Effect of Intramural Course of Coronary Arteries Assessed by Computed Tomography Angiography in Patients With Hypertrophic Cardiomyopathy

Mithal Nassar, MD[a], Ziad Arow, MD[a], Daniel Monakier, MD[a], Oren Zusman, MD[a], Gideon Shafir, MD[b], Ran Kornowski, MD[a], and Ashraf Hamdan, MD[a,*]

This study evaluated the prevalence, anatomical pattern, and prognostic implications of an intramural course of the coronary arteries in patients with hypertrophic cardiomyopathy (HC). The study population consisted of 92 patients with HC and 100 patients without HC. The presence of an intramural course of the coronary arteries was evaluated by coronary computed tomography angiography (CTA), and its length and depth were measured. During follow-up, the occurrence of unstable angina requiring hospitalization, myocardial infarction, and all-cause mortality was evaluated. An intramural course of the coronary arteries was more common in patients with HC than patients without HC (62% vs 25%, p <0.001). In the patients with an intramural coronary artery course, those with HC had a longer course (29.1 ± 15.3 mm vs 23.0 ± 13.0 mm; p = 0.037) with deeper penetration into the left ventricular myocardium (2.8 ± 1.2 mm vs 2.1 ± 0.8 mm; p = 0.007) and more involvement of multiple coronary arteries (38% vs 4%; p <0.001). During follow-up (mean 5.5 ± 3.5 years), cardiac events occurred in 17 of 57 patients (29.8%) with an intramural course and 11 of 35 (31.4%) without an intramural course (p = 0.87). On Kaplan-Meier survival analysis, there was no difference in cumulative event rate between HC patients with or without an intramural course (p = 0.89, log rank test). In conclusion, patients with HC have a high rate of an intramural course of the coronary arteries on CTA. The number of involved arteries and the length and depth of the intramural course differ between patients with and without HC, but apparently have no association with worse clinical outcomes. **(Am J Cardiol 2019;124:1279−1285)**

Analysis of the coronary arteries for stenosis frequently reveals variations in the coronary anatomy. One of the most common findings is an intramural course of the coronary arteries, defined as a segment of coronary artery completely covered by surrounding myocardium.[1] However, it has rarely been evaluated by coronary computed tomography angiography (CTA) in patients with hypertrophic cardiomyopathy (HC). In addition, the prognostic implication of an intramural course of the coronary arteries, identified by invasive coronary angiography, is controversial.[2−4] The aim of the present study was to evaluate anatomical characteristics of an intramural coronary artery course in patients with and without HC referred for coronary CTA and found to be negative for obstructive coronary artery disease (CAD). We also sought to determine if the presence of an intramural course of the coronary arteries in patients with HC was associated with worse outcome.

Methods

The cohort included 92 consecutive patients with HC attending a tertiary medical center and 100 age- and sex-matched control patients without HC, all of whom were referred for coronary CTA by their attending cardiologist to rule out CAD (Table 1). Patients with a history of CAD or a finding of obstructive CAD on coronary CTA (defined as any coronary artery stenosis >50%) were excluded from the analysis. The patients with HC were diagnosed and followed in the hospital's specialized HC clinic. The diagnosis was based on the definition of the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy, namely, wall thickness ≥15 mm in one or more left ventricular myocardial segments not explained solely by loading conditions.[5] Endomyocardial biopsy and genetic testing were not used to reach the diagnosis.[6] Clinical and coronary CTA data were prospectively entered into a database and analyzed retrospectively. The study was approved by the local Institutional Review Board.

All scans were performed with a 256-slice system (Brilliance iCT, Philips Healthcare, Cleveland, Ohio). A nonenhanced scan, for the assessment of the coronary artery calcium score, and a contrast-enhanced coronary CTA were performed. The contrast-enhanced scan data were acquired with a collimation of 96 × 0.625 mm, tube current was 485 mA at 100 kV, pitch value was 0.2, and the gantry rotation time was 330 ms. Sublingual isosorbide

[a]Departments of Cardiology, Rabin Medical Center − Beilinson Hospital, Petach Tikva, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; and [b]Departments of Diagnostic Imaging, Rabin Medical Center − Beilinson Hospital, Petach Tikva, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. Manuscript received May 26, 2019; revised manuscript received and accepted July 8, 2019.

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*Corresponding author: Tel: +972-3 937-7107; fax: +972-3 924-9850.
E-mail address: hamdashraf@gmail.com (A. Hamdan).

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Table 1
Baseline characteristics of patients with and without hypertrophic cardiomyopathy

Parameters	Hypertrophic cardiomyopathy		p Value
	No (N = 100)	Yes (N = 92)	
Age (years)	55.3 ± 12.8	57.0 ± 12.6	0.37
Male	70 (70%)	71 (77%)	0.16
Weight (kg)	80.0 ± 12.1	83.7 ± 15.0	0.06
Height (meters)	1.71 ± 0.08	1.72 ± 0.09	0.62
Body mass index (kg/m^2)	27.3 ± 4.0	28.2 ± 4.0	0.10
Body surface area (m^2)	1.95 ± 0.17	1.99 ± 0.23	0.08
Diabetes mellitus	9 (9%)	8 (22%)	0.56
Hypertension	22 (22%)	25 (27%)	0.26
*Hypercholesterolemia	31 (31%)	27 (29%)	0.45
Smoker	13 (13%)	11 (12%)	0.49
Previous smoker	7 (7%)	5 (5.4%)	0.44
Previous percutaneous coronary intervention	0 (0%)	1 (1.1%)	0.48
Permanent atrial fibrillation	2 (2%)	3 (3.2%)	0.47
Paroxysmal atrial fibrillation	8 (8%)	20 (21.7%)	0.007
Maximum left ventricular thickness (mm)	9.6 ± 1.4	21.7 ± 4.6	<0.001
Left ventricular mass (g)	119.9 ± 24.8	233.8 ± 85.5	<0.001
Left ventricular mass index (g/m^2)	61.5 ± 10.2	118.2 ± 44.9	<0.001
Coronary artery calcium score	120 ± 312	195 ± 389	0.16
Nonobstructive coronary artery disease	38 (38%)	44 (48%)	0.12
Vessel dominance			
Right	78 (78%)	67 (73%)	0.25
Left	14 (14%)	15 (16%)	0.42
Balanced	8 (8%)	10 (11%)	0.33
Coronary plaque composition			
Number of calcified segments	82 (5.1%)	157 (11%)	<0.001
Number of noncalcified segments	2 (0.1%)	26 (1.8%)	<0.001
Number of mixed segments	12 (0.8%)	15 (1.0%)	0.54

* Defined as LDL-C level ≥130 mg/dl.

dinitrate (0.8 mg) was administered immediately before coronary CTA; and whenever the heart rate was >65 beats/min, the patient was given intravenous metoprolol. Intravenous injection of 60 to 80 ml of nonionic contrast agent (Iopromide 370; Bayer Schering, Berlin, Germany) was administered at a flow rate of 5 ml/s and was followed by a 30-ml saline chase bolus. Acquisition was performed during an inspiratory breathhold while the electrocardiogram was recorded simultaneously to allow retrospective gating of data. The 3-dimensional dataset of the contrast-enhanced scan was reconstructed using iterative model reconstruction level 1 and transmitted to a dedicated CTA workstation (Philips Intellispace Portal, version 7.0). The data were analyzed by consensus of 2 experienced readers who were blinded to the patient details and follow-up data. All images were reconstructed with a slice thickness of 0.67 mm and a slice increment of 0.34 mm.

The coronary artery calcium score was calculated according to the Agatston algorithm.[7] To assess the coronary arteries, the dataset was reconstructed at 10% increments at diastole (70%, 80%, and 90%), and the phase with the best image quality was used for reconstruction of the entire coronary artery tree in accordance with the American Heart Association segment model.[8] The coronary arteries were automatically traced from the ostium to the distal part, and delineations were semiautomatically elongated to the most distal visible part. Multiplanar reconstructed images and cross-sectional views of the coronary arteries were created and interpreted to evaluate the presence of an intramural course and its type, length, and depth (Figure 1). An intramural course was defined as any epicardial artery segment that ran intramurally, surrounded by at least 1 mm of myocardium.[9] The length of the intramural course was measured using straightened multiplanar reconstruction (Figure 1), and the depth was determined by perpendicular measurement of the thickness of overlying myocardium on cross-sectional views in which overlying myocardium appeared to be thickest (Figure 1). The intramural course was classified as superficial when the artery was covered with 1 to 2 mm of myocardium, and deep, when the artery was covered with >2 mm of myocardium.[10,11] Coronary plaques were stratified into 3 categories: Calcified plaques containing >50% calcification; mixed plaque containing <50% calcification; and noncalcified plaque containing no calcification.

The follow-up time was defined as the interval between the date of the initial evaluation and the date of the last medical interview. HC clinic is part of a large health management organization with a centralized database that receives and coordinates input from its hospitals, community clinics and pharmacies, and the national registry of the Ministry of the Interior (in the form of death certificates) and can be accessed down to the individual patient. At the end of the study period, data on hospitalizations and outcome of the study cohort were derived by review of the HMO database. The combined end point of the study was unstable angina pectoris requiring hospitalization, myocardial infarction—both defined according to standard definitions[12,13]—and all-cause mortality.

Continuous variables are expressed as mean and standard deviation. Baseline characteristics of the cohort were compared between patients with and without HC using the Mann-Whitney-Wilcoxon test for continuous variables and chi-square test for categorical variables. Cumulative event rates for the combined end points of unstable angina pectoris requiring hospitalization, myocardial infarction, and all-cause mortality included all 3 events were estimated with the Kaplan-Meier method and compared between patients with HC with and without an intermural course of the coronary arteries using the log rank test. Cox proportional hazard models were formulated to assess the association between the characteristics of the intramural course of the coronary arteries and the combined end points. Hazard ratios and their respective 95% confidence intervals were reported. A p value of ≤0.05 was defined as statistically significant. Statistical analysis was performed with SPSS, version 17.0 (SPSS, Chicago, Illinois).

Results

Table 1 shows the demographic and clinical characteristics of the study population, and Table 2 compares demographic, echocardiographic, and clinical characteristics in

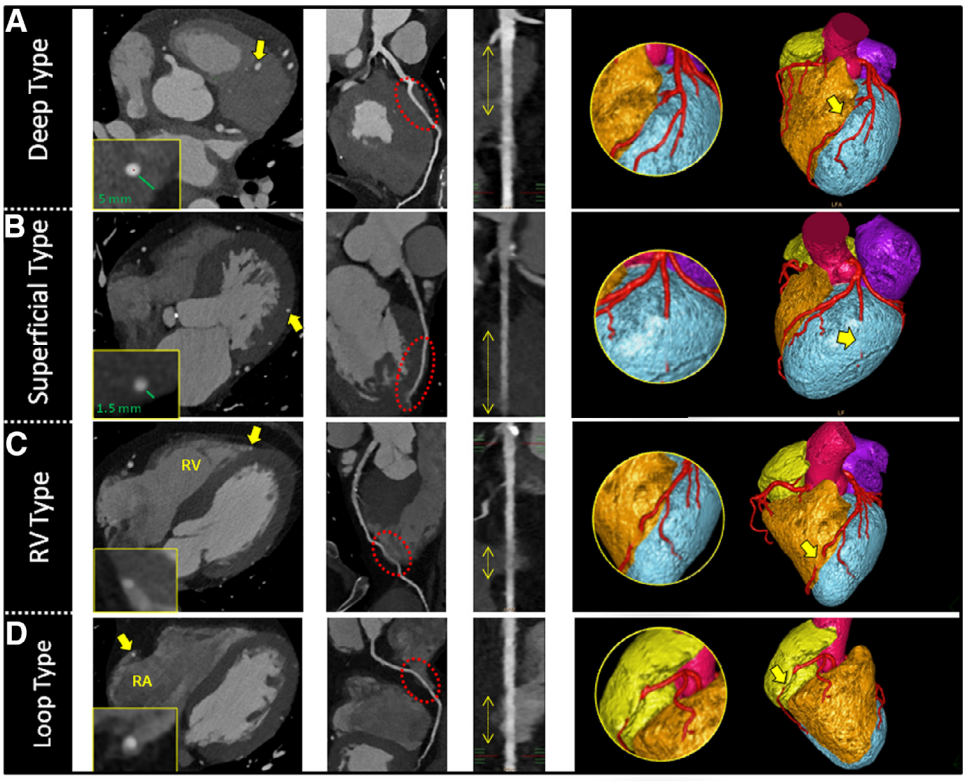

Figure 1. Representative examples of different types of intramural course of the coronary arteries as assessed with CTA. Axial and cross-sectional images (*left*), multiplanar and straightened multiplanar reconstructions (*middle*), and volume rendering (*right*) of (*A*) a deep intramural course of the mid-LAD; (*B*) a superficial intramural course of the first diagonal branch; (*C*) a right ventricular intramural course of the mid-LAD; (*D*) loop type of an intramural course of the mid-RCA. The length of the intramural course was measured using straightened multiplanar reconstruction, and the depth was determined by perpendicular measurement of the thickness of the overlying myocardium on the cross-sectional views in which the overlying myocardium was seen to be thickest.

the patients with HC, between those with and without an intramural course of the coronary arteries. Table 3 and Figure 2 show the morphological characteristics of the intramural course of coronary arteries in patients with and without HC. The intramural course in the HC group was also longer and penetrated deeper into the left ventricular myocardium (Figure 2).

Different anatomical patterns of the intramural course of a coronary artery were identified according to the depth and the course of the intramural segment. For the left anterior descending artery (LAD), 3 patterns were found (1) deep type (Figure 1), with coverage of the intramuscular segment by >2 mm of myocardium; (2) superficial type (Figure 1), with coverage of the intramuscular segment by 1 to 2 mm of myocardium; and (3) right ventricular type (Figure 1), in which the intramuscular segment of the LAD crossed through the right ventricular anterior wall adjacent to the interventicular septum. For the right coronary artery, which was infrequently involved by an intramural course, one pattern was found: loop type, in which the intramural segment crossed the right atrium and remained adjacent to the right atrial wall (Figure 1). In patients without HC, the right ventricular type was the most common, followed by the deep and superficial types (Table 3).

Table 4 details the segmental location of the intramural course in patients with and without HC. In both groups, the most frequent coronary artery with an intramural course was the LAD. Patients with HC had a significantly higher intramural course of diagonal and marginal branches than patients without HC ($p < 0.001$).

Table 5 and Figure 3 summarize the clinical finding of HC patients with and without an intramural course of a coronary artery. The mean follow-up time was 5.5 ± 3.5 years (range 0.5 to 10 years), with no significant difference between the groups. During follow-up, 28 adverse cardiac events occurred: hospitalization due unstable angina pectoris in 24 patients (26.1%) and myocardial infarction in 4 patients (4.3%). There were no deaths. None of the patients experienced >1 event. In patients with HC, there was no association between the combined end point and either the presence or the characteristics of the intramural course of the coronary arteries (Table 6).

Discussion

The present study demonstrates the prevalence, anatomical pattern, and prognostic implications of an intramural coronary artery course in patients with HC. The prevalence was higher in patients with HC (62%) than in patients without HC (25%). In the patients with an intramural coronary artery course, those with HC had a longer course with deeper penetration into the left ventricular myocardium and more involvement of multiple coronary arteries. HC patients with and without an intramural course of the coronary arteries had similar event rates for the combined end point of unstable angina pectoris requiring hospitalization,

Table 2
Baseline characteristics of patients with hypertrophic cardiomyopathy stratified by the presence or absence of an intramural course of the coronary arteries

Parameters	Intramural course		p Value
	Yes (N = 57)	No (N = 35)	
Age (years)	55.8 ± 11.5	58.9 ± 14.0	0.62
Male	46 (81%)	25 (71%)	0.22
Weight, kg	83.3 ± 12.7	84.4 ± 18.2	0.19
Height (meters)	1.72 ± 0.1	1.72 ± 0.1	0.82
Body mass index, kg/m^2	28.1 ± 3.8	28.4 ± 4.3	0.14
Body surface area (m^2)	2.0 ± 0.18	2.0 ± 0.26	0.24
Diabetes mellitus	6 (11%)	2 (6%)	0.35
Hypertension	16 (28%)	9 (26%)	0.50
*Hypercholesterolemia	18 (32%)	9 (26%)	0.36
Smoker	5 (9%)	6 (17%)	0.19
Previous smoker	5 (9%)	0 (0%)	0.09
Previous percutaneous coronary intervention	0 (0%)	1 (3%)	0.38
Permanent atrial fibrillation	1 (2%)	2 (6%)	0.32
Paroxysmal atrial fibrillation	12 (21%)	8 (23%)	0.52
Maximum left ventricular thickness (mm)	22.0 ± 4.9	21.3 ± 4.9	0.48
Left ventricular mass (g)	241 ± 89	221 ± 79	0.62
Left ventricular mass index (g/m^2)	121 ± 41	111 ± 38	0.86
Coronary artery calcium score	146 ± 379	274 ± 397	0.20
Nonobstructive coronary artery disease	29 (51%)	15 (43%)	0.30
Echocardiographic finding			
Left ventricular ejection fraction, %	61.8 ± 7.7	62.4 ± 5.9	0.71
Early left ventricular velocity (cm/s)	79.9 ± 21.9	77.6 ± 22.8	0.78
Late left ventricular velocity (cm/s)	64.4 ± 14.7	69.4 ± 23.5	0.47
Early/late left ventricular velocity	1.33 ± 0.34	1.1 ± 0.2	0.07
Early diastolic velocity of mitral annulus (cm/s)	7.1 ± 2.1	7.6 ± 2.4	0.51
Clinical presentation			
Typical angina	0 (0%)	0 (0%)	-
Atypical angina	3 (5.3%)	1 (2.9%)	0.58
Nonanginal chest pain	24 (42.1%)	13 (37.1%)	0.63
Other chest discomfort	30 (52.6%)	21 (60%)	0.49
NYHA			
Class I	12 (52.2%)	6 (40%)	0.46
Class II	9 (39.1%)	7 (46.7%)	0.65
Class III	2 (8.7%)	2 (13.3%)	0.88
Nonsustained ventricular tachycardia	12 (21%)	8 (23%)	0.44
Vessel dominance			
Right	41 (72%)	26 (74%)	0.50
Left	10 (18%)	5 (14%)	0.46
Balanced	6 (10%)	4 (12%)	0.57
Coronary plaque composition			
Number of calcified segments	86 (9.4%)	71 (12.7%)	0.04
Number of noncalcified segments	12 (1.3%)	14 (2.8%)	0.94
Number of mixed segments	6 (0.7%)	9 (1.8%)	0.08

* Defined as LDL-C level ≥130 mg/dl.

myocardial infarction, and all-cause mortality during long-term follow-up.

The prevalence rates of an intramural course of the coronary arteries in the general population and in patients with HC are controversial. In autopsy studies of the general population, rates ranged widely from 5% to 86%,[14–16] and in invasive coronary angiography studies of patients with HC, the reported rates were 15% to 40%.[2–4] Coronary CTA studies of the general population reported prevalence rates similar to the pathologic studies but higher than the invasive coronary angiography studies.[17] The lower prevalence of an intramural course on invasive coronary angiography compared with coronary CTA can be partially explained by the fact that coronary CTA is able to visualize not only the lumen of the coronary artery but also the overlying muscular band. Conversely, invasive coronary angiography can only detect systolic compression of the artery (milking effect), which can be due to an intramural course, but occurs only in approximately 1/3 of patients with intramural course of the coronary arteries.[18] This might explain the higher prevalence of intramural course of the coronary arteries in patients with HC in our study (62%) compared to invasive coronary angiography studies (15% to 40%).

In concordance with previous studies,[9,15,17] the LAD was the coronary artery that more frequently showed an intramural course in patients with and without HC. However, the marginal and diagonal coronary arteries had an intramural course significantly more often in patients with

Table 3
Comparison of morphological characteristics of an intramural course of the coronary arteries in Patients with and without hypertrophic cardiomyopathy

Morphology	Hypertrophic cardiomyopathy		p Value
	No (N = 100)	Yes (N = 92)	
Number of intramural course	29	103	
Patients with intramural course	25 (25%)	57 (62%)	<0.001
Length (mm)	23.0 ± 13.0	29.1 ± 15.3	0.037
Depth (mm)	2.1 ± 0.8	2.8 ± 1.2	0.007
Patients with multiple intramural course	4 (4%)	35 (38%)	<0.001
Pattern of left anterior descending artery intramural course			
Deep type	10 (35%)	56 (54%)	<0.001
Superficial type	7 (24%)	31 (30%)	<0.001
Right ventricular type	12 (41%)	14 (14%)	<0.001
Pattern of right coronary artery intramural course			
Loop type	0	1 (1.0%)	0.002

than without HC (Table 4). The length and depth of the intramural course in the patients without HC was in accordance with previous studies.[9,17] By contrast, in patients with HC, the course was significantly longer and deeper within the left ventricular myocardium than in patients without HC (Table 3). The deep type was the most common type, and it occurred significantly more often than in the patients without HC, in agreement with the pathology study of Basso et al[15] we also observed that an intramural course at multiple segments of the coronary artery was more common in patients with than without HC.

The impact of an intramural course of the coronary arteries on the clinical outcome of patients with HC is unclear. One invasive coronary angiography study suggested that in children with HC, an intramural coronary artery course was associated with myocardial ischemia and poor outcome.[4] Others, however, found that in adults with HC, an intramural course diagnosed by invasive coronary angiography[2,3] or at autopsy[15] was not a probable cause of cardiac events. In the present study, there was no difference in the rate of occurrence of the combined end point of unstable angina pectoris requiring hospitalization, myocardial infarction, and all-cause mortality during long-term follow-up between

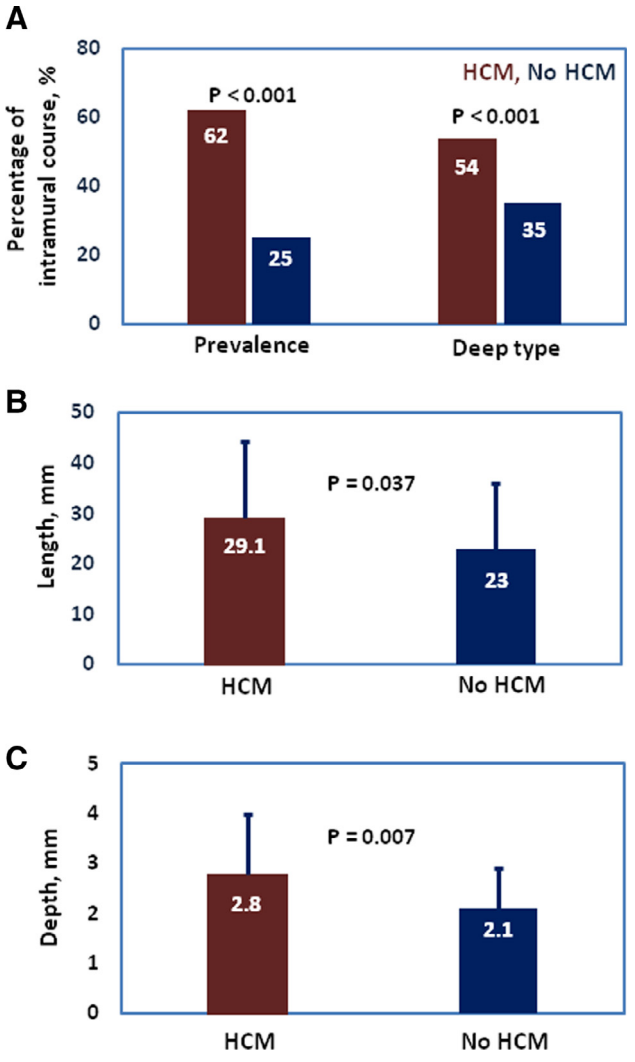

Figure 2. Characteristics of the intramural course of the coronary arteries in patients with and without HC: (*A*) prevalence; (*B*) length; (*C*) depth.

Table 4
Distribution of the intramural course of the coronary arteries in patients with and without hypertrophic cardiomyopathy

Parameters	Hypertrophic cardiomyopathy		p Value
	No (N = 100)	Yes (N = 92)	
Left main	0	0	-
Left anterior descending	23 (79%)	59 (57%)	<0.001
Proximal	0	0	-
Mid	11 (38%)	24 (23%)	0.007
Distal	10 (34%)	7 (7%)	0.56
Diagonal branches	2 (7%)	28 (27%)	<0.001
Circumflex	6 (21%)	43 (42%)	<0.001
Proximal	0	0	-
Distal	0	0	-
Marginal branches	3 (10.5%)	40 (39%)	<0.001
Intermediate branch	3 (10.5%)	3 (3%)	0.92
Right coronary artery	0	1 (1%)	0.37
Proximal	0	0	-
Mid	0	1 (1%)	0.37
Distal	0	0	-
Right descending posterior/posterolateral branch	0	0	-

Table 5
Clinical findings in patients with hypertrophic cardiomyopathy stratified by the presence or absence of an intramural course of the coronary arteries

Variables	Intramural course		p Value
	Yes (N = 57)	No (N = 35)	
Follow-up (years)	5.7 ± 3.4	5.1 ± 3.7	0.40
Unstable angina pectoris requiring hospitalization	16 (28.1%)	8 (22.9%)	0.58
Myocardial infarction	1 (1.8%)	3 (8.6%)	0.12
All-cause mortality	0	0	-
Combined endpoint*	17 (29.8%)	11 (31.4%)	0.87

* Unstable angina pectoris requiring hospitalization, myocardial infarction, and all-cause mortality.

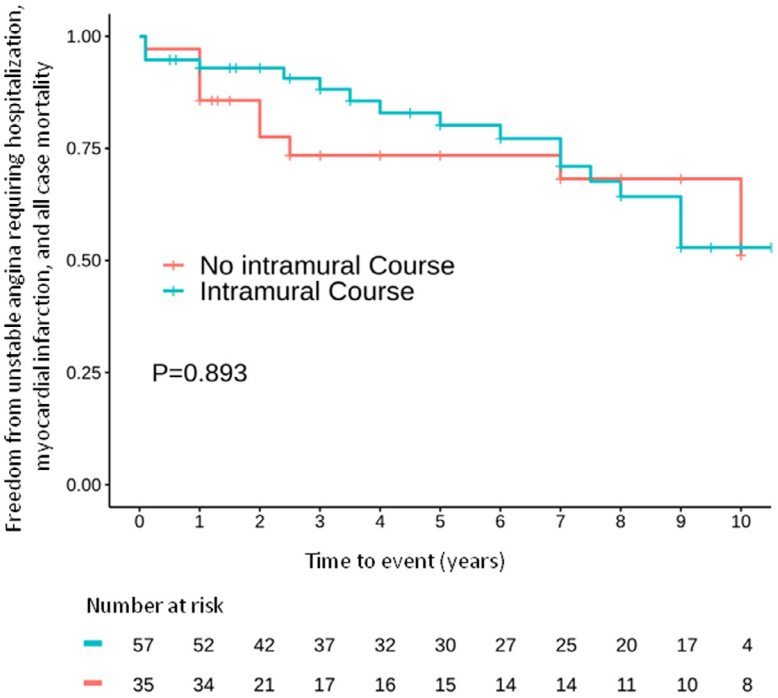

Figure 3. Kaplan-Meier curve for the combined end point of unstable angina pectoris requiring hospitalization, myocardial infarction, and all-cause mortality in patients with and without HC. There was no difference in event rates between patients with or without an intramural course (log-rank p = 0.89).

patients with HC with or without an intramural course of the coronary arteries, which is in line with the impact of an intramural course of the coronary arteries in the general population.[9] In addition, the characteristics of intramural course in the patients with HC did not affect the combined endpoint (Table 6).

This is the first study to use coronary CTA to evaluate the intramural course of the coronary arteries in patients with HC, we recognize that the present study evaluated anatomical relation of the coronary arteries to the surrounding myocardium, but did not evaluate physiological consequences of the intramural course of the coronary arteries like coronary flow reserve. In addition, the present study may have selection bias and perhaps higher prevalence of intramural course of the coronary arteries than in HC patients in general, as patients with more symptoms were more likely to be referred for coronary CTA, and the prevalence of an intramural course of the coronary arteries may vary with patient selection. Furthermore, owing to the retrospective design of the study, the required sample size was not assessed.

Table 6
Univariate analysis for the association of intramural course characteristics with the combined endpoint of unstable angina pectoris requiring hospitalization, myocardial infarction, and all-cause mortality

Intramural course	Hazard ratio	95% Confidence intervals	p Value
Present, absence	0.94	0.44 - 2.04	0.88
Length	1.00	0.96 - 1.05	0.94
Depth	0.75	0.40 - 1.4	0.35
Multiple	3.52	0.77 - 16.0	0.11

In conclusion, an intramural course of the coronary arteries in patients with HC observed by coronary CTA was frequent. The anatomical pattern of the intramural course differs between patients with and without HC. Neither the presence nor the characteristics of the intramural coronary artery course are associated with an increased risk of adverse cardiac events.

Disclosures

The authors have nothing to disclose.

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