



Prevalence and morphology of myocardial crypts in normal and hypertrophied myocardium by computed tomography

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Abstract

Myocardial crypts can be recognized in patients with hypertrophic cardiomyopathy (HCM) using magnetic resonance imaging, but similar studies using computed tomography (CT) are sparse. The aim of the present study was to evaluate the prevalence and morphology of myocardial crypts in patients with HCM, arterial hypertension, and aortic valve stenosis using contrast-enhanced CT. We also investigated the added value of a finding of myocardial crypts on CT scan to the diagnosis of HCM. The study cohort included 73 patients with HCM, 100 patients with arterial hypertension, 120 patients with aortic valve stenosis, and 100 subjects without cardiovascular disease (normal control group). All underwent evaluation for the presence and dimensions of myocardial crypts using 256-slice CT. Crypts were identified in 18 patients (24.7%) with HCM, 7 patients (7%) with hypertension, 8 patients (6.7%) with aortic valve stenosis, and 4 (4%) normal subjects ($P < 0.001$). Values of crypt length, width, area, and penetration into myocardium were highest in the HCM group. Crypt area differentiated patients with HCM from patients with arterial hypertension and aortic valve stenosis, and from normal control subjects. Crypt area was an accurate predictor of HCM, with an area under the receiver-operator characteristic curve of 0.88 (95% CI 0.80–0.96). Myocardial crypts identified by CT are more prevalent and larger in area in HCM than in arterial hypertension and aortic valve stenosis. Crypt area could potentially help to improve the diagnosis of HCM by CT beyond the assessment of left ventricular thickness or mass.

Keywords Computed tomography · Left ventricular hypertrophy · Hypertrophic cardiomyopathy · Aortic valve stenosis · Myocardial crypts

Introduction

Myocardial crypts are slit-like blood-filled invaginations within the left ventricular myocardium. They are mostly observed between muscle bundles in the insertion points between the left and right ventricles [1–3]. Myocardial crypts were first observed in autopsy studies [4] and later by cardiovascular magnetic resonance (CMR) imaging [5]. They were therefore considered in the early reports to be a distinctive morphologic expression or even a phenotypic marker of hypertrophic cardiomyopathy (HCM) [5–8]. More recently, crypts have been detected by CMR imaging also

in patients with a wide variety of cardiac diseases as well as healthy subjects [9–11]. Few studies have investigated the prevalence and morphology of myocardial crypts using computed tomography (CT) [12, 13].

CT is an excellent tool for the accurate assessment of cardiac anatomy. It allows for multiplanar reconstruction with excellent spatial and temporal resolution and isometric voxel size [14]. These advantages together with the improved image quality and reduced image noise of the new-generation CT models and the recent advances in iterative model reconstruction techniques [15] may make CT amenable for use in the recognition and evaluation of myocardial crypts.

The aim of the present study was to investigate the prevalence and dimensions of myocardial crypts in patients with HCM evaluated by CT. Findings were compared to patients with arterial hypertension and severe aortic valve stenosis and to subjects without coronary artery disease. In addition, we sought to determine if the assessment of crypt morphology by CT could aid in the diagnosis of HCM.

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Methods

Study population

The study group consisted of 73 consecutive patients with HCM who underwent electrocardiogram (ECG)-gated CT at our institution from January 2010 to September 2017. The comparison groups consisted of 100 consecutive patients with arterial hypertension, 120 patients with symptomatic severe aortic valve stenosis, and 100 subjects without evidence of coronary artery disease (normal controls) who were included in the study over a 12-month period. The patients with HCM and arterial hypertension and the normal control subjects were initially referred for CT angiography to rule out coronary artery disease, and the patients with severe aortic valve stenosis underwent evaluation by CT before transcatheter aortic valve implantation. Exclusion criteria for all groups were acute coronary syndrome, previous myocardial infarction, pregnancy, and breastfeeding. The patients with HCM were diagnosed and evaluated in the hospital's specialized HCM 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, measured by any imaging technique (echocardiography, CMR, CT), that is not explained solely by loading conditions [16]. Endomyocardial biopsy or genetic testing was not used to reach the diagnosis [17]. The clinical and CT data were prospectively entered into the hospital's database and analyzed retrospectively. The study was approved by the local Institutional Review Board.

Acquisition protocol

CT angiography was performed using a 256-slice system (Brilliance iCT, Philips Healthcare, Cleveland, OH, USA). Data were acquired with a collimation size of 96×0.625 mm and gantry rotation time of 330 ms. Other parameters were as follows: tube current, 485 mA at 100 kV; pitch value, 0.2; scan direction, cranio-caudal. Intravenous injection of 60 to 80 ml of nonionic contrast agent (Iopromide 370; Bayer Schering, Berlin, Germany) at a flow rate of 5 ml/s was followed by a 30-ml saline chase bolus (3 ml/s). Patients with aortic valve stenosis undergoing transcatheter aortic valve implantation were examined using a tube voltage of 80 kV in order to reduce contrast agent load to 50 ml [18]. Automated peak enhancement detection in the descending aorta was used to time the scan. Data acquisition was automatically initiated at a threshold level of 180 Hounsfield units. Acquisition was performed during inspiratory breath-hold, and the ECG was recorded simultaneously to allow for retrospective gating of the data. All images were reconstructed with a slice

thickness of 0.67 mm and a slice increment of 0.34 mm. The three-dimensional dataset of the contrast-enhanced CT scan was reconstructed using iterative model reconstruction level 1 at systole and diastole (40%, 70%, 75%, 80%, and 90% phase of the cardiac cycle) and routed to a dedicated CT workstation (Philips Intellispace Portal, version 7.0).

Image analysis

Crypts were defined as blood-filled invaginations penetrating $> 50\%$ of the thickness of adjoining compact myocardium during diastole, perpendicular to the endocardial border of otherwise normal myocardium [8]. To assess the crypts, the best diastolic phase (70%, 75%, 80%, or 90% of the R-R interval) was used for multiplanar reformation. The standard axial, coronal, and sagittal views were used for initial orientation, and a double oblique plane aligned orthogonally to the axial images through the apex, mitral, and aortic valve was used to generate left ventricular 2-, 3- and 4-chamber and short-axis plans. To assess crypt measurements, a double oblique plane perpendicular to the long axis of the myocardial crypts was displayed as shown in Fig. 1. The resulting reconstruction was used for measurement of crypt length, width, cross-sectional area, and percentage of penetration into the myocardium (Fig. 1). Crypt location and number were recorded on the basis of the 17-segment heart model recommended by the American Heart Association [19].

For assessment of left ventricular myocardial mass and maximal wall thickness, the phase with the largest left ventricular volume was automatically reconstructed. Epicardial and endocardial borders of the left ventricle were automatically detected in short-axis views, and the contours were manually edited as needed. Left ventricular papillary muscles were included in the myocardial mass measurement. To calculate left ventricular myocardial mass, the volume of the myocardium extracted from the imaging data, including the papillary muscle, was multiplied by the myocardial tissue density (1.055 g/ml).

Follow-up

The follow-up time for the HCM study group was defined as the interval from initial evaluation to the date of the last interview. At the end of the study, the hospitals' electronic records were retrospectively reviewed for data on mortality. In addition, we analyzed the ECG Holter ambulatory recordings for the presence or absence of ventricular tachycardia, defined as > 3 beats duration.

To assess interobserver variability, the dimensions of the crypts found in 37 patients were measured by 2 independent experienced observers (Z.A. and M.N.) who were blinded to each other's results and to the clinical data.

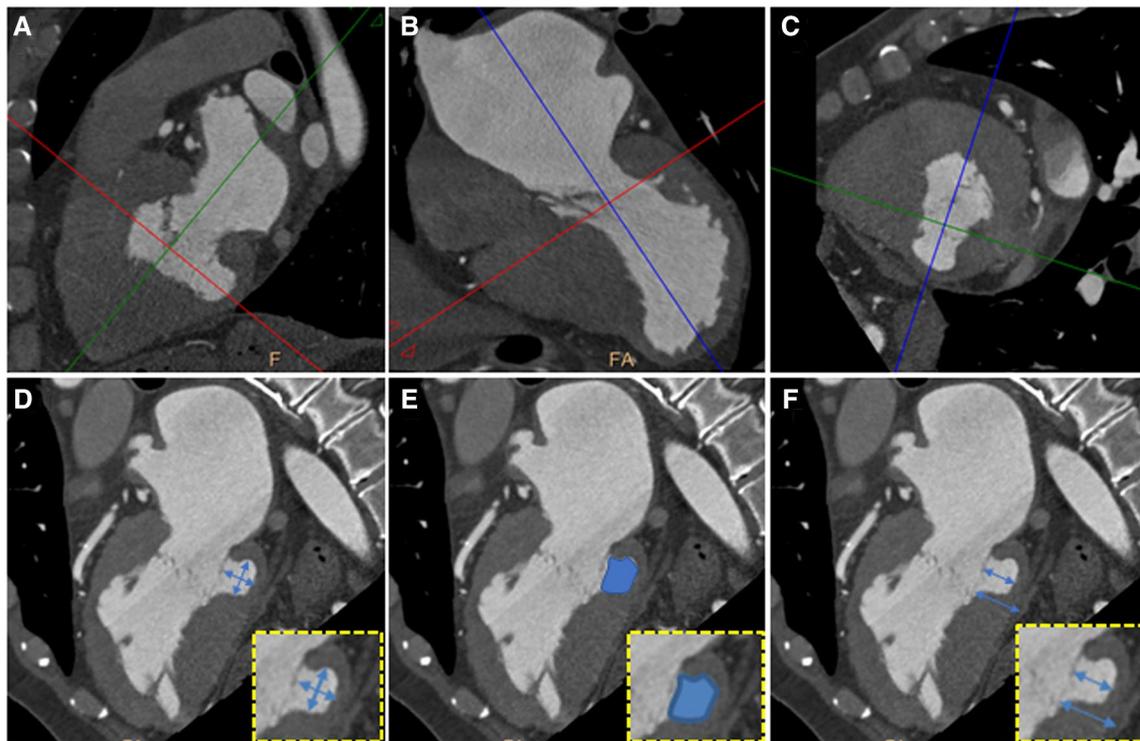


Fig. 1 Reconstruction of myocardial crypts by computed tomography. Different end-diastolic views in a patient with HCM: **a** sagittal view; **b** reconstructed, 4-chamber view; **c** short-axis view. The resulting double oblique plane perpendicular to the long axis of myocar-

dial crypts was used for crypt measurements: **d** length and width; **e** cross-sectional area; **f** percentage of penetration into the myocardium, defined as crypt length divided by myocardial thickness

Statistical analysis

Continuous variables are expressed as mean and standard deviation (SD). Continuous data were compared using unpaired Student's *t*-test or analysis of variance, as appropriate. Categorical variables were compared with Chi square test. A *P* value of ≤ 0.05 was considered indicative of a statistically significant difference. The statistical analysis was performed in two steps. In the first step, we evaluated the value of myocardial crypts for the diagnosis of HCM among the entire study population (patients with HCM, arterial hypertension and aortic valve stenosis, and normal subjects with or without crypts). The second step was limited to patients/subjects in the study population who had crypts and was aimed at identifying the anatomic features of crypts that were relevant for the diagnosis of HCM. Predictors of HCM were analyzed with univariate analysis followed by a multivariate regression model including crypt area, crypt length, crypt width, and left ventricular mass and mass index. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Receiver-operator characteristic (ROC) curves were constructed to analyze the performance of crypt area for the diagnosis of HCM. Inter-observer variability of crypt measurements

was analyzed using Bland–Altman methods. All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS, version 22.0, SPSS, Chicago, IL) and STATA 12 SE (STATA Corp., College Station, TX, USA).

Results

Table 1 shows the demographic and clinical characteristics of the study population. Representative examples of myocardial crypts in the studied population are shown in Fig. 2. Table 2 compares the patients/subjects with and without crypts for the same variables. Left ventricular mass was greater in the patients/subjects with crypts, but not when adjusted for body surface area. Mean heart rate during cardiac CT was similar in normal subjects, patients with HCM, and patients with arterial hypertension (61.1 ± 7.8 , 59.5 ± 11.2 , 60.5 ± 9.5 beats/minutes, respectively; $P=0.37$) and somewhat higher in patients with aortic valve stenosis (71.0 ± 14.4 beats/minute; $P < 0.001$).

Table 3 shows the characteristics of the crypts found in the different groups. Crypts were significantly more

Table 1 Characteristics of study population

Parameters	Normal subjects N = 100	Systemic hypertension N = 100	Aortic stenosis N = 120	Hypertrophic cardiomyopathy N = 73	P value
Age, years	49.4 ± 10.7	58.4 ± 12.57	75.6 ± 11.2	56.9 ± 12.19	< 0.001
Gender, male, n (%)	62 (62)	58 (58)	62 (51.6)	57 (78.1)	0.004
Weight, kg	77.9 ± 14.5	83.3 ± 15.5	78.8 ± 18.3	82.5 ± 13.1	0.043
Height, m	1.71 ± 0.09	1.68 ± 0.09	1.63 ± 0.09	1.72 ± 0.09	< 0.001
Body mass index, kg/m ²	26.78 ± 5.05	29.11 ± 4.69	29.38 ± 6.9	27.77 ± 3.70	0.002
Body surface area (m ²)	1.91 ± 0.2	1.95 ± 0.28	1.88 ± 0.23	1.98 ± 0.19	0.019
Maximum left ventricular thickness (mm)	9.3 ± 1.4	12.0 ± 2.1	12.2 ± 1.9	22.3 ± 2.1	< 0.001
Left ventricular mass (g)	117.6 ± 26.4	147.6 ± 42.7	188.5 ± 60.1	234.9 ± 80.9	< 0.001
Left ventricular mass index (g/m ²)	61.3 ± 11.5	77.4 ± 59.8	99.7 ± 27.3	116.7 ± 36.5	< 0.001
Diabetes	6 (6)	26 (26)	52 (43.3)	6 (8)	< 0.001
Hypertension	0 (0)	100 (100)	97 (80.8)	21 (28.7)	< 0.001
Hypercholesterolemia	18 (18)	51 (51)	79 (65.8)	16 (22)	< 0.001
Smoker	17 (17)	16 (16)	16 (13.3)	8 (11)	0.693
Previous smoker	4 (4)	9 (9)	13 (10.8)	5 (6.8)	0.294
Coronary artery disease	0 (0)	14 (14)	66 (55)	2 (2.7)	< 0.001
Previous CABG	0 (0)	2 (2)	27 (22.5)	0 (0)	< 0.001
Previous PCI	0 (0)	14 (14)	48 (40)	0 (0)	< 0.001
Paroxysmal atrial fibrillation	0 (0)	7 (7)	32 (26.6)	10 (13.7)	0.244
Permanent atrial fibrillation	0 (0)	1 (1)	4 (3.3)	2 (2.7)	< 0.001

Values are mean ± SD or n (%)

CABG coronary artery bypass grafting, PCI percutaneous coronary intervention

prevalent in the patients with HCM (18/73, 24.7%), arterial hypertension (7/100, 7%), and aortic valve stenosis (8/120, 6.7%) than in the normal subjects (4/100, 4%) ($P < 0.001$). Among the three patient groups, crypts were significantly more prevalent in those with HCM than in those with arterial hypertension or aortic valve stenosis ($P < 0.001$). Furthermore, compared to the other three groups, the patients with HCM had longer and wider crypts, with a larger area and deeper penetration into the myocardium (Table 3).

In all groups, crypts were most commonly located in the septum of the left ventricle (58%); infero-basal crypts were observed only in patients with HCM (Fig. 3). The distribution of number of crypts by group is shown in Fig. 4. Patients with HCM had 3 or more crypts whereas patients with arterial hypertension and aortic valve stenosis had 1 or 2 crypts, and normal subjects had only one crypt.

Table 4 shows the results of the univariate and multivariate analyses of predictors of HCM in the patients/subjects with crypts. On univariate analysis, the OR for the diagnosis of HCM was highly significant for crypt area, crypt length, and crypt width, and of borderline significance for left ventricular mass and mass index. Multivariate logistic regression analysis revealed crypt area to be the most powerful

independent predictor for the diagnosis of HCM (OR 1.15, 95% CI 1.03–1.28, $P = 0.013$).

To explore the diagnostic potential of crypts for assessing HCM, we calculated the diagnostic performance of the presence of any crypts among the entire study population (patients/subjects with and without crypts, $n = 393$). Comparison of the HCM group with the arterial hypertension, aortic valve stenosis, and normal groups yielded an area under the curve of 0.60 (95% CI 0.52–0.67). However, a similar comparison of crypt area, which was the best predictor for HCM on multivariate regression analysis, in patients/subjects with crypts ($n = 37$) yielded an area under the curve of 0.88 (95% CI 0.80–0.96). These findings indicate a good ability of CT to differentiate patients with HCM from patients with arterial hypertension or aortic valve stenosis and normal subjects (Fig. 5).

The mean follow-up time of the patients with HCM was 5.7 ± 3.5 years, with no significant difference between those with and without crypts (6.7 ± 3.6 vs. 5.3 ± 3.4 years, $P = 0.16$). None of the patients with HCM died during follow-up. A Holter ECG was worn by 16 of the 18 patients (89%) with crypts and 44 of the 55 patients (80%) without crypts. Non-sustained ventricular tachycardia was noted in 4/16 patients (4%) and 11/44 patients (4%), respectively

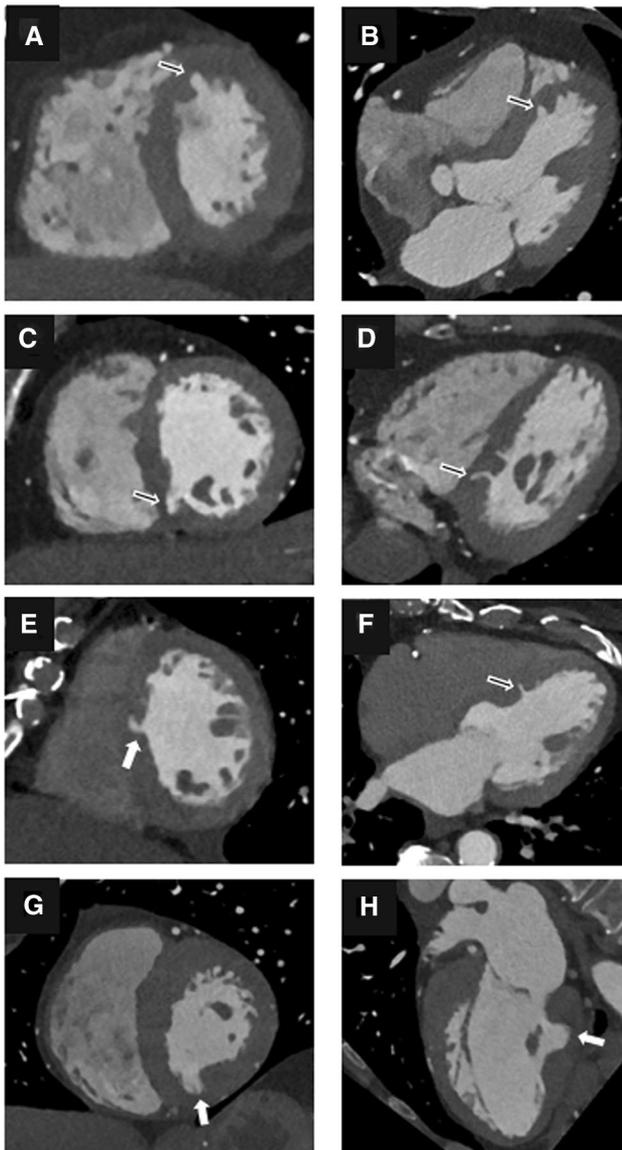


Fig. 2 End-diastolic views in short and long axes for evaluation of myocardial crypts using CT. **a, b** normal subject; **c, d** patient with systemic hypertension; **d, e** patient with aortic valve stenosis; **g, h** patient with HCM. Note the greater length, width, and area of myocardial crypts in the inferobasal segment in the patient with HCM

($P=0.87$). Four patients in the HCM group had an implantable cardiac defibrillator, including 1 of the 18 patients with crypts (5.6%) and 3 of the 55 patients without crypts (5.5%) ($P=1.0$).

In 37 patients with crypts, mean interobserver variability (95% CI) for the various parameters was as follows: length, 0.14 ± 1.80 mm (3.74, -3.46); width, 0.18 ± 0.87 mm (1.92, -1.56); cross-sectional area, 3.1 ± 7.69 mm² (18.48, -12.3); and penetration into myocardium, $0.02 \pm 0.15\%$ (0.32, -0.28).

Table 2 Characteristics of study population with and without crypts

Parameters	Patients with crypts N=37	Patients without crypts N=356	P-value
Age, years	62.6 ± 13.1	60.9 ± 15.7	0.362
Gender, male, n (%)	23 (62)	216 (61)	0.501
Weight, kg	79.7 ± 13.9	80.4 ± 16.1	0.844
Height, m	1.71 ± 0.08	1.68 ± 0.10	0.062
Body mass index, kg/m ²	27.1 ± 4.1	28.5 ± 5.6	0.434
Body surface area (m ²)	1.94 ± 0.19	1.93 ± 0.24	0.182
Left ventricular mass (g)	200.6 ± 84.3	165.3 ± 65.5	0.023
Left ventricular mass index (g/m ²)	103.4 ± 43.0	86.8 ± 41.6	0.063
Diabetes	11 (30)	79 (22)	0.240
Hypertension	21 (57)	197 (55)	0.713
Hypercholesterolemia	14 (38)	150 (42)	0.722
Smoker	6 (16)	51 (14)	0.704
Previous smoker	4 (11)	27 (8)	0.452
Coronary artery disease	6 (16)	76 (21)	0.501
Previous CABG	1 (3)	28 (8)	0.213
Previous PCI	4 (10)	58 (16)	0.412
Permanent atrial fibrillation	1 (3)	6 (2)	0.630
Paroxysmal atrial fibrillation	7 (19)	42 (12)	0.112

Values are mean ± SD or n (%)

CABG coronary artery bypass grafting, PCI percutaneous coronary intervention

Discussion

The assessment of crypts by CT could potentially help to improve the diagnosis of HCM beyond the assessment of left ventricular thickness or mass and aid clinicians in distinguishing HCM from arterial hypertension and aortic valve stenosis. In the present study, we evaluated the presence and dimensions of myocardial crypts in patients with HCM, arterial hypertension, and aortic valve stenosis and subjects without coronary artery disease using contrast-enhanced ECG-gated CT. In this manner, we extended previous analyses from a one- to a two-dimensional definition of crypts. Myocardial crypts were identified in all studied groups, but they were more prevalent and higher in number in the patients with HCM. In addition, the crypt area was significantly greater in the patients with HCM than in the other groups, and it was the most accurate predictor of HCM (Table 4), with an area under the ROC curve of 0.88 (95% CI 0.80–0.96) (Fig. 5).

We used standard contrast-enhanced CT combined with iterative model reconstruction on routine ECG-gated examinations. The high spatial resolution of CT highlighted the left ventricular morphology in modified

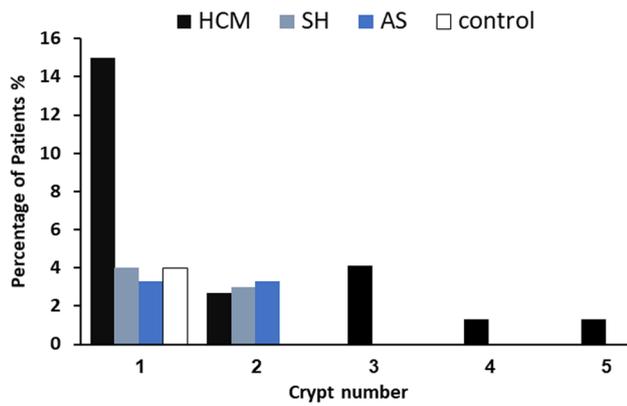


Fig. 4 Distribution of number of crypts in normal subjects, patients with HCM, and patients with hypertension or aortic valve stenosis. In the HCM group, 39% of patients had 2 or more crypts and 28% had 3 or more. By contrast, normal subjects had only 1 crypt, and patients with hypertension or aortic valve stenosis had 1 or 2. Only patients with HCM had 3 or more crypts

conventional imaging planes [5, 8]. These factors may partly explain some inconsistencies in the prevalence and clinical implications of crypts in CMR studies including patients with phenotypic and genotypic HCM [2–8]. Maron et al. [7] and Germans et al. [5] reported a high prevalence of crypts in HCM mutation carriers without left ventricular hypertrophy (81% and 61%, retrospectively). They suggested that myocardial crypts represent one of the early pathologic alterations of the myocardium that ultimately progress to manifest HCM. Other studies introduced a note of caution, highlighting the prevalence of crypts even in normal subjects and in a wide variety of patients other than those with HCM who are referred for CMR [9–11]. Deva et al. [6] studied consecutive patients with HCM and found that infero-basal crypts occurred more frequently in those who had the disease-causing mutation than those who did not. These results, however, could not be duplicated in a large population of consecutive patients undergoing CMR imaging [11]. Despite the conflicting data, most previous studies showed that patients with HCM have multiple crypts, and the crypts were more likely to be in the infero-basal segments. These findings are in line with our study (Figs. 3, 4).

Table 4 Univariate analysis and multivariate logistic regression of predictors of HCM in the study population with crypt

Parameter	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Crypt area	1.19	1.1–1.3	<0.001	1.15	1.03–1.28	0.013
Crypt length	1.58	1.2–2.1	0.001	–	–	–
Crypt width	1.23	1.0–1.5	0.024	–	–	–
Left ventricular mass (g)	1.01	1.0–1.02	0.062	–	–	–
Left ventricular mass index (g/m ²)	1.02	1.0–1.03	0.071	–	–	–

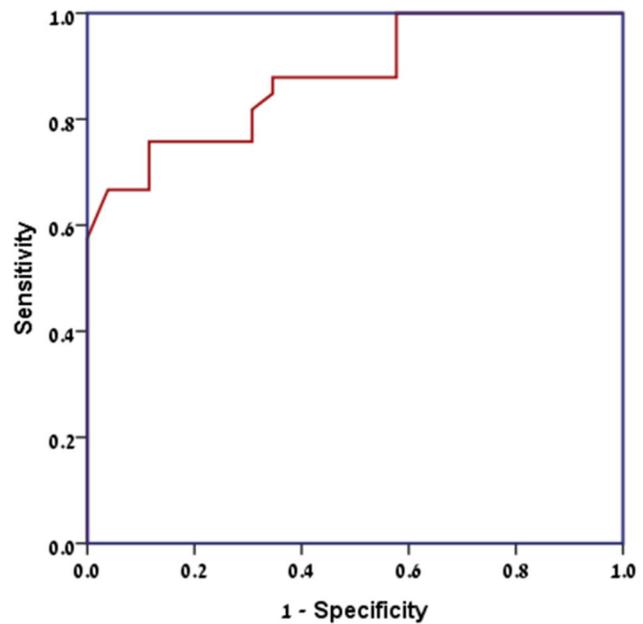


Fig. 5 ROC curve of crypt area for prediction of HCM. The area under the curve was 0.88 (95% CI 0.80 to 0.96)

Our results are also in keeping with previously published data on the prevalence of myocardial crypts in consecutive patients undergoing routine cardiac CT. The overall prevalence of myocardial crypts in the present study was 9.4%, which is comparable but slightly higher than the 6.7% reported in a retrospective CT study of 2093 patients [13]. The difference might be attributable to our inclusion of patients with HCM which is associated with a high rate of myocardial crypts. When patients with HCM were excluded, the prevalence of crypts in our study was 5.9%. Others reported a considerably lower prevalence of 2.2% in 675 patients with known or suspected coronary artery disease [12], However, these authors identified the crypts from the clinical reports and did not specifically search for them.

Our observations have caused us to be mindful of the two-dimensional definition of myocardial crypts and their location and number. The present study, conducted in a cohort of patients with HCM, arterial hypertension, or aortic valve

stenosis and normal subjects, demonstrated for the first time that crypt area may serve as a helpful morphologic marker of HCM which could potentially help to improve the diagnosis of HCM by CT.

Limitations

The limitations of our study include the retrospective design, absence of genome analysis, and small study population. However, the study was intended to reflect routine clinical practice and provide information on the prevalence of crypts in a representative and consecutive group of patients with HCM defined on the basis of contemporary guidelines (i.e., minimal wall thickness of ≥ 15 mm that is not explained solely by loading conditions) [16] (Table 1). The different groups had different baseline characteristics (Table 1): the patients with HCM were predominantly male; the patients with aortic valve stenosis were older; and the normal subjects had a smaller body size. However, crypts are disease-specific and unrelated to sex or age [6–8].

Conclusion

The use of contrast-enhanced CT to investigate myocardial crypts revealed that crypts are more prevalent, larger in area, and more abundant in patients with HCM than crypts in patients with arterial hypertension, aortic valve stenosis and normal subjects. Crypt area as measured by CT was a strong predictor of HCM and could potentially help to improve the diagnosis of HCM beyond the assessment of the left ventricular thickness and mass. A prospective study with genome analysis may be justified to investigate the diagnostic value and clinical implications of myocardial crypts, especially in patients with HCM.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

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