Frequency and Significance of Coronary Artery Disease and Myocardial Bridging in Patients With Hypertrophic Cardiomyopathy

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The etiology of chest pain in hypertrophic cardiomyopathy (HC) is diverse and includes coronary artery disease (CAD) as well as HC-specific causes. Myocardial bridging (MB) has been associated with HC, chest pain, and accelerated atherosclerosis. We compared HC patients with age-, gender- and CAD pre-test probability-matched outpatients presenting with chest pain to investigate differences in the presence of MB and CAD using coronary computed tomography angiography (CCTA). We studied 84 HC patients who underwent CCTA and compared these with 168 matched controls (age 54 ± 11 years, 70% men, pre-test probability 12% [5% to 32%]). MB, calcium score, plaque morphology and presence and extent of CAD were assessed for each patient. Linear mixed models were used to assess differences between cases and controls. MB was more often seen in HC patients (50% vs 25%, p <0.001). Calcium score and the presence of obstructive CAD were similar in both groups (9 [0 to 225] vs 4 [0 to 82] and 18% vs 19%; p = 0.22 and p = 0.82). In the HC group, MB was associated with pathogenic DNA variants (p = 0.04), but not with the presence of chest pain (74% vs 76%, p = 0.8), nor with worse outcome (log-rank p = 0.30). In conclusion, the prevalence and extent of CAD was equal among patients with and without HC, demonstrating that pre-test risk prediction using the CAD Consortium clinical risk score performs well in HC patients. MB was twice as prevalent in the HC group compared with matched controls, but was not associated with chest pain or decreased event-free survival in these patients. **(Am J Cardiol 2020;00:1−9)**

Hypertrophic cardiomyopathy (HC) is the most common inherited cardiac disease that affects at least 0.2% of the general population.[1] Although many patients diagnosed with HC present without or with minimal physical symptoms, a substantial group will experience mild to severe chest pain. The etiology of chest pain in HC patients is complex and includes myocardial ischemia, an increased metabolic demand and reduced myocardial blood supply.[1-3] HC patients are not exempt from coronary artery disease (CAD).[1,4] HC patients with concomitant CAD are at a higher risk of cardiac death compared with those without coexistent CAD.[4,5] Therefore, early diagnosis of CAD is important in symptomatic HC patients. Coronary computed tomography angiography (CCTA) is an excellent tool in the evaluation of chest pain, particularly to rule out CAD, especially in patients with low-to-intermediate risk for CAD.[3,6] Another added benefit of CCTA is the assessment of myocardial bridging (MB), which is reported to be particularly prevalent in HC.[7-9] MB is generally benign, but a relation with accelerated atherosclerosis, vasospasm, chest pain, and sudden cardiac death has been described.[10-12] Limited data exists on the value of CCTA in patients with HC and chest pain in the context of MB and CAD. In this study, we aimed to evaluate differences in the prevalence of MB and CAD using CCTA between HC patients and a group of age-, sex- and pre-test probability (PTP)-matched outpatients presenting with chest pain.

Methods

For this single-center retrospective observational study, we screened patients enrolled in the Inherited Cardiomyopathy registry of the Erasmus Medical Center, Rotterdam, the Netherlands. We included those diagnosed with HC and who underwent CCTA between September 2005 and May 2018 for chest pain, angina equivalent symptoms (e.g., exertional dyspnea), or other indications. Chest pain was categorized as typical angina, atypical angina, or nonanginal chest pain. Typical angina was defined as (1) substernal chest discomfort of characteristic quality and duration, (2) provoked by

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exertion or emotional stress, and (3) relieved by rest and/or nitrates within minutes.[6] Chest pain was considered atypical or non-anginal if two, respectively one or none of the above-mentioned characteristics were met. The diagnosis of HC was based on a maximal wall thickness ≥15 mm in probands or ≥13 mm in first-degree relatives, not solely explained by loading conditions.[1] Patients with HC caused by Anderson-Fabry disease, Danon disease, Noonan syndrome, amyloidosis, or other confirmed metabolic or mitochondrial disorders or malformation syndromes were excluded.

The control group consisted of adult patients with stable chest pain or angina equivalent symptoms who were referred to the Erasmus Medical Center for the evaluation of CAD and underwent CCTA between September 2006 and March 2017. Patients were not eligible if they were known to have left ventricular hypertrophy (LVH) or had elektrocardiogram findings consistent with LVH to minimize the possibility of including HC patients in the control group, and were also excluded whenever CT scans were incomplete (i.e., scans without contrast) or when image quality was insufficient. Patients were matched by an optimal matching algorithm in a 1:2 ratio on age (caliper distance ± 5 years), gender and PTP for CAD (±3%), as calculated using the CAD Consortium clinical risk score.[6,13] This is a validated risk score incorporating age, gender, type of chest pain, and cardiac risk factors (diabetes, hypertension, dyslipidemia, and past or current smoking). The institutional review board approved this study. Participants were not involved in the design and conduct of the current research.

CCTA was performed on a 64-slice or more advanced CT system (Somatom Definition or Definition Flash, Siemens Healthineers) with radiation minimizing strategies, heartbeat, and vasodilatation policies according to guidelines and local protocols. All control patients were scanned in a fast-track chest pain outpatient clinic setting, described previously.[14] Assessment of image quality and analysis were performed by one experienced radiologist (YY), using Syngo.via (Client 1.2, Siemens). Calcium scores were calculated using the Agatston method.[15] The extent of CAD was evaluated using an 18-segment model as recommended by the Society of Cardiovascular Computed Tomography.[16] Stenosis severity was classified per segment as 0%, <25%, 25% to 49%, 50% to 69%, 70% to 99%, or a total occlusion (100%). Obstructive CAD was defined as the presence of ≥1 coronary vessel with ≥50% lumen diameter reduction. Plaques were scored on degree of calcification and divided in calcified, noncalcified and mixed plaques. MB was defined as a segmental intramyocardial course of any epicardial coronary artery, only when fully enveloped by the myocardium without further requirements for length and depth. Bridge dimensions were measured using multiplanar reconstruction images.

Baseline was defined as the date of CCTA. Data were collected from outpatient visit medical records and included medical (family) history, physical examination, electrocardiography, and transthoracic echocardiography. Hypertension was defined as a blood pressure ≥140/90 mm Hg or treatment with antihypertensive medication.[17] Diabetes mellitus was defined as a fasting glucose level of ≥7.0 mmol/L or the need for insulin or oral hypoglycemic agents.[18] Dyslipidemia was defined as a total serum cholesterol level of ≥5.2 mmol/L or treatment with lipid-lowering medication. A positive family history for cardiovascular disease was defined as a history of CAD in first degree relatives less than 55 years in males and less than 65 years in females.[19]

For the HC group, follow-up data were collected until December 2018, which included all-cause mortality, cardiac transplantation, aborted sudden cardiac death, and heart failure. Aborted sudden cardiac death was defined as resuscitation after cardiac arrest or appropriate implantable cardioverter-defibrillator intervention. Heart failure was defined as (1) the presence of clinical signs of congestion (including dyspnea, fatigue, and edema) requiring the use of diuretics in an outpatient setting, or (2) an episode of decompensation requiring hospital admission. Acute myocardial infarction and admissions for unstable angina were registered but were not included in the combined end point due to the absence of these events during follow-up. Clinical data was retrieved from our hospital patient records and mortality data was retrieved from civil service population registers.

Continuous data were tested for normality before analysis using the Kolmogorov-Smirnov test and were expressed as mean ± standard deviation (SD) or median [interquartile range], as appropriate. Categorical variables were presented as number (%). We compared baseline characteristics and aspects of CAD between those with HC and their matched controls. To account for matching of the data, general and generalized linear mixed-effects models were used for continuous and categorical dependent variables, respectively, with random intercepts for pairs of matched subjects. Case-control status was entered as the independent variable. Subsequently, we compared characteristics of HC patients according to presence or absence of MB. Continuous variables were compared using Student's t test and categorical data were compared using Pearson's χ^2 test. Kaplan-Meier survival analysis was performed to estimate the cumulative survival for the combined end point sudden cardiac death, cardiac transplantation, heart failure, and all-cause mortality in HC patients with and without MB. All analyses were 2-tailed; p values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 24 (IBM Corp., Armonk, New York) and R statistical software version 3.4.2, using packages *nlme, lme4* and *car*.

Results

A total of 84 patients diagnosed with HC and 168 age-, sex- and PTP-matched control patients were included in this study (Figure 1). Baseline patient characteristics of both groups are summarized in Table 1. Overall, the mean age was 54 ± 11 years, 70% were male and the majority had a low PTP score for CAD (12 [4 to 32]). The groups were similar in respect to most demographic characteristics, but differed regarding CT indications. Patients in the HC group were less likely to undergo CCTA for nonanginal chest pain, but more often underwent CCTA for other indications, including preintervention screening and exclusion of ischemia for reasons other than symptoms, that is a reduced ejection fraction or an akinetic apex on echocardiography. β-blocker and calcium channel blocker usage was

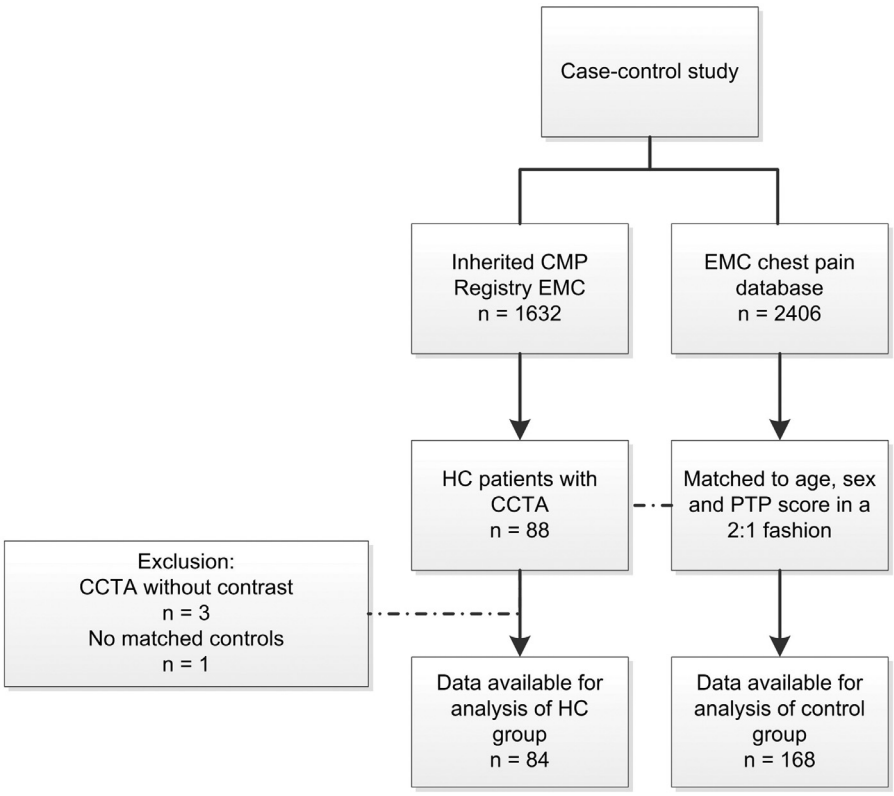

Figure 1. Flowchart patient selection.
Abbreviations: CCTA = coronary computed tomography angiography; CMP = cardiomyopathy; EMC = Erasmus Medical Center; HC = hypertrophic cardiomyopathy; PTP = pre-test probability score.

more prevalent in the HC group and use of statins as well as aspirin and other antiplatelet agents at baseline was not statistically significant between the groups.

In the HC group, half of the patients were classified as NYHA II and nearly half were known with a pathogenic DNA variant. In 90% of HC patients left ventricular systolic function was normal or mildly reduced, and over half had stage I or II diastolic dysfunction. The median maximal wall thickness was 17 [14 to 20], 14 patients had obstructive morphology, and 10 had a history of septal reduction therapy.

Differences in CAD characteristics between cases and controls are shown in Table 2. Groups were similar with regard to calcium score, presence of obstructive CAD, plaque morphology, and extent of disease. MB was far more prevalent in the HC group compared with controls, both on the group-level and individually, with MB present in 50% of HC patients compared with 25% of controls and with a larger proportion of HC patients having multiple bridges. There was a predilection for MB in the mid-left anterior descending artery in both groups. Typically, the length and depth of MB was higher in the HC group, although this did not reach statistical significance. Also, no relationship was found between maximal wall thickness and depth and/or length of MB in both groups. Examples of MB on CCTA are shown in Figure 2.

HC patients were stratified according to the presence or absence of MB (Table 3). HC patients with and without MB were similar in regard to demographic factors, cardiac risk profile, and HC disease severity according to NYHA classification and echocardiographic parameters. However, pathogenic DNA variations were more prevalent in patients with MB compared with patients without MB. Chest pain was equally prevalent in both groups, and there were no differences regarding chest pain characteristics. Also, the presence of CAD was lower in HC patients with MB. This difference was also seen when comparing patients with and without MB in the entire cohort (obstructive CAD: 23% vs 10%, all CAD: 58% vs 42%; $p < 0.05$ for both), but not in the control subgroup only (obstructive CAD: 23% vs 10%; $p = 0.36$; all CAD: 58% vs 42%; $p = 0.21$).

During a median follow-up of 3.7 [1.8 to 6.1] years a total of 25 cardiac events ([aborted] sudden cardiac death, cardiac transplantation, heart failure, and all-cause mortality) occurred, 14 in the MB group and 11 in the group without MB. There was no significant difference in event-free survival for the composite end point between both groups (log-rank $p = 0.30$; Figure 3). Also, no significant difference in event-free survival was found in HC patients with and without obstructive CAD (log-rank $p = 0.25$, Figure S1). No myocardial infarction or admissions for unstable angina occurred during follow-up. A total of 12 HC patients underwent coronary arterial revascularization (percutaneous coronary intervention, n = 10, or coronary artery bypass grafting, n = 2), 9 of which were performed following baseline CCTA results and 3 after a follow-up of 2, 7, and 11 years. MB was present in 25% of treated patients.

In a sensitivity analysis including only the 52 HC patients who underwent CCTA for chest pain and their matched controls, the results were comparable to the presented data including the whole cohort (data not shown).

Table 1
Baseline characteristics

Variable	HC (n = 84)	Controls (n = 168)	p value
Age (years)	54 ± 11	54 ± 10	0.96
Men	59 (70%)	118 (70%)	1.0
Body mass index (kg/m^2)	26.8 ± 4.0	26.8 ± 4.7	0.96
Pre-test probability score	13.5 [4.7 − 29.8]	11.8 [4.3 − 32.0]	0.88
Indication for CCTA			
Chest pain			
Typical	20 (24%)	46 (27%)	0.54
Atypical	26 (31%)	67 (40%)	0.17
Non-specific	6 (7%)	42 (25%)	0.001
No chest pain	32 (38%)	13 (8%)	<0.001
Pre-surgery	10 (12%)		
Pre-ablation	9 (11%)		
Other	13 (15%)		
Hypertension	31 (37%)	67 (40%)	0.65
Dyslipidemia	30 (36%)	57 (34%)	0.79
Diabetes mellitus	9 (11%)	16 (10%)	0.78
Smoker			
Current	21 (25%)	40 (24%)	0.84
Past	25 (30%)	17 (10%)	<0.001
HC characteristics			
NYHA class			
I	35 (42%)		
II	42 (50%)		
III	7 (8%)		
Pathogenic DNA variant	39 (46%)		
Cardiac device			
PM	3 (4%)		
ICD	11 (13%)		
Septal reduction therapy	10 (12%)		
Maximal wall thickness (mm)	17 [14 − 20]		
Peak LVOT gradient (mm Hg)	6 [4 − 8]		
Presence of LVOT obstruction (peak gradient ≥30 mm Hg)	14 (17%)		
Left atrial diameter (mm)	45 [39 − 49]		
Presence of systolic anterior movement	21 (25%)		
LV ejection fraction*			
>51%	59 (72%)		
41% - 51%	17 (21%)		
30% - 40%	4 (5%)		
<30%	2 (2%)		
LV diastolic function**			
Normal	13 (16%)		
Stage I	18 (23%)		
Stage II	40 (51%)		
Stage III	8 (10%)		
Medications			
ß-blocker	48 (57%)	51 (31%)	<0.001
Calcium channel blockers	23 (27%)	24 (14%)	0.01
Diuretics	23 (27%)	21 (13%)	<0.01
Statins	28 (33%)	68 (41%)	0.27
ACE inhibitors	17 (20%)	23 (14%)	0.20
Aspirin	20 (24%)	53 (32%)	0.19
Antiplatelet agents	1 (1%)	11 (6%)	0.08

(*continued*)

Table 1 (***Continued***)

* Data available in 82 patients.

** Data available in 79 patients.

Abbreviations: ACE = angiotensin converting enzyme; CCTA = coronary computed tomography angiography; HC = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; LV = left ventricle; LVOT = left ventricle outflow tract obstruction; NYHA = New York Heart Association; PM = pacemaker. Data presented as mean +/ SD, median with IQR or n (%).

p values are from mixed models.

Table 2
Assessment of coronary artery disease by cardiac Coronary Computed Tomography Angiography

Variable	HC (n = 84)	Controls (n = 168)	p value
Patient based analysis			
Coronary artery disease			
Agatston score*	9 [0 − 225]	4 [0 − 82]	0.22
No. of patients with score*			0.07
0	31 (43%)	77 (47%)	
1 − 99	16 (22%)	52 (32%)	
100 − 399	18 (25%)	20 (12%)	
>400	8 (11%)	15 (9%)	
Obstructive CAD	15 (18%)	32 (19%)	0.82
Artery affected			0.80
1	10 (12%)	17 (10%)	
2	3 (4%)	10 (6%)	
3/left main	2 (2%)	5 (3%)	
Only non-calcified plaques	13 (15%)	31 (18%)	0.56
Myocardial bridging			
No. of patients with MB	42 (50%)	42 (25%)	<0.001
No. of arteries with MB			<0.001
1	34 (40%)	39 (23%)	
2	8 (10%)	3 (2%)	
No. of pts. with >1 MB segments	12 (14%)	4 (2%)	<0.001
Per segment			
Location of MB			
Left anterior descending			
Proximal	0	0	n/a
Mid	34 (40%)	30 (18%)	<0.001
Distal	9 (11%)	2 (1%)	0.001
Diagonal	2 (2%)	3 (2%)	1.0
Left circumflex			
Proximal	0	0	n/a
Distal	0	0	n/a
Obtuse marginal	6 (7%)	5 (3%)	0.19
Intermediate branch	5 (6%)	6 (4%)	0.51
Right coronary	1 (1%)	0	0.33
Dimensions of MB (length and depth in mm)			
Left anterior descending	21 ± 14	17 ± 8	0.18
	2 ± 2	2 ± 1	0.47
Left circumflex	24 ± 14	28 ± 12	0.51
	2 ± 1	2 ± 1	0.42
Right coronary	20	-	-
	1	-	-

* Data missing in 11 HC patients and in 4 control patients respectively.

Abbreviations: CAD = coronary artery disease; MB = myocardial bridging.

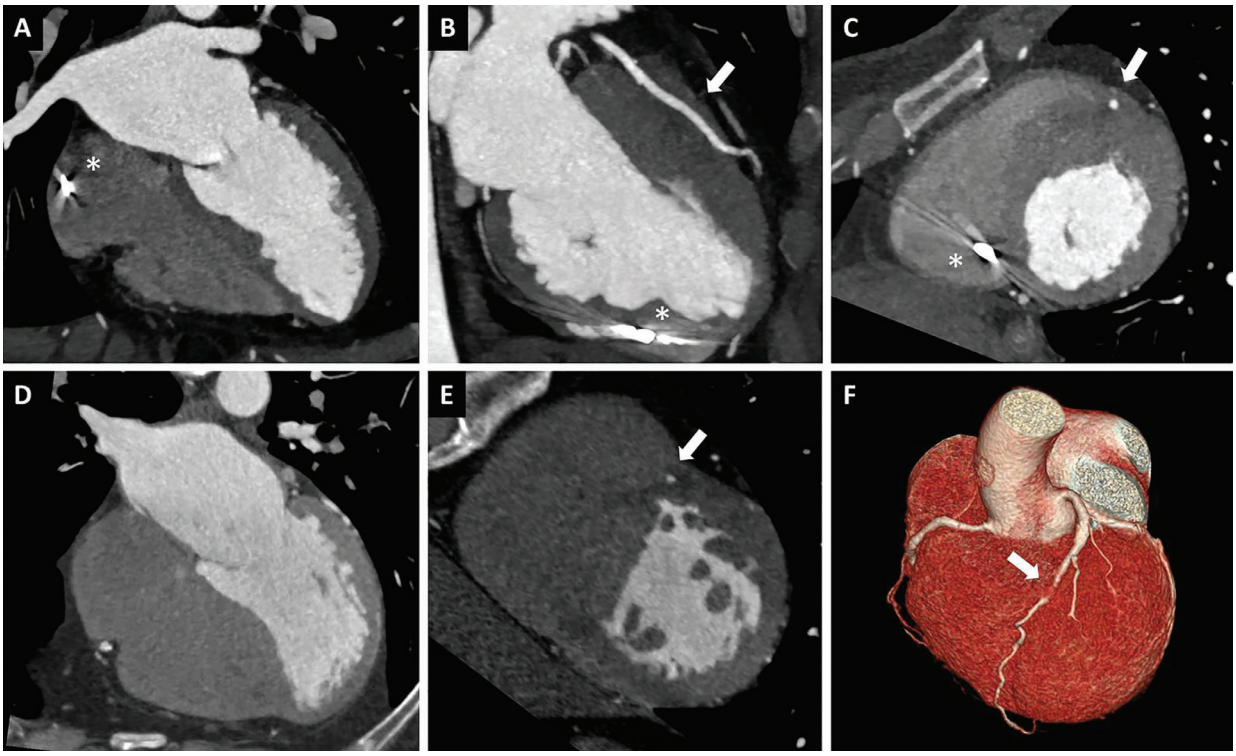

Figure 2. Examples of myocardial bridging on cardiac Coronary Computed Tomography Angiography in HC patients.
Multiplanar reformats in 2 representative HC patients.
Patient 1 (A-C): Respectively 4 chamber, modified 2 chamber and short axis view showing myocardial bridging of the left anterior descending artery (white arrow). Asterix indicates ICD lead.
Patient 2 (D-F): Respectively 4 chamber and short axis view and 3D reconstruction showing myocardial bridging of the left anterior descending artery (white arrow).

Discussion

In this study, we evaluated the prevalence of MB and CAD in HC patients and compared these results with age-, gender- and CAD PTP-matched outpatients presenting with chest pain. The main findings are that the prevalence of obstructive CAD was comparable and that MB was present in 50% of HC patients, twice as much as in controls. The location of MB was predominantly in the (mid) left anterior descending artery, with only a minority of bridging in other vessels. HC patients with MB were more likely to have pathogenic DNA variants and less likely to have (obstructive) CAD, but did not differ regarding the presence of chest pain or worse outcome compared with those without MB.

The prevalence of obstructive CAD in our study was 19%, which is similar to other cohorts with low or intermediate PTP.[4,5] Concomitant CAD in HC is associated with decreased survival, demonstrating the importance of a prompt, and accurate diagnostic work-up. In HC patients presenting with chest pain, this work-up is similar to non-HC patients. Common abnormalities on resting electrocardiograms and the reduced discriminatory power of nuclear imaging and cardiovascular magnetic resonance imaging with regard to causes of perfusion defects imply a high likelihood of false-positive results, limiting the use of these modalities in differentiating CAD from other causes of chest pain.[1] Moreover, as the etiological spectrum of chest pain in HC patients is wider than in the general population, use of prediction models for CAD could theoretically overestimate the true presence of CAD in this patient group. However, our data illustrate that, using a 1:2 matched analysis, both absolute calcium scores as well as the presence of obstructive CAD are similar across groups. Previous research has shown that CCTA is an excellent modality particularly for ruling out CAD in HC patients.[20,21] This combined with the noninvasive and generally safe nature of this modality, demonstrates that CCTA is a useful modality for the evaluation of chest pain in HC.

Several other studies have investigated the prevalence of CAD in HC, with rates ranging from 6.6% to 26%.[4,8,22] The differing rates are most likely explained by differences in age and patient selection, with a 13% presence of CAD in an autopsy study done on 115 HC patients with a median age of 29 and a 26% prevalence of CAD in 433 HC patients with a median age of 63 who were referred for invasive coronary angiography. However, in a case-control study evaluating CCTA done by Shiarat et al. in 91 HC patients and 91 controls, rates of CAD were remarkably lower in HC patients (6.6%) and higher in controls (33%). It is possible that more elaborate matching on risk score mitigates the observed difference in their study, although prevalence of risk factors was comparable among their study groups. Other potentially relevant factors are differences in gender distribution (70% males in our population vs 54% males in the population of Shiarat et al.) and chest pain type. As

Table 3
Patient characteristics of HC patients stratified according the presence or absence of myocardial bridging

Variable	Bridging (n = 42)	No bridging (n = 42)	p value
Age (years)	54 ± 11	55 ± 12	0.55
Men	28 (67%)	31 (74%)	0.47
Body mass index (kg/m^2)	27.1 ± 4.1	26.4 ± 3.6	0.39
Median pre-test probability	14.1 [4.8 − 29.1]	12.1 [4.5 − 33.6]	0.83
Hypertension	15 (36%)	16 (38%)	0.82
Dyslipidemia	17 (40%)	13 (31%)	0.36
Diabetes mellitus	5 (12%)	4 (10%)	0.72
Smoker			
Current	10 (24%)	11 (26%)	0.80
Past	12 (29%)	13 (31%)	0.81
NYHA class			0.86
I	17 (41%)	18 (43%)	
II	22 (52%)	20 (48%)	
III	3 (7%)	4 (10%)	
Symptoms			
Chest pain	31 (74%)	32 (76%)	0.80
Dyspnea	20 (48%)	23 (55%)	0.51
Palpitations	15 (36%)	13 (31%)	0.64
Syncope	6 (14%)	4 (10%)	0.50
Genetics			
Patient genetically tested	37 (88%)	38 (91%)	0.72
Pathogenic DNA variant (% of whole group)	26 (62%)	17 (41%)	0.049
Pathogenic DNA variant (% of tested group)	26 (70%)	17 (45%)	0.03
MYBPC3	16 (43%)	10 (26%)	0.12
MYH7	5 (14%)	1 (3%)	0.08
Other	5 (14%)	6 (16%)	0.78
CCTA			0.71
Indications			
Chest pain			0.80
Typical	13 (31%)	13 (31%)	
Atypical	11 (26%)	9 (21%)	
Non-anginal	4 (10%)	2 (5%)	
No chest pain	14 (33%)	18 (41%)	
Agatston score*	0 [0 − 88]	44 [0 − 320]	0.02
Presence of CAD	16 (38%)	26 (62%)	0.03
Obstructive CAD	2 (5%)	13 (31%)	<0.01
HC characteristics			
Cardiac device			
PM	2 (5%)	1 (2%)	0.56
ICD	6 (14%)	5 (12%)	0.75
Septal reduction therapy	5 (12%)	5 (12%)	1.0
Maximal wall thickness (mm)	18 ± 6	17 ± 4	0.17
Peak LVOT gradient (mmHg)	6 [4 − 8]	6 [4 − 12]	0.18
Presence of obstruction	5 (12%)	9 (22%)	0.24
Left atrium diameter (mm)	43 [39 − 49]	46 [40 − 49]	0.4
Presence of systolic anterior movement	8 (20%)	13 (32%)	0.21
LV ejection fraction†			0.10
>51%	28 (68%)	31 (76%)	
41% - 51%	9 (22%)	8 (20%)	
30% - 40%	4 (10%)	0	
<30%	0	2 (5%)	
LV diastolic function‡			0.40
Normal	6 (16%)	7 (17%)	
Stage I	7 (18%)	11 (27%)	
Stage II	19 (50%)	21 (51%)	
Stage III	6 (16%)	2 (5%)	
Medications			
ß-blocker	26 (62%)	22 (52%)	0.38
Calcium channel blockers	8 (19%)	15 (36%)	0.09
Diuretics	14 (33%)	9 (21%)	0.22
Statins	15 (36%)	13 (31%)	0.64
ACE inhibitors	9 (21%)	8 (19%)	0.79
Aspirin	10 (24%)	10 (24%)	1.00
Antiplatelet agents	1 (2%)	0	0.32

Other pathogenic DNA variants include *TNNI3* (2 vs 2), *ALPK3* (1 vs 1), *MYL2* (1 vs 1), *MYL3* (0 vs 1), *PKP2* (0 vs 1), *FHL1* (1 vs 0).

Abbreviations: ACE = angiotensin converting enzyme; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; HC = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; LV = left ventricle; LVOT = left ventricular outflow tract; NYHA = New York Heart Association; PM = pacemaker.

* Data available in 39 patients with MB and 35 without MB.

† Data available in 41 patients of both groups.

‡ Data available in 38 patients with MB and in 41 patients without MB.

angina was not subdivided in the aforementioned study, we cannot readily draw conclusions on this.

The prevalence of MB ranges in the literature ranges from 1% to 86% and varies according to the method of evaluation, the definition of bridging, and the population of interest. The highest rates are generally reported in autopsy studies and lower rates are seen in studies involving CCTA and invasive coronary angiography.[7,22,23] The presence of MB in HC cohorts is higher than in the general population, with reported rates of up to 41%.[7,8] In concordance with the literature, our study shows a prevalence of MB of 50% in HC patients, compared with 25% in controls. The most commonly affected coronary segment was the mid-left descending artery, which seems to be consistent across most studies.[7] The different rates seen in CCTA and invasive coronary angiography studies can be explained by the properties of both methods and the physiological properties of MB. Higher detection rates of MB are expected with CCTA due to its capability to show the anatomical course of the coronary arteries with quantification of length and depth of MB.[5] Invasive coronary angiography generally relies on the presence of systolic compression of the affected segment (i.e., the milking effect), which makes it more likely for smaller or noncompressing MBs to not be recognized.[7] Detection of MB may be relevant to explain the cause of chest pain, but currently no scientifically proven therapy is available. Symptomatic patients can be treated with negative chronotropic drugs, which would lessen the burden of MB by prolonging the diastolic phase.[24] In our study, chest pain characteristics as well as its overall prevalence did not differ among HC patients with and without MB. Interestingly, Kawai et al. recently illustrated the association of MB with coronary vasospasm, a well-known etiological substrate of chest pain which offers another explanation as to how MB can cause chest pain.[25] However, the current study suggests the lack of an association between MB and chest pain, and despite the high prevalence of MB in this HC cohort, the clinical relevance of this finding seems limited at best.

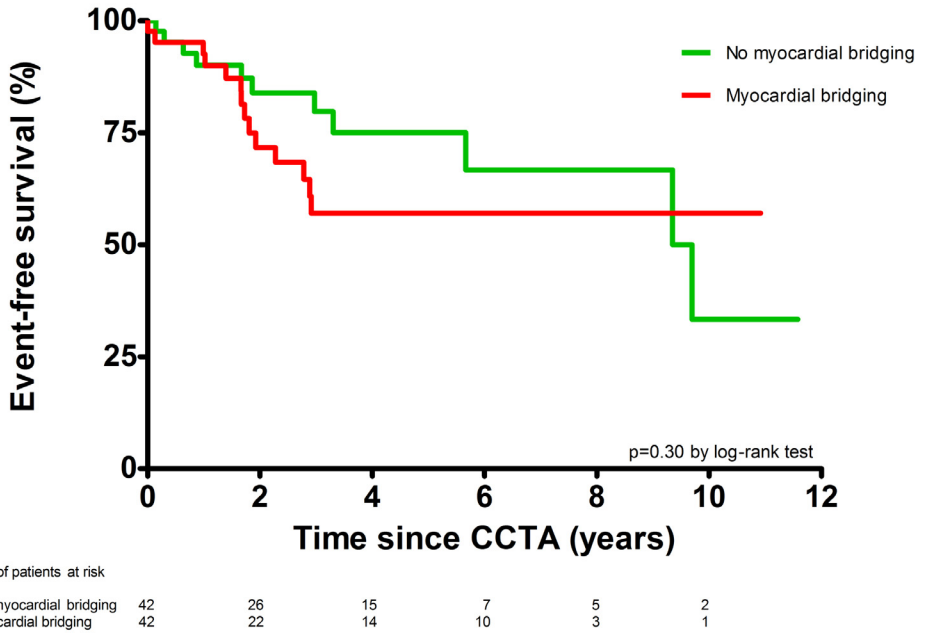

Figure 3. Kaplan-Meier estimates of the combined end point aborted sudden cardiac death, cardiac transplantation, heart failure and all-cause mortality in hypertrophic cardiomyopathy patients with and without myocardial bridging.
CCTA = coronary computed tomography angiography.

In a subset of HC patients who were genetically tested, a significant association was found between MB and the presence of pathogenic DNA variations. The mechanism behind the increased prevalence of MB in HC has, to our knowledge, not been elucidated yet. Although MB is often considered to be a congenital anomaly, there are reports suggesting that MB can be an acquired, particularly in the context of LVH.[26,27] However, our study showed no relationship between the severity of MB and maximal wall thickness of the left ventricle. Adding to previously reported literature, we did not find evidence for worse prognosis in our relatively small population of HC patients with MB.[28,29]

This study has several limitations. First, this study is sensitive for recall bias due to its retrospective design. Secondly, selection bias was present as CCTA was performed in a small population of HC patients with chest pain. We aimed to overcome these limitations by employing a matched case-control design and by taking into account the paired nature of the data in our analysis. Furthermore, we acknowledge that our analyses are prone to type II errors owing to the relatively small sample size of our study. Additionally, as the clinical impact of MB in HC patients has, to our knowledge, only been demonstrated in children, it is possible that our survival analysis is influenced by a survival bias.[20,21] By excluding known LVH in the control group, it is possible that the incidence of MB is underestimated. Lastly, no follow-up data was available in the control group.

In conclusion, the prevalence and extent of CAD was equal among patients with and without HC, demonstrating that pre-test risk prediction using the CAD Consortium clinical risk score performs well in HC patients. MB was twice as prevalent in the HC group compared to matched controls, but was not associated with chest pain or decreased event-free survival in these patients.

Author Contribution Section

N. van der Velde: Investigation, Formal analysis, Writing – Original draft preparation

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Conflict of Interest

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Ethical Approval

According to the institutional review board, this study did not meet the requirements of a study that is subject to the Medical Research Involving Human Subjects Acts.

Patient Consent for Publication

Not required.

Patient and Public Statement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

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Supplementary materials

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