Usefulness of Neuromuscular Co-morbidity, Left Bundle Branch Block, and Atrial Fibrillation to Predict the Long-Term Prognosis of Left Ventricular Hypertrabeculation/Noncompaction

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The prognosis of patients with left ventricular hypertrabeculation/noncompaction (LVHT) is assessed controversially. LVHT is associated with other cardiac abnormalities and with neuromuscular disorders (NMD). Aim of the study was to assess cardiac and neurological findings as predictors of mortality rate in adult LVHT-patients. Included were patients with LVHT diagnosed between 1995 and 2019 in 1 echocardiographic laboratory. Patients underwent a baseline cardiologic examination and were invited for a neurological investigation. In January 2020, their survival status was assessed. End points were death or heart transplantation. LVHT was diagnosed by echocardiography in 310 patients (93 female, aged 53 ± 18 years) with a prevalence of 0.4%/year. A neurologic investigation was performed in 205 patients (67%). A specific NMD was found in 33 (16%), NMD of unknown etiology in 123 (60%) and the neurological investigation was normal in 49 (24%) patients. During follow-up of 84 ± 71 months, 59 patients received electronic devices, 105 patients died, and 6 underwent heart transplantation. The mortality was 4.7%/year, the rate of heart transplantation/death 5%/year. By multivariate analysis, the following parameters were identified to elevate the risk of mortality/heart transplantation: increased age ($p = 0.005$), inpatient ($p = 0.001$), presence of a specific NMD ($p = 0.0312$) or NMD of unknown etiology ($p = 0.0365$), atrial fibrillation ($p = 0.0000$), ventricular premature complexes ($p = 0.0053$), exertional dyspnea ($p = 0.0023$), left bundle branch block ($p = 0.0201$), and LVHT of the posterior wall ($p = 0.0158$). In conclusion, LVHT patients should be systematically investigated neurologically since neurological co-morbidity has a prognostic impact. **(Am J Cardiol 2020;128:168−173)**

Left ventricular hypertrabeculation/noncompaction (LVHT) is a cardiac abnormality, characterized by prominent trabeculations and intertrabecular recesses within the left ventricle.[1] The etiology and pathogenesis of LVHT is unknown. Some pathogenetic theories assume a disturbance of the embryonic development of the myocardium, other theories postulate postnatal acquired mechanisms.[2,3] Patients with LVHT may develop heart failure, arrhythmias, and embolic events, but LVHT is also diagnosed in asymptomatic patients. LVHT is usually diagnosed by different imaging methods and rarely by pathoanatomic investigation of the heart postmortem or postexplantation.[4] Unfortunately, various diagnostic criteria for echocardiography and cardiac magnetic resonance (CMR) exist and there is, so far, no universally accepted definition.[1] LVHT is diagnosed more frequently by CMRI than by echocardiography and there are concerns that LVHT is overdiagnosed by CMRI.[5] If systematically screened, LVHT is associated with neuromuscular disorders (NMD) in the majority of the cases.[6] There are indications that presence or absence of NMD influences the prognosis of patients with LVHT.[7] Data about the prognosis of LVHT derive from relatively small series with short observation periods.[8] Aim of the present long-term follow-up study was to assess the prognostic role of baseline parameters in a cohort of adult patients in whom LVHT had been diagnosed by echocardiography, applying the same criteria during the whole study period. Since patients in our cohort also underwent systematic screening for NMD, we also investigated the prognostic role of NMD.

Methods

Included were all patients in whom LVHT was diagnosed in the echocardiography laboratory of the cardiologic department between June 1995 and December 2019. For the diagnosis of LVHT, end-systolic as well as end-diastolic images were used. Two-dimensional and Doppler-echocardiographic criteria for the diagnosis of LVHT were >3 trabeculations protruding from the left ventricular wall, apically to the papillary muscles, visible in 1 echocardiographic image plane at end-diastole; trabeculations form the noncompacted part of a 2-layered myocardial structure, best visible at end-systole; intertrabecular spaces perfused

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from the ventricular cavity during diastole, as visualized on color Doppler imaging.

Trabeculations were defined as structures moving synchronously with the ventricular contractions, which are distinct from ventricular bands, false tendons and prominent papillary muscles. The location of LVHT was assessed and 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. The diagnostic criteria remained the same during the entire study period.[9] Measurements of left ventricular dimensions and wall thickness were performed in the parasternal short-axis view according to standard recommendations.[10] Calculation of the ejection fraction from the 2-dimensional picture to measute left ventricular systolic function was not feasible because of the trabeculations, thus left ventricular systolic function was assessed by calculation of the left ventricular fractional shortening from the M-mode picture. Valvular abnormalities were registered and quantified by using 2-dimensional and Doppler echocardiography. Additional CMRI studies were carried out in several cases, however, patients were only included in the study if they fulfilled the echocardiographic diagnostic criteria for LVHT.

All patients underwent a baseline cardiologic examination at which they were asked for their medical history (arterial hypertension, diabetes mellitus) and cardiovascular symptoms (exertional dyspnea, angina pectoris, edema, palpitations, vertigo, and syncope). A clinical examination was carried out. Heart failure was diagnosed if the patients presented with (1) exertional dyspnea or edema and (2) echocardiographic signs of systolic or diastolic dysfunction. A 12-lead electrocardiogram was registered and the following abnormalities were recorded: tall QRS complex, ST/T wave abnormality, left bundle branch block, ventricular ectopic beats, pathologic Q waves, and atrial fibrillation. Screening of other family members and genetic investigation were done in some cases. Concomitant coronary artery disease or valvular disease was no reason for exclusion.

All patients were invited for a neurological investigation comprising the history, a clinical neurological examination and noninvasive or invasive instrumental investigations, if a NMD was suspected. A NMD was diagnosed if clinical or instrumental findings indicated the presence of a NMD. NMDs were assessed as "specific" if a definite diagnosis could be established. In cases where the neurological investigations suggested the presence of a NMD but could not detect a specific cause, a "NMD of unknown etiology" was diagnosed.

The pharmacotherapy and decisions about coronary angiography, implantation of any cardiac electronic devices or referral for heart transplantation were carried out by the treating physicians and not according to a protocol. In January 2020, the patients or their treating physicians were contacted by telephone. It was assessed if the patient was alive or not. If he was deceased, the cause of death was asked and if available registered. Additionally, the computer information system of all community hospitals in Vienna was screened for information about the patients, and the death registry of the Austrian statistical office was interrogated. Furthermore, it was tried to asses from the treating physicians and records of the patients whether cardiac electronic devices were implanted, if patients had undergone heart transplantation, and whether they had suffered from stroke or embolism. End points were death or heart transplantation.

For statistical analysis, group comparisons in baseline characteristics between survived and deceased LVHT patients were done by using the *t* test for differences in mean values from noncategorical data and contingency table methods, including the chi-square test and the Fisher exact test, if applicable, for categorical data, respectively. Differences in survival status in LVHT patients were tested using the log-rank test. The multivariate analysis was conducted by applying Cox proportional hazard regression. Model building followed purposeful selection based on the Likelihood Ratio Test and the Akaike Information Criterion, if applicable, with stepwise inclusion of covariates. The final model included the variables age at diagnosis, outpatient status, neuromuscular disorders, left bundle branch block, ventricular ectopic beats, atrial fibrillation, posterior wall, exertional dyspnea, and pathological Q waves. All statistical analyses were performed by using the statistical software package Stata 16.[11]

The study was approved by the institutional review board of the community of Vienna (EH 19-109-VK).

Results

LVHT was diagnosed in 310 patients. Clinical, neurologic, electrocardiographic and echocardiographic baseline findings are listed in Tables 1−3. Some of these patients these patients have been previously published.[12] Three patients were African blacks, 3 came from Asia (Japan, Vietnam, and India) and the remaining were Caucasians.

Neurologically investigated were 205 patients (64%). The remaining 105 patients (36%) refused or were not investigated due to organizational reasons. A specific NMD was diagnosed in 33 patients: Metabolic myopathy (n = 20), Leber's hereditary optic neuropathy (n = 3), myotonic dystrophy (n = 4), Becker muscular dystrophy (n = 2), postpoliomyelitis syndrome (n = 1), Duchenne muscular dystrophy (n = 1), MYH7 myopathy (n = 1), and myotilinopathy (n = 1). A NMD of unknown etiology was diagnosed in 123 patients (40%), and the neurological investigation was normal in 49 patients (16%). The follow-up duration ranged from 1 day to 22.5 years, with a mean of 84 ± 71 months. According to the information provided by treating physicians and hospital records, electronic devices were implanted in 59 patients (cardiac resynchronization device/defibrillator n = 22, cardioverter/defibrillator n = 21, antibradycardic pacemaker n = 12, cardiac resynchronization device n = 4) and 48 patients suffered from stroke/embolism. Of the 48 patients with stroke/embolism, the baseline electrocardiogram showed atrial fibrillation in 14 and sinus rhythm in the remaining 34 patients (29% versus 15%, p = 0.012).

Information about the survival status was obtained from all patients. Hundred-five patients (34%) were not alive any more. Causes of death were cardiac failure (n = 34), pneumonia (n = 14), sudden death (n = 15), stroke (n = 8),

Table 1
Baseline clinical cardiologic and neurological findings of 310 patients with left ventricular hypertrabeculation/noncompaction

Characteristic	All patients (n = 310)	Survivors (n = 205)	Deaths (n = 105)
Age (years [mean, ±SD])	53 (18)	49 (17)	61 (16)‡
Outpatients	131 (42%)	103 (50%)	28 (27%)‡
Female	93 (30%)	65 (32%)	28 (27%)
Male	217 (70%)	140 (68%)	77 (73%)
Specific NMD	33 (11%)	18 (9%)	15 (14%)
NMD of unknown etiology	123 (40%)	65 (32%)	58 (55%)‡
Neurologically normal	49 (16%)	39 (19%)	10 (10%)*
Neurol. not investigated	105 (34%)	83 (41%)	22 (21%)‡
Exertional dyspnea	192 (62%)	101 (49%)	91 (87%)‡
Angina pectoris	81 (26%)	61 (30%)	20 (19%)*
Edema	74 (24%)	36 (18%)	38 (36.2%)‡
Palpitations/vertigo/syncope	98 (32%)	73 (36%)	25 (24%)*
Diabetes mellitus	56 (18%)	27 (13%)	29 (28%)†
Arterial hypertension	136 (44%)	89 (43%)	47 (45%)
Heart failure	197 (64%)	105 (51%)	92 (88%)‡
NYHA I	20 (7%)	13 (6%)	7 (7%)
NYHA II	60 (19%)	40 (20%)	20 (19%)
NYHA III	66 (21%)	28 (14%)	38 (36%)‡
NYHA IV	51 (17%)	24 (12%)	27 (26%)†
Asymptomatic§	35 (11%)	29 (14%)	6 (6%)*

* p = 0.050.
† p = 0.010.
‡ p = 0.001.
§ asymptomatic = absence of the following symptoms: dyspnea, angina pectoris, palpitations, syncope, vertigo, and edema.

Table 2
Baseline electrocardiographic findings of 310 patients with left ventricular hypertrabeculation/noncompaction

Characteristic	All patients (n = 310)	Survivors (n = 205)	Deaths (n = 105)
No ECG abnormality	40 (13%)	36 (18%)	4 (4%)*
>2 ECG abnormalities	85 (27%)	51 (25%)	34 (32%)
Tall QRS complex	95 (31%)	61 (30%)	34 (32%)
ST/T wave abnormality	179 (58%)	125 (61%)	54 (51%)
Left bundle branch block	56 (18%)	25 (12%)	31 (30%)*
Ventricular ectopic beats	28 (9%)	16 (8%)	12 (11%)
Pathologic Q waves	41 (13%)	23 (11%)	18 (17%)
Atrial fibrillation	52 (17%)	20 (10%)	32 (31%)*
Left anterior hemiblock	38 (12%)	24 (12%)	14 (13%)
Right bundle branch block	14 (5%)	9 (4%)	5 (5%)
WPW-syndrome	6 (2%)	5 (2%)	1 (1%)
Low QRS voltage	20 (7%)	11 (5%)	9 (9%)
Sinus tachycardia	28 (9%)	20 (10%)	8 (8%)

* p = 0.001.

Table 3
Baseline echocardiographic findings of 310 patients with left ventricular hypertrabeculation/noncompaction

Characteristic	All patients(n = 310)	Survivors(n = 205)	Deaths(n = 105)
Left ventricular enddiastolic diameter >57 mm	161 (52)	88 (43)	73 (70)†
Left ventricular fractional shortening <25%	165 (53)	89 (43)	76 (72)†
Interventricular septum >11mm	163 (53)	104 (51)	59 (56)
Left ventricular posterior wall >11mm	176 (57)	108 (53)	68 (65)*
Valvular abnormalities	170 (55%)	91 (44%)	79 (75%)†
LVHT location:			
Apex	301 (97%)	199 (97%)	102 (97%)
Anterior wall	20 (7%)	14 (7%)	6 (6%)
Posterior wall	57 (18%)	38 (19%)	19 (18%)
Lateral wall	168 (54%)	105 (51%)	63 (60%)
LVHT affecting >2 ventricular parts	59 (19%)	39 (19%)	20 (19%)

LVHT = left ventricular hypertrabeculation/noncompaction.
* p = 0.050.
† p = 0.001.

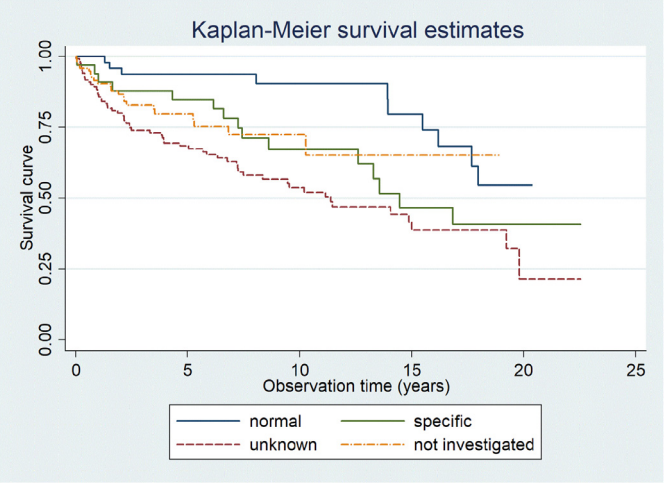

Figure 1. Survival curves (death or heart transplantation) of patients with left ventricular hypertrabeculation/noncompaction according to the results of the neurologic investigation: neurologically not investigated (yellow), neurologically normal (blue), specific neuromuscular disorder (green) and neuromuscular disorder of unknown etiology (red). (Color version of figure is available online.)

malignancy (n = 10), sepsis (n = 11), hepatic failure from cirrhosis (n = 5), pulmonary embolism (n = 3), renal failure (n = 3), and encephalopathy (n = 2), and did not differ between patients with and without NMD. Six patients underwent heart transplantation. The mortality was 4.7%/year, the rate of heart transplantation/death 5%/year. A comparison between patients who survived and died is listed in Tables 1−3.

By using the log-rank test, a predictor for increased mortality risk on univariate analysis was increased age at baseline. Applying a Cox hazard regression model, with each additional year above the mean age, the mortality increased by 4.8% (p = 0.000). Further predictors for increased mortality risks were inpatient status when LVHT was diagnosed (p = 0.0000), NMD of unknown etiology (p = 0.0012) (Figure 1), exertional dyspnea (p = 0.0000), angina pectoris (p = 0.0147), edema (p = 0.000), diabetes mellitus (p = 0.0002), heart failure (p = 0.0000), presence of ≥3 electrocardiographic abnormalities (p = 0.0000), left bundle branch block (p = 0.0000), ventricular ectopic beats (p = 0.0123), atrial fibrillation (p = 0.0000), left ventricular end-diastolic diameter >57 mm (p = 0.0003), left ventricular fractional shortening <25% (p = 0.0000), valvular abnormalities (p = 0.0000), LVHT affecting the lateral wall (p = 0.0008), and LVHT affecting more than 2 ventricular parts (p = 0.0279). Variables associated with a lower rate of mortality/heart transplantation were LVHT in outpatients (p = 0.000), a normal neurological investigation (p = 0.0012), absence of symptoms (p = 0.0271), and absence of electrocardiographic abnormalities (p = 0.0007).

Multivariate analysis identified predictors for an elevated risk of mortality/heart transplantation − increased age (p = 0.005), inpatient (p = 0.001), specific NMD (p = 0.0312) or NMD of unknown etiology (p = 0.0365), atrial fibrillation (p = 0.0000), ventricular ectopic beats (p = 0.0053), exertional dyspnea (p = 0.0023), left bundle branch block (p = 0.0201), and LVHT of the posterior wall (p = 0.0158).

Discussion

Initially, LVHT was shown to have a poor prognosis with 10%/year mortality, but further studies showed a lower mortality.[8,13] In our cohort, the largest cohort of adult LVHT patients with the longest follow-up duration, the mortality was 4.7%/year. The rate of mortality/heart transplantation in our cohort was elevated for increased age, inpatient status when LVHT was diagnosed, presence of a specific NMD or NMD of unknown etiology, atrial fibrillation, ventricular ectopic beats, exertional dyspnea, left bundle branch block, and LVHT of the posterior wall.

It is assessed controversially if LVHT patients have a worse prognosis than patients with dilated cardiomyopathy. A review showed that patients with LVHT have similar risks of cardiovascular mortality, all-cause mortality, thromboembolic complications, and ventricular arrhythmias compared with patients with dilated cardiomyopathy.[8] On the contrary, in 65 LVHT-patients during a follow-up of 61 months the number of cardiac events was higher than in 247 age-matched patients with dilated cardiomyopathy.[14] These results have to be interpreted with caution since data about systolic function of the patients with dilated cardiomyopathy are missing and they seem to be highly selected.[14]

LVHT has been described in a variety of NMD like Barth syndrome, mitochondrial disorders, zaspopathy, and myotonic dystrophies. NMDs only occasionally presenting with LVHT are the dystrobrevinopathy, laminopathies, dystrophinopathies, myoadenylat-deaminase deficiency, hereditary inclusion body myositis, and the hereditary neuropathy CMT1A.[15] A causal relation between NMD and LVHT is likely, although the exact relation and pathogenetic association remain elusive. The role of NMD as prognostic factor in LVHT has only been assessed in our cohort, since in other cohort studies, no systematic neurological examinations have been carried out. Cardiac problems may precede the neurologic abnormalities or they may be so

subtle that they are overlooked by cardiologists and only detected at neurological investigation.[16]

Those patients with LVHT and NMD have a worse prognosis than patients with normal neurologic findings may be explained as follows: (1) Patients with NMD are more prone to arrhythmias than patients without because NMD may also affect the cardiac conduction system.[17] (2) Patients with NMD suffer more frequently from respiratory problems due to affection of the respiratory muscles.[18] (3) Occasionally, NMD are multiorgan diseases affecting the endocrine, gastrointestinal, immune, or other systems. Thus, patients with LVHT and NMD are generally "sicker" patients than LVHT patients without NMD. (4) Mobility of NMD patients is frequently reduced or they are immobile and thus perform only a reduced amount of cardiovascular training. They are frequently less fit than patients without NMD due to muscle weakness, their increased fatigability and reduced stimulation or motivation. (5) Cardiac involvement in NMD frequently affects the myocardium and the conduction system and, in some cases, also the supplying autonomic network responsible for the central input in cardiac function and the reaction of the nervous system to impaired cardiac function.[19] It has been shown that in patients with Duchenne/Becker muscular dystrophy those with LVHT have a worse prognosis than those without LVHT.[20]

Left bundle branch block was a further indicator for mortality. This may be due to the fact that only 17 of our 56 patients (30%) with left bundle branch block received a cardiac resynchronization device. There are indications that LVHT patients might benefit especially from cardiac resynchronization.[21]

Atrial fibrillation, a further indicator for a dismal prognosis in LVHT, is generally acknowledged to be associated with increased cardiovascular morbidity, hospitalizations, and mortality.[22] Atrial fibrillation may lead to embolic complications, which occurred in our cohort more in atrial fibrillation than in sinus rhythm patients. Although there are no data from randomized studies, anticoagulant therapy is recommended in LVHT patients when their systolic function is reduced or atrial fibrillation is detected.[23] Vitamin-K-antagonists should be preferred in LVHT patients since it remains unclear whether the thrombi develop in the left atrium or in the left ventricle.

That inpatient status, exertional dyspnea and increased age were associated with a dismal prognosis seems evident since hospitalization, increased age and advanced stages of heart failure are indicators of a more severe and advanced stage of disease than young age, outpatient status and absence of heart failure. Similar results were found in a metaregression analysis of 28 studies enrolling 2501 LVHT patients, where the percentage of individuals with NYHA >2 was positively associated with all-cause mortality.[8]

Surprisingly, LVHT affecting the posterior wall increased the rate of mortality/heart transplantation in multivariate analysis, whereas the prevalence of posterior LVHT in surviving and death patients was similar in the univariate analysis (Table 3). This may be explained by the phenomenon that patients with LVHT of the posterior wall had more extensive LVHT, more dilated left ventricles and were more often referred for heart transplantation than patients with LVHT of another segment.

Whether the extent of LVHT is of prognostic relevance, is assessed controversially. Studies using CMRI in healthy subjects and in patients with dilated cardiomyopathy did not find an influence of the amount of trabeculated myocardium, expressed either as the ratio of noncompacted to compacted myocardium, or quantified as noncompacted/compacted length in the long-axis view and as the ratio of noncompacted/compacted mass in the short-axis view, on the prognosis.[24,25] When investigating echocardiographically diagnosed LVHT patients by CMRI, a left ventricular noncompacted myocardial mass >20% was more frequent in patients with cardiac events than without.[26]

Research about LVHT is impeded by the lack of uniformly accepted diagnostic criteria, a high interobserver variability and by the potential of overdiagnosis, especially when using CMRI.[5,9] The advantage of our study is, that the same echocardiographic criteria were used during the whole period and that all echocardiographic investigations were carried out by the same echocardiographer (C.S.). Patients, in whom only CMRI showed LVHT, were not included in the study.

Limitations are the lack of a control group. The pharmacotherapy was not assessed. Laboratory data like creatine kinase, natriuretic peptides, or troponin were not registered. The decisions about coronary angiography, device implantation, or heart transplantation were not carried out according to a protocol. These limitations are inherent to a registry. Probably, the number of strokes or embolic events and the rate of implantation of devices might be higher since we did not obtain complete information from all patients. Not all patients were investigated neurologically due to organizational obstacles and refusal of the patients. Genetic studies have been carried out only sporadically although there are indications that the results of genetic investigations may be helpful in assessing the prognosis.[27] Follow-up was carried out by telephone interviews in several patients or by searching electronic datasets, implying that essential information might have been overlooked.

From our findings, we conclude that the prognosis of patients with LVHT is dependent on neuromuscular comorbidity, which substantiates the need to refer them to a neurologist as soon as the diagnosis is established.

Author Contributions

Claudia Stöllberger: Corresponding author, investigation of the patients, data collection, drafting of the manuscript. **Matthias Hasun**: Investigation of the patients, data collection, drafting of the manuscript. **Maria Winkler-Dworak**: Design of the data base, statistical analysis, drafting of the manuscript. **Josef Finsterer**: Investigation of the patients, data collection, drafting of the manuscript.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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