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Clinical Investigations

Coronary Angiography in Patients With Left Ventricular Hypertrabeculation/Noncompaction

Nicolas de Cillia, MD[1]; Josef Finsterer, MD, PhD[2]; Radu Campean, MD[1]; Ashkan Noorian, MD[1]; Maria Winkler-Dworak, PhD[3]; Claudia Stöllberger, MD[1]

[1]Klinik Landstrasse, Second Medical Department With Cardiology and Intensive Care Medicine, Vienna, Austria
[2]Klinik Landstrasse, Vienna, Austria
[3]Vienna Institute of Demography, Wittgenstein Centre for Demography and Global Human Capital (University of Vienna), Vienna, Austria

Abstract

Background: Left ventricular hypertrabeculation/noncompaction (LVHT) is a cardiac abnormality of unknown pathogenesis, frequently associated with neuromuscular disorders. The relevance of coronary artery disease (CAD) in LVHT is largely unknown. This study aimed to assess the role of CAD as a prognostic marker in LVHT.

Methods: Data from patients with LVHT were collected from an echocardiographic laboratory. The hospital information system was retrospectively screened for coronary angiography. The association of CAD with clinical, echocardiographic, and neurologic baseline parameters was assessed. End points were all-cause death and heart transplantation.

Results: A total of 154 patients (mean [SD] age, 57 [13.7] years; 31% female) who had undergone coronary angiography between 1995 and 2020 were included in the study. Coronary angiography disclosed CAD in 53 of 154 patients. Patients with CAD were older (mean [SD] age of , 64.2 [12.9] years vs 52.7 [12.4] years; $P < .001$); more frequently had angina pectoris ($P = .05$), diabetes ($P = .002$), and hypertension ($P = .03$); and more frequently had 3 or more electrocardiographic abnormalities ($P = .04$) than patients without CAD. During a median (IQR) follow-up period of 6.48 (2.44-11.20) years, 39% of patients reached an end point (death, n = 56; heart transplantation, n = 4). Mortality was 4.5% per year, and the rate of death or heart transplantation did not differ between patients with and without CAD ($P = .26$). Patients with 3-vessel disease had a worse prognosis than patients with 1- or 2-vessel disease ($P = .046$).

Conclusion: In patients with LVHT, CAD does not appear to be associated with an increased rate of death or heart transplantation.

Keywords: Coronary artery disease; heart failure; cardiomyopathies; echocardiography; coronary angiography

Introduction

Left ventricular hypertrabeculation/noncompaction (LVHT) is a cardiac abnormality of unclear pathogenesis that occurs congenitally and as an acquired disorder.[1] In healthy patients, the left ventricle shows up to 3 trabeculations apically to the attachment of the papillary muscles, but in patients with LVHT it has more than 3 trabeculations. Left ventricular hypertrabeculation/noncompaction most often affects the apex and the lateral and inferior wall segments of the left ventricle.[2] It is most frequently diagnosed by transthoracic echocardiography but can also be diagnosed by cardiac magnetic resonance imaging, computed tomography, or ventriculography.[1-3] The diagnosis of LVHT by imaging methods is complicated by differences in diagnostic criteria and considerable interobserver

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Corresponding author: Claudia Stöllberger, MD; Anton-Sattler-Gasse 4/22, A-1220 Wien, Austria (claudia.stoellberger@chello.at)

variability.[4-6] Left ventricular hypertrabeculation/noncompaction may remain asymptomatic; when it becomes symptomatic, it can present with heart failure, arrhythmias, or thromboembolism.[4] The condition is frequently associated with neuromuscular disorders or congenital heart diseases.[4]

In rare cases, LVHT has been reported in association with coronary artery anomalies or fistulas.[7-9] The prevalence and prognostic relevance of atherosclerotic coronary artery disease (CAD) in patients with LVHT has to date been investigated only in 2 small retrospective studies, neither of which found differences in survival between patients with LVHT and CAD and patients with LVHT but without CAD.[10,11]

The aim of the current study of patients with LVHT who had undergone coronary angiography was to assess the prevalence of CAD and compare the baseline data and prognosis of patients with LVHT and CAD with those of patients who have LVHT but not CAD. The severity of CAD (1-, 2-, or 3-vessel disease or main stem stenosis), revascularization therapy, and the presence of coronary abnormalities were also registered. The current investigation is an extension of a study of an LVHT database with more patients and a longer follow-up period, the results of which were published in 2011.[11]

Key Points

- The relevance of CAD in patients with LVHT is largely unknown.
- The role of CAD as a prognostic marker in LVHT was assessed retrospectively in 154 patients.
- Patients with CAD were older; more frequently had angina pectoris, diabetes, and hypertension; and more frequently had electrocardiographic abnormalities than patients without CAD.
- During the 6.48-year median follow-up period, the mortality rate was 4.5% per year and did not differ between patients with and without CAD.
- In patients with LVHT, CAD does not appear to be associated with an increased rate of death.

Abbreviations and Acronyms

CAD	coronary artery disease
LVHT	left ventricular hypertrabeculation/noncompaction

Patients and Methods

This retrospective study included consecutive patients with LVHT listed in an echocardiographic database who had been diagnosed between January 1995 and June 2020 and who had undergone coronary angiography. Neither valvular heart disease nor arterial hypertension was an exclusion criterion.[12]

The diagnostic criteria for LVHT remained the same during the entire study period.[5] Two-dimensional and Doppler echocardiographic criteria at transthoracic echocardiography for the diagnosis of LVHT were as follows: (1) more than 3 trabeculations protruding from the left ventricular wall, apically to the papillary muscles, visible in 1 echocardiographic image plane at end diastole; (2) trabeculations form the noncompacted part of a 2-layered myocardial structure, best visible at end systole; and (3) intertrabecular spaces perfused from the ventricular cavity, as visualized on color Doppler imaging. Trabeculations were defined as structures moving synchronously with the ventricular contractions and were discerned from ventricular bands, false tendons, and prominent papillary muscles (Fig. 1). The location of LVHT was categorized as apical if it involved the left ventricular apex or as anterior, lateral, or posterior if it involved the anterior, lateral, or posterior parts of the left ventricular wall, respectively. All echocardiographic investigations were carried out by 1 investigator, and interobserver agreement was assessed as reported.[5] Echocardiographic measurements of left ventricular dimensions and wall thickness were performed in parasternal short-axis view according to standard recommendations. Because the extensive trabeculations made it impossible to measure left ventricular systolic function by calculating the left ventricular ejection fraction, left ventricular systolic function was determined by calculating left

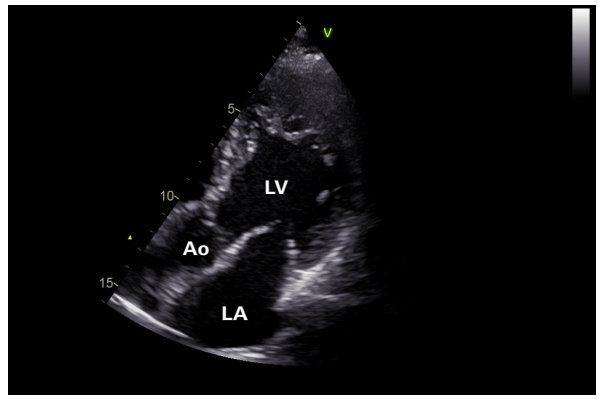

Fig. 1 Modified transthoracic echocardiogram, with an apical 3-chamber view, shows the left atrium, left ventricle, and ascending aorta. The apical region and lateral wall of the left ventricle show hypertrabeculation/noncompaction.

Ao, ascending aorta; LA, left atrium; LV, left ventricle.

ventricular fractional shortening from the motion-mode image. Baseline clinical, electrocardiographic, and echocardiographic data were collected at the time of LVHT diagnosis.

All patients were invited to undergo a neurologic investigation comprising medical history and a clinical examination. If there were indications for polyneuropathy, an established screening program, including blood testing, cerebrospinal fluid investigation, and sometimes nerve biopsy, was carried out. If there were indications for myopathy, screening was initiated that included examination of muscle enzymes, electromyography, and occasionally muscle biopsy. Neuromuscular disorders were assessed as "specific" if a diagnosis could be established. Cases in which no specific diagnosis could be established were assessed as "neuromuscular disorder of unknown etiology."

Decisions on whether to perform coronary angiography, use cardiac electronic devices, and initiate pharmacologic or invasive therapy were made by the treating physicians according to clinical needs, not a study protocol.

Follow-up was carried out yearly either by personal contact with the patients or their treating physicians or by searching the hospital's electronic database. End points were defined as the occurrence of all-cause death or heart transplantation. The follow-up period ended in December 2020.

In July 2020, patients' records were screened to confirm whether coronary angiography had been carried out. Subsequently, the reports were reviewed to assess whether coronary angiography had shown atherosclerotic CAD or coronary anomalies (myocardial bridges, coronary fistulas, or abnormal origin or course of coronary arteries). The coronary angiograms were reviewed to determine the severity of CAD and to screen for coronary anomalies. The review was performed by a diploma student under the supervision of 2 interventional cardiologists. The threshold value for a hemodynamically relevant stenosis was narrowing of the vessel lumen greater than 50%. The severity of CAD was quantified as 1-, 2-, or 3-vessel disease or main stem stenosis, depending on how many coronary vessels were affected. The therapy applied—percutaneous intervention, coronary artery bypass graft, or conservative therapy—was also registered.

Statistical Analysis

Statistical analyses were carried out using the statistical software package Stata 18 (StataCorp LLC) and R, version 4.3.2 (R Foundation for Statistical Computing). For statistical analysis of noncategorical data for normally distributed variables, group comparisons of baseline and follow-up characteristics were performed using the *t* test for a difference in means. The assumption of a normal distribution was checked with the Shapiro-Wilk test. For non-normally distributed variables, the Mann-Whitney test was used. Patients were grouped according to the time at which coronary angiography was performed (before or after LVHT diagnosis) and according to the results of coronary angiography (CAD or no CAD, severity of CAD). For categorical data, the χ^2 test and Fisher exact test were used, when applicable. The differences in survival between patients with LVHT with and without CAD and the effects of baseline clinical parameters on all-cause mortality were examined using the log-rank test. $P < .05$ was considered statistically significant.

To eliminate selection bias, Mahalanobis matching was carried out. To account for baseline differences between patients with and without CAD, patients were matched using 4:1 nearest-neighbor matching based on the Mahalanobis difference on selected variables using the *R MatchIt* package.[13] Matching was performed with replacement because of the small sample size. A caliper was imposed on the variable of age at diagnosis to achieve balance. The balance between the 2 groups was assessed by computing the standardized mean difference on the baseline variables (see Supplemental Figure 1). All 53 patients with CAD could be matched to 64 of 101 patients without CAD, with a standardized mean difference less than 0.2, indicating a satisfactory balance. The study was approved by the institutional review board (EK 20-264-VK).

Results

Between January 1995 and June 2020, LVHT was diagnosed in 313 patients with a mean (SD) age at baseline of 53.1 (13.7) years (30% female). Included in the study were 154 (49%) patients for whom reports of coronary angiography were found (Table I). Coronary angiography was carried out before the diagnosis of LVHT in 89 (58%) patients and after diagnosis in 65 (42%) patients.

Coronary angiography detected CAD in 53 (34%) of the 154 patients. There were nearly equal numbers of patients with 1-vessel disease (n = 17), 2-vessel disease (n = 18; 1 of them also had main stem stenosis), and 3-vessel disease (n = 18; 2 of them also had main stem stenosis).

TABLE I. Baseline Parameters of Patients With LVHT, With and Without Coronary Artery Disease

Characteristic	Finding at coronary angiography		
	No coronary artery disease (n = 101)	Coronary artery disease (n = 53)	*P* value
Demographic characteristics			
Age, mean (SD), y	52.7 (12.4)	64.2 (12.9)	<.001
Female sex, No. (%)	34 (33.7)	13 (24.5)	.24
Clinical characteristics			
Thromboembolic event before LVHT diagnosis, No. (%)	4 (4.0)	10 (18.9)	.01
Angina pectoris, No. (%)	28 (27.7)	23 (43.4)	.05
Edema, No. (%)	23 (22.8)	18 (34.0)	.14
Exertional dyspnea, No. (%)	74 (73.3)	40 (75.5)	.77
Palpitations, vertigo, or syncope, No. (%)	26 (25.7)	15 (28.3)	.73
Asymptomatic, No. (%)	6 (5.9)	3 (5.7)	>.99
Diabetes, No. (%)	17 (16.8)	21 (39.6)	.002
Arterial hypertension, No. (%)	48 (47.5)	35 (66.0)	.03
Heart failure by New York Heart Association class, No. (%)	74 (73.3)	46 (86.8)	.055
Class I	9 (8.9)	6 (11.3)	.63
Class II	23 (22.8)	12 (22.6)	.99
Class III	20 (19.8)	20 (37.7)	.02
Class IV	22 (21.8)	8 (15.1)	.32
Neurologic findings, No. (%)			
Neurologically normal	17 (16.8)	9 (17.0)	.98
Specific neuromuscular disorder	13 (12.9)	2 (3.8)	.07
Neuromuscular disorder of unknown etiology	40 (39.6)	19 (35.8)	.65
Neurologically not investigated	31 (30.7)	23 (43.4)	.12
Electrocardiographic findings, No. (%)			
No electrocardiographic abnormality	4 (4.0)	5 (9.4)	.28
≥3 electrocardiographic abnormalities	29 (28.7)	24 (45.3)	.04
Tall QRS complex	40 (39.6)	14 (26.4)	.10
ST–T-wave abnormality	70 (69.3)	37 (69.8)	.95
Left bundle-branch block	28 (27.7)	9 (17.0)	.14
Pathologic Q waves	9 (8.9)	12 (22.6)	.02
Ventricular ectopic beats	12 (11.9)	2 (3.8)	.14
Atrial fibrillation	15 (14.9)	12 (22.6)	.23
Left anterior hemiblock	9 (8.9)	11 (20.8)	.04
Right bundle-branch block	0 (0)	6 (11.3)	.001
Low voltage	8 (7.9)	6 (11.3)	.56
Wolff-Parkinson-White syndrome	0 (0)	1 (1.9)	.34

Continued

TABLE I. Baseline Parameters of Patients With LVHT, With and Without Coronary Artery Disease, continued

Characteristic	Finding at coronary angiography		
	No coronary artery disease (n = 101)	Coronary artery disease (n = 53)	*P* value
Sinus tachycardia	11 (10.9)	7 (13.2)	.67
Echocardiographic findings			
Left ventricular end-diastolic diameter, mean (SD), mm	63.9 (12.7)	60.4 (12.8)	.04
Left ventricular fractional shortening, mean (SD), %	20.8 (9.7)	22.3 (8.8)	.19
Interventricular septal thickness, mean (SD), mm	12.2 (2.8)	11.9 (2.7)	.93
Left ventricular posterior wall thickness, mean (SD), mm	12.7 (3.0)	11.9 (2.5)	.13
Valvular abnormalities, No. (%)	64 (63.4)	36 (67.9)	.57
Segments with LVHT, No. (%)			
Apex	98 (97.0)	53 (100)	.55
Anterior wall	10 (9.9)	7 (13.2)	.53
Posterior wall	23 (22.8)	7 (13.2)	.15
Lateral wall	55 (54.5)	34 (64.2)	.25
Septal wall	1 (1.0)	3 (5.7)	.12
LVHT affecting >2 ventricular parts	23 (22.8)	12 (22.6)	.99

LVHT, left ventricular hypertrabeculation/noncompaction.

P < .05 was considered statistically significant.

One patient with 1-vessel disease had an atypical origin of the right coronary artery. Almost two-thirds (64%) of patients with CAD underwent revascularization in the form of percutaneous intervention (n = 29) or coronary artery bypass graft surgery (n = 5). The remaining 19 patients (36%) received conservative treatment.

Patients with CAD were older (mean [SD] age, 64.2 [12.9] years vs 52.7 [12.4] years; *P* < .001); more frequently experienced angina pectoris (*P* = .05), diabetes (*P* = .002), and hypertension (*P* = .03); and more frequently had 3 or more electrocardiographic abnormalities (*P* = .04) than patients without CAD. Patients with CAD had a smaller left ventricular end-diastolic diameter than patients without CAD (*P* = .04). The total observation time of all patients was 1,216 years, with a median (IQR) of 6.48 (2.44-11.20) years at risk.

A total of 60 (39%) patients reached an end point: 56 died, and 4 underwent heart transplantation. The most common causes of death were heart failure (n = 21), sudden cardiac death (n = 11), and pneumonia (n = 7). The mortality rate was 4.50%, and the rate of death or heart transplantation did not differ between patients with and without CAD (*P* = .26) (Fig. 2). Patients with 3-vessel disease had a worse prognosis than patients with 1- or 2-vessel disease (Fig. 3) (*P* = .046). The results of the Mahalanobis matching did not differ from the analysis of the entire cohort and showed no differences regarding the prognosis between patients with and without CAD (Fig. 4).

Discussion

In this retrospective analysis of patients with LVHT who underwent CAG, those with CAD were older; more frequently had comorbidities such as angina pectoris, diabetes, and hypertension; and were more likely to have electrocardiographic abnormalities than patients without CAD. The mortality rate was 4.5% per year and did not differ between patients with and without CAD, except for patients with 3-vessel disease, who had a higher mortality rate than patients with 1- or 2-vessel disease. To the best of the authors' knowledge,

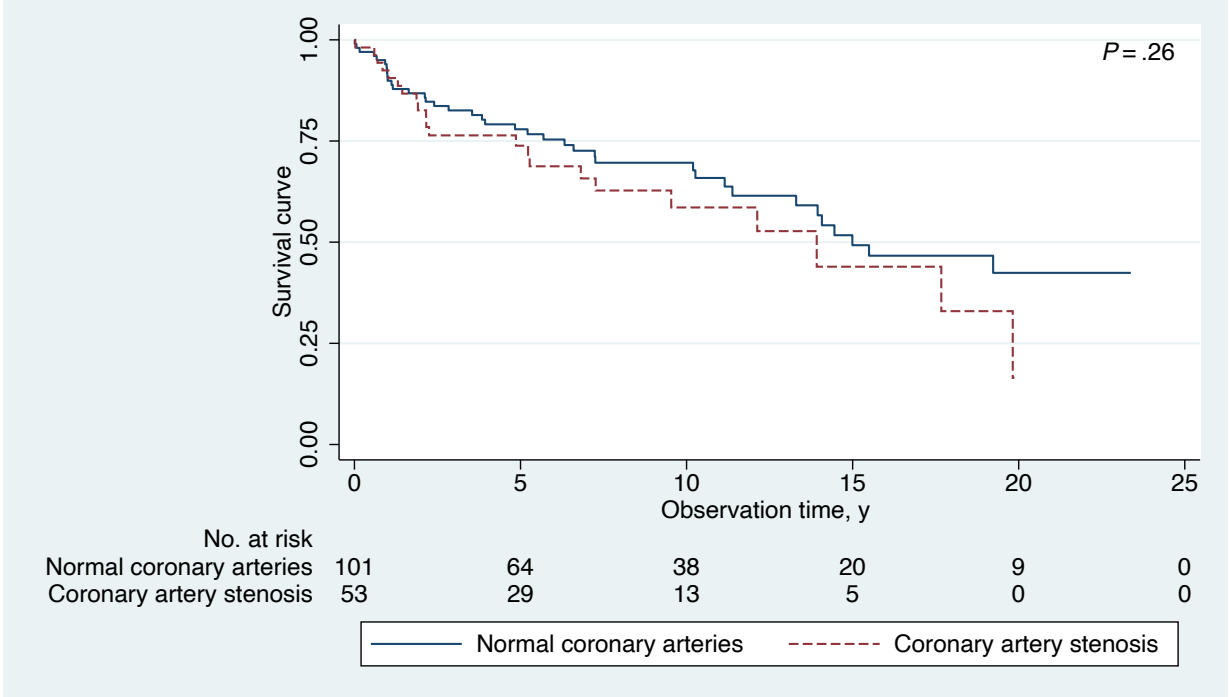

Fig. 2 A line graph compares survival (rate of death or heart transplantation) in patients with left ventricular hypertrabeculation/noncompaction with and without coronary artery disease who had undergone coronary angiography (*P* = .26).

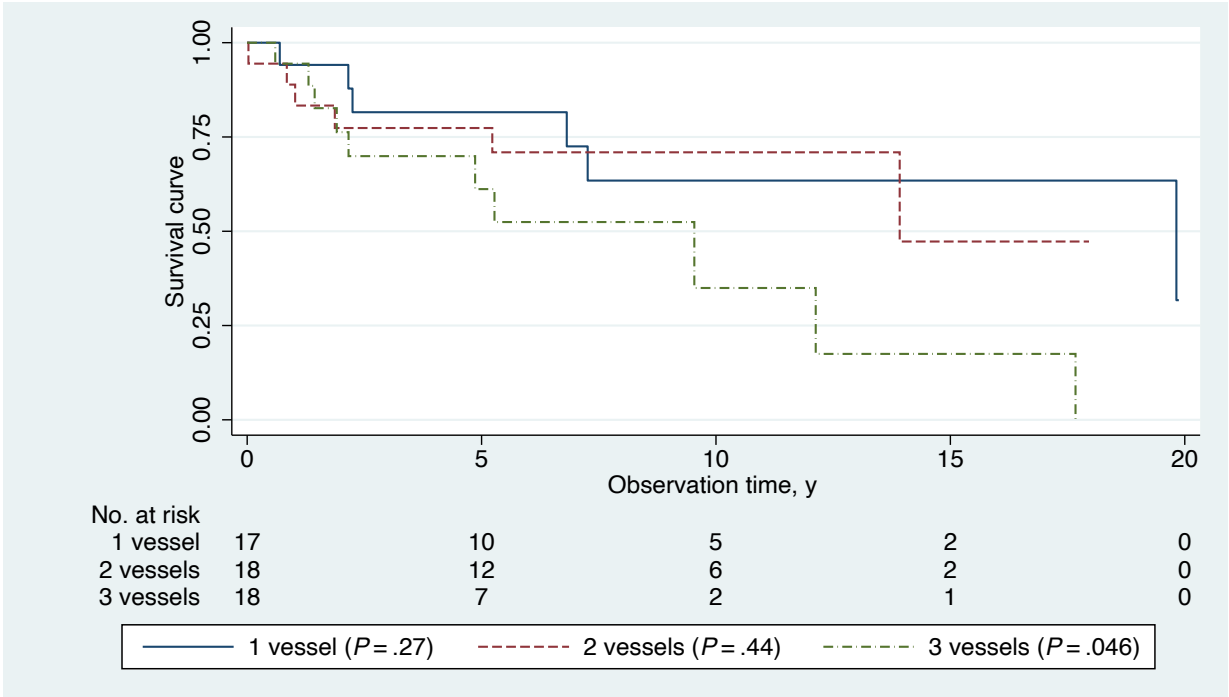

Fig. 3 A line graph compares survival (rate of death or heart transplantation) in patients with left ventricular hypertrabeculation/noncompaction and coronary artery disease based on the number of affected vessels (*P* = .046).

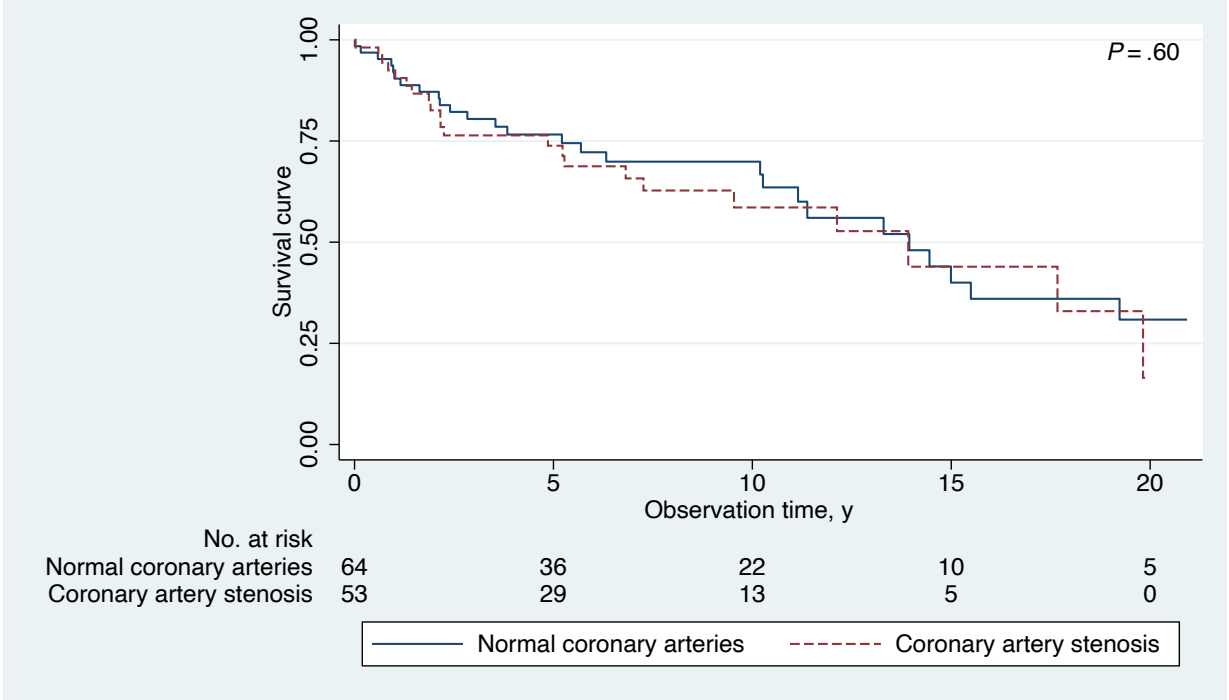

Fig. 4 A line graph compares survival in patients with left ventricular hypertrabeculation/noncompaction with and without coronary artery disease who had undergone coronary angiography after Mahalanobis matching (*P* = .60).

this study had the largest number of patients with both LVHT and CAD to date.

The prevalence of CAD in patients with LVHT who underwent CAG was 34% in the present study. Previous studies reported a prevalence of CAD in patients with LVHT between 29% and 39%.[10,14,15] Only 1 study reported a prevalence of CAD in patients with LVHT of 67%.[16] None of the studies, including the present study, used specific protocols to decide whether to perform coronary angiography, so differences in the decision process and in patient characteristics may explain discrepancies among study findings.

A surprising finding was that patients with CAD had a smaller left ventricular end-diastolic diameter than patients without CAD. An enlarged left ventricle could be indicative of dilated cardiomyopathy, and patients with an enlarged left ventricle underwent coronary angiography more often than patients with a normal ventricle. In these patients, coronary angiography was most likely carried out to assess or exclude an ischemic etiology of left ventricular enlargement.

That CAD has no effect on mortality in patients with LVHT is consistent with previous studies that have addressed this question.[10,11] This result is reinforced by the current study's larger number of patients with LVHT and CAD (n = 53) and the longer follow-up period (median, 6.48 years) compared with those of previous studies. Gao et al[10] had a mean follow-up period of 1.75 years, Aras et al[14] of 2.5 years, and Tian et al[17] of 2.9 years. Differentiating patients with CAD according to disease severity revealed that patients with 3-vessel disease had a worse prognosis than those with 1- or 2-vessel disease.

Whereas neuromuscular disorders have been identified as prognostic indicators for mortality in patients with LVHT, the association between CAD and neuromuscular disorders in patients with LVHT was not relevant in the present study.[12]

That only 1 of the 154 patients who underwent coronary angiography had a coronary anomaly indicates the rarity of sporadically reported congenital coronary anomalies in LVHT.[7-9] The rarity of the coexistence of LVHT and coronary anomalies may be an argument against the frequently cited hypothesis of the exclusive embryonic pathogenesis of LVHT. During embryonic development, the compaction process of the trabeculated ventricular myocardium and the development of coronary arteries occur simultaneously.[18] The coexistence of CAD and LVHT in patients without classical risk

factors for atherosclerosis raises the suspicion that the biology of coronary arteries may be affected in LVHT.[19]

The echocardiographic diagnostic criteria for LVHT were developed in the authors' institution and remained unchanged across the entire study period because they were considered more applicable and more convenient than other criteria reported in the literature.[20]

Limitations

The limitations of the current study include the low number of patients observed and the study's retrospective character. There were no uniform criteria by which to decide when to perform coronary angiography; the decision was made by the treating physicians according to clinical needs. Only echocardiographic criteria developed in the authors' institution were used to diagnose LVHT; no other diagnostic criteria, such as cardiac magnetic resonance imaging, reported in the literature and in other investigations were used.[20] The severity of CAD was not quantified by methods such as the SYNTAX or Gensini score.[21] In addition, microcirculatory dysfunction, which was reported in patients with LVHT, cannot be diagnosed by coronary angiography.[22] Finally, several cardiovascular risk factors, including nicotine consumption, dyslipidemia, obesity, and pharmacotherapy, were not assessed.[23]

Conclusion

In this observational retrospective study of adult patients with LVHT, CAD did not influence mortality. Only patients with 3-vessel disease had a worse prognosis than patients with 1- or 2-vessel disease. Congenital coronary anomalies seem to be rare in patients with LVHT.

Article Information

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