronary artery disease (CAD), whether an intramural course of a coronary artery is associated with worse outcome compared with patients without an intramural course of the coronary arteries.

Background. The prognostic value of an intramural course of the coronary arteries on coronary CTA in patients without obstructive CAD is not well-known.

Methods. The study population consisted of 947 patients with a low-to-intermediate pre-test probability who were referred for coronary CTA and who did not have obstructive CAD. During follow-up, the occurrence of unstable angina pectoris that required hospitalization, nonfatal myocardial infarction and all-cause mortality was evaluated.

Results. On coronary CTA, 210 (22%) patients had an intramural course of a coronary artery. The median depth of the intramural course was 1.9 mm (IQR 1.4-2.6 mm). In 84 patients (40%) the depth of the intramural course was considered deep (>2 mm surrounding myocardium). During a median follow-up of 4.9 years (interquartile range (IQR) 3.2-6.9 years) a total of 43 events occurred: hospitalization due to unstable angina pectoris in 13 patients (1.4%), 7 patients (0.7%) had a nonfatal myocardial infarction and 23 patients died (2.4%). The 6-year cumulative event rate of unstable angina pectoris requiring hospitalization (0.0% vs. 1.1%), nonfatal myocardial infarction (0.5% vs. 0.4%), all-cause mortality (1.9% vs. 2.2%) as well as the combined endpoint of all 3 events (2.4% vs. 3.7%) was similar in patients with and without an intramural course of a coronary artery.

Conclusion. In patients without obstructive CAD on coronary CTA, the presence of an intramural course of a coronary artery was not associated with worse outcome.

Introduction

Coronary computed tomography angiography (CTA) is increasingly used to assess or exclude coronary artery disease (CAD) in patients with low-to-intermediate pre-test probability.[1,2] When analysing the coronary arteries for stenosis, variations in coronary anatomy are frequently observed. One of the most common findings on coronary CTA is an intramural course of the epicardial coronary arteries. The intramural course of a coronary artery is defined as any epicardial segment that runs intramurally through the myocardium that completely surrounds the vessel.[3] The reported prevalence of the intramural course of coronary arteries on coronary CTA ranges from 6% to 58%.[4] This large variation may be explained by the use of different imaging techniques and recent improvements in computed tomography (CT) technology that provide high spatial resolution and permit more precise analyses. In addition, the definition of the intramural course of the coronary artery (depth and length) differs among studies.[4]

Although an intramural course of a coronary artery is considered a benign anomaly, small case series have linked the presence of an intramural course of the coronary artery to myocardial infarction[5,6], arrhythmias[7] and sudden cardiac death[8]. However, prognostic data in a large population with an intramural course on coronary CTA are nonexistent. Accordingly, the present study evaluated, in patients with a low-to-intermediate pre-test probability who were referred for coronary CTA and without obstructive CAD, whether an intramural course of a coronary artery was associated with worse outcome compared with patients without an intramural course of the coronary arteries.

Methods

Patients

A total of 1,000 patients (from the Leiden University Medical Centre, the Netherlands and the Turku University Hospital, Turku, Finland) with cardiac complaints and/or an increased cardiovascular risk profile and low-to-intermediate pre-test probability[2] who were clinically referred for coronary CTA were included in the present analysis. Patients with a history of CAD (previous myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft surgery), heart failure, valvular heart disease, arrhythmia or congenital heart disease were excluded. In addition, patients with obstructive

CAD on coronary CTA (defined as any coronary artery stenosis ≥50%), a nondiagnostic coronary CTA study, and patients lost to follow-up were not included in this analysis.

Clinical and coronary CTA data were prospectively entered into the database and analyzed retrospectively. For retrospective analysis of clinically acquired data, the Institutional Review Board of the Leiden University Medical Centre waived the need for written informed consent. Similarly, the Ethics Committee of the Hospital District of Southwest Finland approved the study protocol and waived the need for written informed consent. All clinically acquired data were handled anonymously.

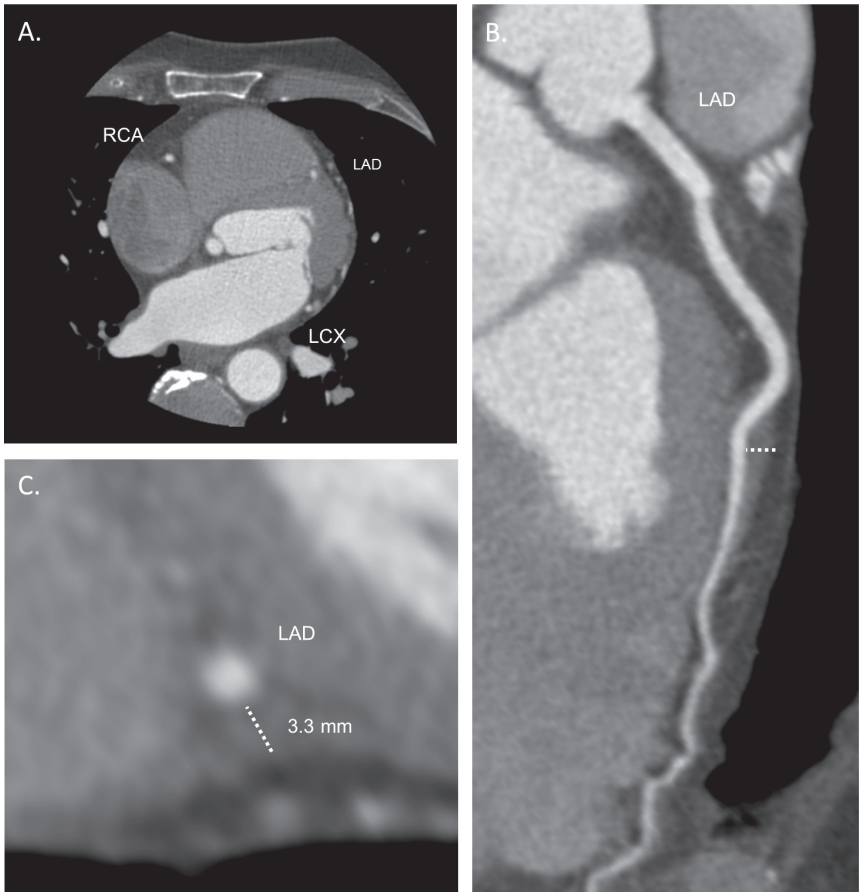
Coronary computed tomography

All coronary CT scans were performed using a 64- or 320-detector row CT scanner (64-slice: Aquillon 64, Toshiba Medical Systems, Otawara, Japan; 320-slice: Aquillon ONE, Toshiba Medical System, Otawara, Japan) in the Netherlands and a 64-detector row scanner (GE Discovery VCT, General Electric Medical Systems, Waukesha, Wisconsin, USA) in Finland. A nonenhanced CT scan (for the assessment of the coronary artery calcium [CAC] score) and a contrast-enhanced CT scan (for noninvasive coronary angiography) were performed. Coronary CTA was performed as previously described.[9,10] For the 64-slice scanner, a collimation of 64 x 0.5 mm, rotation time of 400 ms, and tube voltages and currents (adjusted to the body mass index) of 120 to 135 kV and 250 to 500 mA, respectively, were used. For the 320-slice scanner, a collimation of 320 x 0.5 mm, rotation time of 350 ms, and tube voltages and currents of 100 to 135 kV and 200 to 580 mA, respectively, were used. Advanced iterative reconstruction algorithms were applied. The average contrast dose was 76 ± 14 ml. For the coronary CTA data acquired in Finland, a collimation of 64 x 0.625 mm, a gantry rotation time of 350 ms, tube current between 600 and 750 mA, and voltage between 100 to 120 kV, depending on patient size, were used. The average contrast volume used was 60 to 80 ml.[11] If not contraindicated, beta-blockers were administered orally (25 to 125 mg metoprolol) 1 hour or intravenously (5 to 30 mg metoprolol) a few minutes before the coronary CTA in patients with a heart rate of > 60 beats/min. The mean heart rate at the time of image acquisition was 57 ± 8 beats/min. Sublingual nitroglycerine (0.4 to 0.8 mg) was administered before the coronary CTA acquisition in the absence of contraindications.

Post-processing of the scans was performed with dedicated software (Vitrea FX 1.0, Vital Images, Minnetonka, [in the Netherlands] and General Electric, GE ADW 4.5, Piscataway, New Jersey [in Finland]).

As previously described,[9] the CAC score was calculated according to the algorithm of Agatston.[12] All coronary CTAs were analyzed according to the modified 17-segment American Heart Association classification.[13] Coronary artery segments with a diameter of ≥ 1.5 mm were included for analysis. The severity of coronary stenosis in each segment was stratified into three categories: 1) normal if no plaques were present; 2) non-obstructive CAD if the plaque covered 1-49% of the lumen; and 3) obstructive CAD if the plaque covered ≥ 50%.

Figure 1. *Assessment of Intramural Course of Coronary Artery With Coronary Computed Tomography Angiography.*



Coronary computed tomography angiography images of a patient with an intramural course of the mid LAD coronary artery demonstrated on the axial image (A.), multiplanar reconstructed image (B.), and cross-section image (C.) at the side of the intramural course demonstrating the measurement of the depth (3.3mm). LAD: left anterior descending coronary artery; mm: millimeter; RCA: right coronary artery; LCX: left circumflex coronary artery.

Supplemental table 1. *Comparison of baseline characteristics of the patients excluded for analysis due to lost at follow-up in comparison with the patients included for analysis.*

Variable	Patients excluded N=53	Patients included N=947	P-value
Clinical characteristics			
Age (years)	47±13	53±12	**0.001**
Men (%)	46	44	0.78
Risk factors			
BMI >30 (%)	23	19	0.52
Hypercholesterolemia* (%)	26	35	0.18
Hypertension† (%)	26	40	0.06
Current smoking (%)	17	15	0.70
Family history of CAD (%)	54	48	0.41
Diabetes mellitus (%)	28	27	0.88
Coronary CTA			
Vessel dominance			0.22
Right (%)	75	84	
Left (%)	17	12	
Balanced (%)	8	4	
Intramural course of a coronary artery	23	22	0.94
Coronary artery calcium score (IQR) n=811	0 (IQR 0-11)	0 (IQR 0-12)	0.44
Non-obstructive CAD (%)	64	58	0.41
Coronary plaques (composition)			
No. of calcified lesions	0.2 ± 0.5	0.3 ± 1.0	0.51
No. of mixed lesions	0.8 ± 0.3	0.4 ± 1.1	0.52
No. of non-calcified lesions	0.8 ± 2.3	0.5 ± 1.4	0.37

Definitions and abbreviations as in tabel 1.

Coronary plaques were stratified into 3 groups: calcified (plaque containing ≥ 50% calcification); mixed (plaque containing <50% calcification) and non-calcified (plaque containing no calcification). To evaluate the presence of an intramural course of the coronary artery, multiplanar reconstruction images and cross sectional views of the coronary arteries were created and interpreted (Figure 1). Intramural course was defined as any epicardial artery segment that ran intramurally, surrounded by at least 1 mm of myocardium.[3] The intramural course was classified as superficial when the course was covered with 1 to 2 mm myocardium or as deep when covered with >2 mm myocardium.[14, 15]

Follow-up data

Follow-up data for the Dutch group of patients were obtained from hospital's files review, municipal civil registry and contacting the patients. For the Finnish group of patients, follow-up data were obtained from the national health statistics and patients' electronic medical records. The combined endpoint consisted of time to unstable angina pectoris that required hospitalization, nonfatal myocardial infarction or all-cause mortality. Both, unstable angina pectoris that required hospitalization[13] and nonfatal myocardial infarction[14] were defined according to standard definitions. Coronary CTA data analysis was performed blinded to the clinical follow-up data.

Statistical analysis

Normally distributed continuous variables were expressed as mean ± standard deviation and as median with 25-75 interquartile range (IQR) if not normally distributed. Categorical variables were presented as frequencies and percentages. Continuous variables were compared between groups with the independent samples t-test (if normally distributed) or with the Mann-Whitney U test (for non-Gaussian variables). Categorical variables were compared between groups using the Chi-Square test. Cumulative event rates for the endpoints of unstable angina pectoris that required hospitalization, nonfatal myocardial infarction and all-cause mortality and the combined endpoint comprising of the first time of all 3 events were estimated with the Kaplan-Meier method and compared among groups using the Log-Rank test. Cox proportional hazard models were used to assess the association between clinical characteristics and coronary CTA results with the combined endpoint of unstable angina pectoris requiring hospitalization, nonfatal myocardial infarction and all-cause mortality. Hazard ratios (HR) and their respective 95% confidence intervals (CI) were reported. Statistical analysis was performed using the SPSS software Version 22.0 (IBM Corp., Armonk, New York, USA). A 2-sided P-value of <0.05 was considered statistically significant.

Table 1. *Baseline characteristics of the patients stratified according to the presence or absence of an intramural course on coronary CTA.*

Variable	All patients N=947	Patients with intramural course N=210	Patients without intramural course N=737	P-value
Clinical characteristics				
Age (years)	53±12	54±11	53±12	0.19
Men (%)	44	40	45	0.21
Risk factors				
BMI >30 (%)	19	11	21	**0.004**
Hypercholesterolemia* (%)	35	36	35	0.74
Hypertension† (%)	40	40	39	0.82
Current smoking (%)	15	16	15	0.62
Family history of CAD (%)	48	52	47	0.21
Diabetes mellitus (%)	27	29	26	0.35
Chest pain	57	53	58	0.37
Typical angina pectoris (%)	11	9	11	0.36
Non-anginal chest pain or atypical angina pectoris (%)	46	44	47	0.41
Early invasive diagnostic tests and treatment	*(<6 months)*			
Coronary angiography (< 6 months) (%)	6.5	5.2	6.9	0.39
Revascularization (< 6 months) (%)	0.8	0.5	0.9	0.51
PCI (%)	0.7	0.5	0.8	0.61
CABG (%)	0.1	0	0.1	0.59
Coronary CTA				
Vessel dominance				0.45
Right (%)	84	87	83	
Left (%)	12	9	12	
Balanced (%)	4	4	5	
Coronary artery calcium score (IQR) n=811	0 (0-12)	0 (0-27)	0 (0-8)	**0.04**
Non-obstructive CAD (%)	58	62	57	0.24
Coronary plaques (composition)				
No. of calcified lesions	0.3±1.0	0.3±0.8	0.3±1.0	0.27
No. of mixed lesions	0.4±1.1	0.5±1.1	0.4±1.1	0.64
No. of non-calcified lesions	0.5±1.4	0.5±1.3	0.5±1.4	0.76

* *Serum total cholesterol ≥230 mg/dl and/or serum triglycerides ≥200 mg/dl or treatment with lipid lowering drugs,*

† *Defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or the use of antihypertensive medication.*

BMI: body mass index; CABG: coronary artery bypass grafting; CAD: coronary artery disease; IQR: interquartile range; No: number; PCI: percutaneous coronary intervention.

Table 2. *Distribution of segments on CTA among 210 patients with an intramural course.*

Distribution of segments with an intramural course	N=210
LAD coronary artery	*99 (47)*
Proximal	4 (2)
Mid	56 (27)
Distal	22 (10)
Diagonal branch	17 (8)
LCX coronary artery	*109 (52)*
Intermediate / anterolateral	98 (47)
Proximal or Distal	9 (4)
OM	2 (1)
Right coronary artery	*2 (1)*
Distal	1 (0.5)
RDP	1 (0.5)

Values are N (%). LAD: left anterior descending; OM: obtuse marginal branches; LCX: left circumflex; RDP: right descending posterior.

Table 3. *Events stratified to the presence of an intramural course on coronary CTA.*

Events	Total N=947	Intramural course N=210	No intramural course N=737	P-value
Follow-up period in years	4.9 (3.2;6.9)	4.6 (3.2;6.6)	5.0 (3.3;7.0)	0.15
Unstable angina pectoris requiring hospitalization	13 (1.4)	2 (1)	11 (1.5)	0.64
Nonfatal myocardial infarction	7 (0.7)	2 (1.0)	5 (0.7)	0.57
All-cause mortality	23 (2.4)	4 (1.9)	19 (2.6)	0.69
Combined endpoint*	43 (4.5)	8 (3.8)	35 (4.7)	0.73

Values are median (IQR) or N (%).

* *Including unstable angina pectoris requiring hospitalization, nonfatal myocardial infarction or all-cause mortality.*

Results

Patients

Of the 1,000 patients initially included, 53 patients (5%) were lost to follow-up and excluded from the analysis. All baseline characteristics of the patients excluded for analysis were similar to the patients included in the present analysis, except for age which was lower in the exclusion group (47±13 years versus 53±12 years, P=0.001) as demonstrated in supplemental Table 1. The clinical characteristics of the remaining 947 patients without obstructive CAD on coronary CTA (56% women, mean age 53±12 years) are presented in Table 1.

Coronary computed tomography

CAC score analysis was feasible in 811 (86%) patients. The median CAC score was 0 (IQR: 0 to 12). Most of the patients (63%) had a CAC score of 0, and 74 patients (9%) had a CAC score >100. The results of the coronary CTA are presented in Table 1. Non-obstructive CAD was observed in 553 (58%) patients whereas the remaining patients (42%) had no coronary artery stenosis. The mean number of calcified segments and segments with mixed plaque were 0.3 ± 1.0 and 0.4 ± 1.1, respectively, and, on average, 0.5 ± 1.4 segments had noncalcified plaque.

Presence of an intramural course

On coronary CTA, 210 (22%) patients had an intramural course of a coronary artery. The median depth of the intramural course was 1.9 mm (IQR: 1.4 to 2.6 mm). In 84 (40%) patients the depth of the intramural course was considered deep (>2 mm surrounding myocardium).

Table 2 describes the segmental location of the intramural course. The most frequent segments that shows an intramural course were the mid / distal left anterior descending (LAD) coronary artery (37%) and the intermediate / anterolateral coronary artery (47%).

Table 1 shows the differences in clinical characteristics between patients with versus without an intramural course of the coronary artery. Patients without an intramural course of the coronary artery were more frequently obese in comparison with patients with an intramural course of the coronary artery (21% versus 11%, respectively; P=0.004). On coronary CT scan, the median CAC score was significantly higher in patients with an intramural course compared with patients without an intramural course (0; IQR: 0 to 27 versus 0; IQR: 0

to 8, respectively; P=0.04). There were no differences in the presence of non-obstructive CAD or the number of calcified / mixed and non-calcified plaques between both groups.

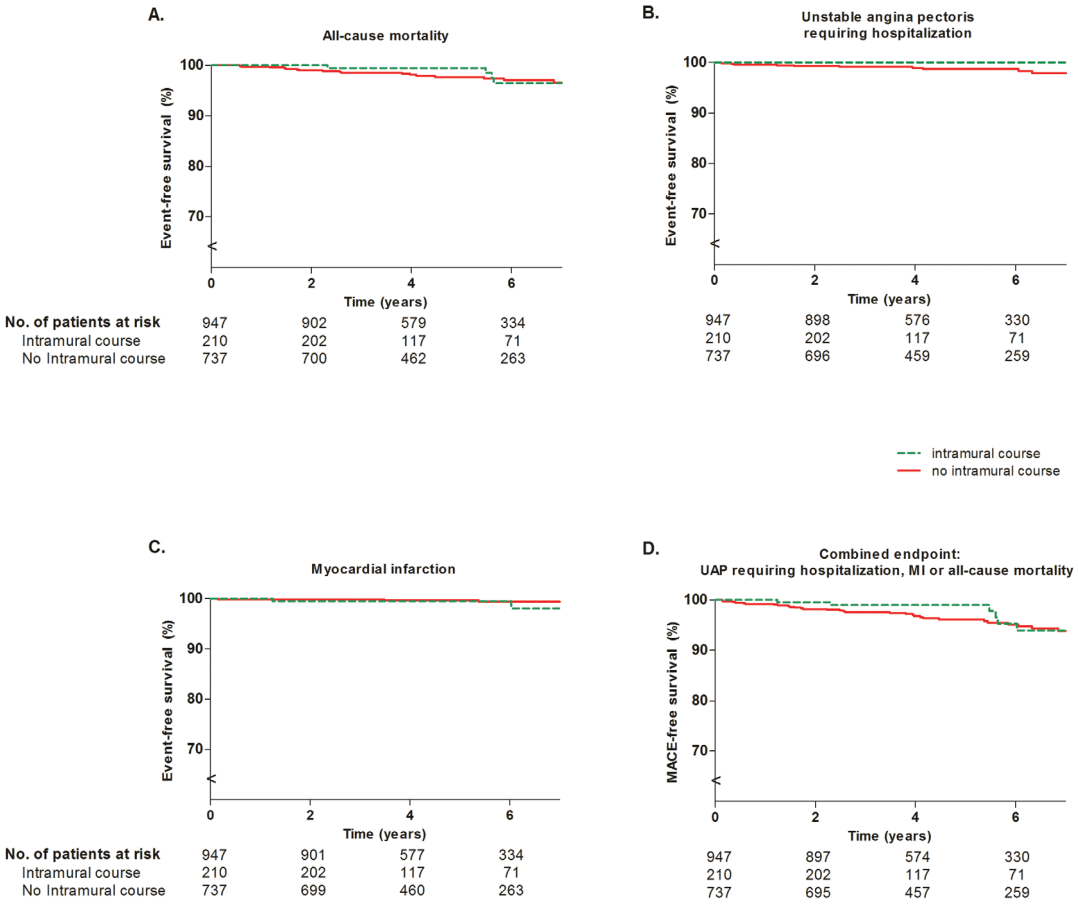
Patient outcome

As shown in Table 3, the median follow-up was 4.9 years (IQR: 3.2 to 6.9 years) and was similar in patients with and without an intramural course on coronary CTA (4.6; IQR: 3.2 to 6.6 versus 5.0; IQR: 3.3 to 7.0 years respectively, P=0.15). During follow-up, 43 events occurred; hospitalization due to unstable angina pectoris in 13 patients (1.4%), 7 patients (0.7%) had a nonfatal myocardial infarction and 23 patients died (2.4%). No patient experienced > 1 event. As shown in Figure 2A-2C, unstable angina pectoris that required hospitalization, nonfatal myocardial infarction and all-cause mortality occurred similarly in patients with and patients without an intramural course of a coronary artery. At 6-year follow-up, the cumulative event rates for unstable angina pectoris that required hospitalization were 0.0% versus 1.1%; for nonfatal myocardial infarction 0.5% versus 0.4%; and for all-cause mortality 1.9% versus 2.2%.

The Kaplan-Meier event-free survival for the combined endpoint of unstable angina pectoris that required hospitalization, nonfatal myocardial infarction, and all-cause mortality stratified according to the presence of an intramural course of a coronary artery is shown in Figure 2D. Patients with an intramural course of the coronary artery had similar 6-year cumulative event rates of the combined endpoint compared with patients without an intramural course (the cumulative event rates were 2.4% vs. 3.7%, respectively; Log Rank P=0.73).

Associates for the combined endpoint of unstable angina pectoris that required hospitalization, nonfatal myocardial infarction and all-cause mortality are presented in Table 4. The intramural course of coronary arteries was not significantly associated with the combined endpoint (HR 0.87; 95%CI 0.40 to 1.88, P=0.73). In contrast, age, CAC score and the number of calcified and mixed plaques were associated with the combined endpoint of unstable angina pectoris requiring hospitalization, nonfatal myocardial infarction and all-cause mortality during long-term follow-up.

Figure 2. *Kaplan-Meier Event-Free Survival Curves for Patients With and Without Intramural Course of the Coronary Artery.*



Kaplan-Meier curves for the endpoint (A.) all-cause mortality, (B.) unstable angina pectoris requiring hospitalization, (C.) nonfatal myocardial infarction and (D.) the combined endpoint.
MI: myocardial infarction; No.: number; UAP: unstable angina pectoris.

Table 4. *The association of clinical and coronary CTA characteristics with the combined endpoint: unstable angina pectoris requiring hospitalization, nonfatal myocardial infarction or all-cause mortality.*

Variable	Event*	No event*	Univariate analysis		
	N=43	N=904	HR	95% CI	P-value
Clinical characteristics					
Age (years)	60±12	53±12	1.06	1.03-1.09	**<0.001**
Women (%)	54	56	1.04	0.57-1.90	0.90
Risk factors					
BMI >30 (%)	24	18	1.54	0.75-3.13	0.24
Hypercholesterolemia†(%)	24	36	0.61	0.3-1.24	0.17
Hypertension‡ (%)	44	39	1.07	0.58-1.98	0.83
Current smoking (%)	14	15	0.88	0.37-2.07	0.76
Family history of CAD (%)	37	49	0.61	0.33-1.13	0.11
Diabetes mellitus (%)	24	27	0.88	0.43-1.79	0.72
Coronary CTA					
Calcium score (IQR) (n=811)	8 (0-247)	0 (0-11)	1.002	1.001-1.002	**<0.001**
Non-obstructive CAD (%)	70	58	1.57	0.82-3.00	0.18
Intramural course of the coronary arteries (%)	19	22	0.87	0.40-1.88	0.73
Coronary plaques (composition)					
No. of calcified lesions	0.98±1.68	0.26±0.90	1.34	1.16-1.56	**<0.001**
No. of mixed lesions	1.07±1.97	0.39±1.05	1.26	1.09-1.45	**0.002**
No of non-calcified lesions	0.42±0.76	0.49±1.40	0.95	0.72-1.24	0.69

* *Including unstable angina pectoris requiring hospitalization, nonfatal myocardial infarction or all-cause mortality.*

† *Serum total cholesterol ≥230 mg/dl and/or serum triglycerides ≥200 mg/dl or treatment with lipid lowering drugs.*

‡ *Defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or the use of antihypertensive medication.*

BMI: body mass index; CAD: coronary artery disease; IQR: interquartile range.

Discussion

The present study evaluated, in a large cohort of patients without obstructive CAD, the prognostic implications of an intramural course of a coronary artery assessed on coronary CTA. An intramural course of a coronary artery was observed in 22% of patients. Patients with and without an intramural course of the coronary artery had similar low cumulative event rates for the combined endpoint of nonfatal myocardial infarction, unstable angina pectoris that required hospitalization or all-cause mortality during long-term follow-up.

Presence of intramural course of a coronary artery

Intramural course of the coronary artery was for the first time described on invasive coronary angiography by Porstmann et al. in 1960.[18] Coronary CTA is a more sensitive imaging tool than invasive coronary angiography to characterizes the course of the coronary arteries, and, accordingly, studies have reported a prevalence of intramural course of coronary arteries on coronary CTA that is more than twice as high as observed on invasive angiography (0.5 to 11.8%).[19, 20] Among 100 patients who underwent coronary CTA and invasive angiography, Leschka et al. observed an intramural course of the coronary artery in 26 patients on coronary CTA compared with only 12 patients on invasive angiography.[21] The lower prevalence of an intramural course on invasive angiography compared with coronary CTA can be partially explained by the fact that these 2 techniques detect different phenomena. Coronary CTA visualizes the anatomical relationship of the coronary artery to the surrounding myocardium. Conversely, invasive angiography can only detect systolic compression of the artery, which can be the consequence of an intramural course (also referred to as myocardial bridging[22]), but occurs only in a minority of patients with intramural course of the coronary artery. Uusitalo et al. demonstrated that only approximately one-third of the patients with an intramural course on coronary CTA showed systolic compression during invasive coronary angiography.[11]

The prevalence of an intramural course of a coronary artery on coronary CTA in the current study was 22%. This is in accordance with studies using 64-slice and 128-slice CT scanners, who have reported prevalences of 26% and 21%, respectively.[23, 24] Similarly to the present study, the LAD coronary artery is the coronary artery more frequently showing an intramural course, regardless of the methodology used.[15, 21] In addition, the present study also demonstrated that the intermediate / anterolateral coronary artery was frequently involved.

Intramural course of the coronary artery and long-term outcome

Some case reports have suggested that the presence of an intramural course of a coronary artery is associated with sudden cardiac death.[7, 23] The present study revealed similar survival rates for both groups during long-term follow-up. In addition, the occurence of the combined endpoint of unstable angina pectoris that required hospitalization, nonfatal myocardial infarction, or all-cause mortality during long-term follow-up was similar in patients with and without an intramural course of a coronary artery. Rubinshtein et al. demonstrated in 334 patients that the presence of an intramural course of a coronary artery assessed with coronary CTA did not have a prognostic impact for the composite endpoint cardiovascular death or nonfatal myocardial infarction.[26] In their study, during a mean follow-up duration of 6 years, there was no significant difference in cumulative event rates between both groups (5.1% in patients with versus 3.2% in patients without an intramural course of a coronary artery; P=0.40). The reason that the frequently present intramural course of the coronary artery on coronary CTA was not associated with adverse events was probably because an intramural course only in the minority of the cases is associated with systolic compression ("bridging").[11]

Study limitations

The present study visualized the anatomical relationship of the coronary artery to the surrounding myocardium, and therefore, cyclic changes in coronary artery flow nor dynamic compression could be evaluated. Because the study was retrospective, no assessment of the required sample size was performed.

Conclusion

In patients without obstructive CAD on coronary CTA, an intramural course of a coronary artery is not associated with worse outcome.

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