ORIGINAL ARTICLE

Quantitative Electrocardiographic Measures, Neuromuscular Disorders, and Survival in Left Ventricular Hypertrabeculation/Noncompaction

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Background: Left ventricular hypertrabeculation/noncompaction (LVHT) is frequently associated with neuromuscular disorders (NMDs) and electrocardiographic (ECG) abnormalities. Quantitative ECG-measures (QEMs) are risk markers for mortality in cardiomyopathies. We measured QEMs in the ECGs in LVHT patients with and without NMDs.

Methods: Included were patients in whom (a) LVHT was diagnosed between 1995 and 2011 and (b) baseline ECG recordings were available. All underwent a clinical examination and were invited for a neurological investigation. QRS duration, QT, QTc and PR intervals were analyzed. Survival status was assessed in June 2011.

Results: In 141 patients (mean age 54 years, 49 females) QRS duration ranged from 40 to 200 ms, a QRS duration >120 ms was found in 19% and was associated with increased age, heart failure, left ventricular dilatation and systolic dysfunction ($P < 0.001$). QT intervals ranged from 240 to 600 ms. The QTc intervals ranged from 302 to 612 ms, a QTc interval >440 ms was found in 38% and was associated with left ventricular dilatation and systolic dysfunction ($P < 0.001$). PR intervals ranged from 90 to 360 ms, a PR interval >200 ms was found in 16% and associated with left ventricular dilatation ($P < 0.01$). No QEM differences were found in 86 patients with and 13 without NMD. During 59 months follow-up 45 patients died. QEMs were no mortality predictors, whereas multivariate analysis identified heart failure ($P < 0.01$), atrial fibrillation ($P < 0.01$) and diabetes mellitus ($P < 0.05$) as mortality predictors.

Conclusions: Prolonged QRS complexes, PR and QTc intervals in LVHT are associated with heart failure and left ventricular dilatation, but not with NMD. The prognostic role of QEMs in LVHT needs further investigations in larger series.

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cardiomyopathy; noncompaction; QT; QRS; mortality

Left ventricular hypertrabeculation/noncompaction (LVHT) is characterized by trabeculations in the inner core of the myocardium and a thinner than usual external compact myocardial core. LVHT is frequently associated with neuromuscular disorders (NMDs), if patients are systematically screened.¹ Electrocardiographic (ECG) abnormalities including arrhythmias are frequent in LVHT patients and comprise intraventricular conduction delay, voltage signs of left ventricular

hypertrophy, repolarization abnormalities, and atrial fibrillation.^{2–4} Quantitative ECG measures (QEMs) of repolarization have been identified as risk markers for mortality after coronary bypass grafting,⁵ in epidemiological studies,⁶ Chagas' disease,⁷ dilated cardiomyopathy⁸ and patients with chronic heart failure.⁹

The prognostic relevance of QEMs in LVHT and its dependency on NMD is largely unknown. The following QEMs were assessed in the baseline ECG

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of LVHT patients: QRS duration, QT and QTc interval, and PR interval. QEMs were compared between patients with and without NMDs and the influence of QEMs on survival was studied.

METHODS

Included were patients in whom (a) LVHT was diagnosed between 1995 and 2011 and (b) baseline ECG recordings were available. 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 one echocardiographic image plane at end-diastole; trabeculations form the noncompacted part of a two-layered myocardial structure, best visible at end-systole; intertrabecular spaces perfused from the ventricular cavity, as visualized on color Doppler imaging. Trabeculations were defined as structures moving synchronously with the ventricular contractions, distinct from ventricular bands, false tendons and prominent papillary muscles. The diagnostic criteria remained the same during the study period. The location of LVHT was assessed and categorized as apical if it involved the left ventricular apex and as anterior, lateral or posterior, if it involved the anterior, lateral or posterior parts of the left ventricular wall. All patients underwent a baseline cardiologic examination at which they were asked for their medical history and cardiovascular symptoms. A clinical examination was carried out and a 12-lead ECG was registered. All patients were invited for a neurological investigation comprising the history and a clinical neurological examination, and further 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 diagnosis could be established. Cases where no specific diagnosis could be established were assessed as "NMD of unknown etiology." Cardiologic and neurologic follow-up were carried out either by the referring physicians or the treating hospitals.

In June 2011, the patients or their treating physicians were contacted by telephone by one of the authors (CS). It was assessed if the patient was alive or not. In November 2011, from the baseline ECG recordings, the following parameters were measured: PR intervals, QRS duration, and

duration of the QT interval. QTc intervals were calculated according to Bazett's formula in patients with a heart rate of 60–100/min. In patients below and above that rate, Fredericia's formula was applied.

Equality of survivor functions was tested using the log-rank test. All statistical analyses were performed by using the statistical software package R Version 2.10.0.¹⁰

RESULTS

Between 1995 and June 2011, LVHT was diagnosed in 172 patients (53 females, mean age 53 ± 16 , range 14–94 years). Clinical findings of these patients have been reported previously.¹ In 141 of these patients (49 females, mean age 54 years), baseline ECG recordings were available for measurement (Table 1). In the remaining 31 patients the ECGs were not available any more due to technical or organizational reasons.

Ninety-nine patients (70%) were investigated neurologically. A specific NMD was diagnosed in 18 patients (13%): Metabolic myopathy $n = 11$; Leber's hereditary optic neuropathy $n = 2$; myotonic dystrophy $n = 2$; Becker muscular dystrophy $n = 1$; post-poliomyelitis syndrome $n = 1$, and Duchenne muscular dystrophy $n = 1$. A NMD of unknown etiology was diagnosed in 68 patients (43%), and the neurological investigation was normal in 13 patients.

PR intervals ranged from 90 to 360 ms, a PR interval >200 ms was found in 20 patients (16%) and was associated with left ventricular dilatation ($P < 0.01$). QRS duration ranged from 40 to 200 ms, a QRS duration >120 ms was found in 27 patients (19%) and was associated with increased age, heart failure, left ventricular dilatation and systolic dysfunction ($P < 0.001$). QT intervals ranged from 240 to 600 ms. The QTc intervals ranged from 302 to 612 ms, a QTc interval >440 ms was found in 54 patients (38%) and was associated with left ventricular dilatation and systolic dysfunction ($P < 0.001$). No QEM-differences were found between the 86 patients with and the 13 patients without NMD.

During a follow-up period of 58.6 months, 44 patients died. Causes of death were heart failure ($n = 12$), pneumonia ($n = 8$), malignancy ($n = 5$), sudden death ($n = 5$), stroke ($n = 4$), sepsis ($n = 3$), hepatic failure ($n = 3$), pulmonary

Table 1. Baseline Findings of 141 patients with Left Ventricular Hypertrabeculation/Noncompaction Whose ECGs Were Available for Analysis

Characteristics	All (n = 141)	Survivors (n = 97)	Deaths (n = 44)
Age, years (mean ± SD)	54 (17)	51 (16)	60 (18) ^{a*}
Duration of follow-up, years (mean ± SD)	5 (4)	6 (5)	4 (3) ^{a***}
Female, n (%)	49 (35)	37 (38)	12 (27)
Neurologically normal, n (%)	13 (9)	13 (13)	0 (0)*
Specific NMD, n (%)	18 (13)	9 (9)	9 (21)
NMD of unknown etiology, n (%)	68 (48)	42 (43)	26 (59)
Neurologically not investigated, n (%)	42 (30)	33 (34)	9 (21)
Exertional dyspnea, n (%)	92 (65)	56 (58)	36 (82)*
Angina pectoris, n (%)	38 (27)	31 (32)	7 (16)
Edema, n (%)	37 (26)	19 (20)	18 (41)**
Palpitations/vertigo/syncope, n (%)	29 (21)	25 (26)	4 (9)
Diabetes mellitus, n (%)	27 (19)	13 (13)	14 (32)**
Arterial hypertension, n (%)	52 (37)	39 (40)	13 (30)
Heart failure, n (%)	96 (68)	57 (59)	39 (89)**
NYHA I, n (%)	9 (6)	8 (8)	1 (2)
NYHA II, n (%)	21 (15)	14 (14)	7 (16)
NYHA III, n (%)	38 (27)	18 (19)	20 (46)**
NYHA IV, n (%)	28 (20)	17 (18)	11 (20)
ECG			
No ECG abnormality, n (%)	16 (11)	16 (17)	0 (0)*
Tall QRS complex, n (%)	42 (30)	28 (29)	14 (32)
ST/T wave abnormality, n (%)	63 (46)	48 (50)	15 (34)
Left bundle branch block, n (%)	29 (21)	13 (13)	16 (36)*
Atrial fibrillation, n (%)	24 (17)	8 (8)	16 (36)***
Left anterior hemiblock, n (%)	12 (9)	9 (9)	3 (7)
Right bundle branch block, n (%)	7 (5)	5 (5)	2 (5)
PR >200 msec†, n (%)	20 (17)	15 (17)	5 (18)
QRS >120 msec, n (%)	27 (19)	13 (13)	14 (32)
QTc >440 msec, n (%)	54 (38)	35 (36)	19 (43)
Echocardiography			
LV end-diastolic diameter, mm (mean ± SD)	61 (13)	59 (13)	65 (13)
LV fractional shortening, % (mean ± SD)	24 (11)	26 (11)	20 (10) ^{a***}
Interventricular septum, mm (mean ± SD)	12 (3)	12 (3)	13 (3)
LV posterior wall, mm (mean ± SD)	13 (3)	12 (3)	13 (4)
Valvular abnormalities, n (%)	86 (61)	56 (58)	30 (70)
LVHT location: Apex, n (%)	132 (94)	89 (92)	43 (98)
Anterior wall, n (%)	7 (5)	5 (5)	2 (5)
Posterior wall, n (%)	27 (19)	17 (18)	10 (23)
Lateral wall, n (%)	77 (55)	52 (54)	25 (57)
LVHT-affected walls (mean ± SD)	1.7 (1)	1.7 (1)	1.8 (1) ^{a*}

^aCategorized by the mean.

† n = 117, since the ECGs of 24 patients with atrial fibrillation were excluded.

LV, left ventricular; LVHT, left ventricular hypertrabeculation/noncompaction; NMD, neuromuscular disorder.

*P < 0.050.

**P < 0.010.

***P < 0.001.

embolism (n = 2), renal failure (n = 1) and coma due to leucoencephalopathy (n = 1). Univariate predictors for mortality are listed in Table 1. None of the QEMs were indicators for mortality (Fig. 1), however QRS >120 ms tended to be associated with mortality (Log rank p = 0.1185). By multivariate analysis heart failure (P < 0.01), atrial fibrillation (P < 0.01) and diabetes mellitus (P < 0.05) were predictors for mortality.

DISCUSSION

QT prolongation was detected in 38%, QRS-broadening in 19% and PR prolongation in 16% of LVHT patients. Surprisingly, neither QT-prolongation nor QRS-duration were predictors for mortality in LVHT patients.

Our findings are very similar to a previously reported analysis of ECGs of 78 LVHT patients,

Figure 1. Kaplan-Meier survival curves according to quartiles of QRS duration (in ms).

which found a AV block I in 15%, left bundle branch block in 19%, right bundle branch block in 3%, and QTc prolongation in 52%. Unfortunately, no follow-up of this patients was carried out.

Prolongation of the PQ interval, also termed first-degree AV block, needs no particular therapy. AV block is characterized by a prolongation of the conduction between the sinus and the AV node due to affection of the cardiac conduction system by coronary heart disease, infiltrative heart disease, infectious disease, collagen vascular disease, traumatic, postsurgical, tumors or NMDs. It is unknown if first-degree AV block is more frequent in patients with LVHT than without. In children with LVHT, a first-degree AV block was found in 4/46 of the cases.¹¹ In adults, a first-degree AV block was reported in a 61-year-old male with heart failure and myotonic dystrophy type 2¹² and in a 34-year-old male with heart failure.¹³ In a series of 78 adult LVHT patients first degree AV block was associated with left ventricular dysfunction and left atrial enlargement.² In a follow-up study from the same cohort, PQ duration was an independent predictor of a poor prognosis.³ These discrepant results may be explained by differences in the patients characteristics. In our study, PR interval prolongation did not differ between patients with and without NMDs. Since we did not obtain follow-up ECGs it cannot be assessed in how many patients first-degree AV block turned into higher grade AV blocks.

Possibly, changes in the depth distribution and/or extent of the Purkinje ventricular conduc-

tion network in patients with LVHT may lead to altered intraventricular conduction. Furthermore, the underlying cardiomyopathy might be responsible for changes in intraventricular conduction or repolarization. In a previous analysis of our LVHT patients, left bundle branch block has been identified by univariate analysis among others as a predictor for mortality, however on multivariate analysis, significant predictors for mortality were heart failure, atrial fibrillation and presence of NMDs.⁴ Why in the present analysis, broadening of the QRS complex only tended to predict mortality, may be explained by the low number of cases and by the fact that 9 of the 29 patients (31%) with left bundle branch block received cardiac resynchronization devices during follow-up which might have improved their prognosis.¹⁴

Prolongation of the QT interval occurs as an inherited or sporadic disorder, or it might be acquired. The cellular mechanisms behind the lengthened QT interval are prolonged ventricular action potentials. Recent genetic studies have shown that congenital long-QT syndrome (LQTS) is an electrical disease caused by the mutation of genetic coding for specific ion channels. Although prolongation of the QT interval is not an arrhythmia per se, patients with prolonged QT intervals are at risk for syncope due to torsade-de-pointes tachycardia and sudden death due to ventricular fibrillation. The prevalence of QT prolongation among LVHT patients was investigated only in a series of 78 patients. Among these patients, 40 (52%) had a prolonged QT interval, which was the second frequent ECG abnormality.² In this cohort, QT prolongation was associated with higher age, larger left ventricles and left atria, and a lower left ventricular ejection fraction, similar to our study. However, while in the mentioned study, prolonged QTc was a predictor for mortality that was not the case in our study, which may be again explained by different patient characteristics.

Why diabetes mellitus was a predictor for mortality on multivariate analysis is surprising and previously not reported in LVHT. Further studies in a larger cohort of patients and a longer observation period are necessary to clarify that phenomenon.

Limitations of the study are the low number of patients, that only baseline ECGs were available and that no specific diagnosis of a NMD could be established in every patient. A further limitation is that we did not evaluate the fragmentation of the

QRS complex, which has been recently identified as a prognostic indicator in patients with LVHT.¹⁵

CONCLUSION

Prolonged QRS complexes, PR and QTc intervals in LVHT are associated with heart failure and left ventricular dilatation, but not with NMD. Whether QEM indeed are not prognostic parameters in LVHT needs to be further investigated in a larger series of LVHT patients.

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