Original articles

Multiparametric electrocardiographic evaluation of left ventricular hypertrophy in idiopathic and hypertensive cardiomyopathy

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Electrocardiography; Heart rate variability; Hypertrophic cardiomyopathy; Left ventricular hypertrophy; QT interval.

Background. **Electrophysiological abnormalities underlying the increased arrhythmogenicity of left ventricular hypertrophy (LVH) are still under investigation. The aim of this study was to assess non-invasively the electrophysiologic alterations in two different types of LVH,**

Methods. **Multiparametric non-invasive ECG analysis (R-R interval, QRS and QT intervals, QT dispersion, T-wave complexity, activation-recovery interval [ARI] dispersion, standard deviation of RR intervals [SDNN], filtered QRS duration [fQRS], root-mean-square voltage of the terminal 40 ms of the fQRS [RMS_{40}] and low amplitude signal duration (< 40 µV) in the terminal portion of the fQRS [LAS]) was performed in 57 patients with hypertensive LVH and hypertrophic cardiomyopathy (HCM), and in 105 healthy subjects.**

Results. **The R-R interval and SDNN were similar in hypertrophic patients and controls. QRS and QT intervals were longer in hypertrophic patients without any differences between hypertensive LVH and HCM. QT dispersion, T-wave complexity and fQRS were greater in hypertrophic patients; QT dispersion was the greatest in HCM. ARI dispersion was lesser in hypertrophic patients without any differences between subgroups of LVH. fQRS showed a trend toward higher values in hypertensive patients. LAS at 25 Hz had a trend toward lower values in HCM patients, while LAS at 40 Hz and RMS_{40} showed no difference between controls and hypertrophic patients. Left ventricular mass index was not correlated with any of the above-mentioned parameters.**

Conclusions. **The QT interval and dispersion did not identify the type of hypertrophy. Similarly, ARI dispersion which explores local variations of repolarization duration, and T-wave complexity could not distinguish patients with hypertensive LVH from those with HCM indicating that multiparametric ECG data are affected more by the presence of LVH, than by its type.**

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Introduction

Left ventricular hypertrophy (LVH) is a strong independent risk factor for cardiovascular morbidity and mortality[1,2]. The Framingham study indicated that patients with LVH have a 3-fold increase in the incidence of acute myocardial infarction and a 5-fold increase in the incidence of sudden cardiac death[1]. In patients with hypertension and LVH, the relation between sudden cardiac death and ventricular arrhythmias is still under investigation, although the arrhythmogenic effect of LVH is well established.

Several factors may account for the increased left ventricular ectopic activity in patients with LVH. Greater irritability of myocytes and fibrosis in the hypertrophied myocardium leading to electrophysiologic inhomogeneity, stretching of isolated myocardial cells, increased myocardial oxygen consumption, altered membrane permeability to various ions, and increased sympathetic activity are suggested pathophysiologic factors of the increase in ventricular arrhythmias in LVH[3-5].

From an electrophysiologic point of view, the most consistently observed abnormality is prolongation of both action potential duration and refractoriness, which sets the stage for arrhythmias based on early or delayed afterdepolarizations and triggered activity. In addition, non-uniform prolongation of the action potential in LVH may be pro-arrhythmic by leading to increased dispersion of repolarization or refractoriness which favors reentry[6].

In order to assess clinically the electrophysiologic alterations in two different types of LVH, we performed a simultaneous evaluation of multiple ECG parameters (RR intervals, QRS and QT intervals, QT dispersion, T-wave complexity, activation-recovery interval [ARI] dispersion, stan-

dard deviation of RR intervals [SDNN], filtered QRS duration [fQRS], root-mean-square voltage of the terminal 40 ms of the fQRS [RMS_{40}], amount of time that the terminal vector magnitude complex remains < 40 μV [LAS]) able to examine different pathophysiologic features relevant to the genesis of life-threatening arrhythmias in a group of patients with hypertensive LVH and in a group of patients with hypertrophic cardiomyopathy (HCM); a group of healthy subjects was used as a control group.

Methods

Patient population. The hypertrophic group comprised 57 subjects (33 males, 24 females, mean age 56 ± 2 years) divided in hypertensive LVH (n = 29, 19 males, 10 females, mean age 66.8 ± 1.8 years) and HCM (n = 28, 14 males, 14 females, mean age 44.4 ± 2.8 years). All the patients had an echocardiographic diagnosis of LVH inferred from a left ventricular mass[7] > 125 g/m^2 in the case of symmetric hypertrophy and from a septal thickness > 15 mm in the case of asymmetric hypertrophy.

As a control group we included 105 healthy subjects (51 males, 54 females, mean age 42.5 ± 1.5 years) without remarkable past medical history and with normal physical examination, echocardiogram, exercise tolerance test, and laboratory findings. None of the healthy subjects was on any medications before and during the study period, while 15 patients of the hypertensive hypertrophy group and 24 of the HCM group were. All subjects and patients gave their informed written consent to participate in the study, which conformed to the declaration of Helsinki and was approved by the local Ethics Committee.

Data acquisition. After a 20 min equilibration period in the resting position, a standard 10 s 12-lead ECG, and a 5 min recording of the 12-lead extended length ECG were recorded and stored onto a memory card using the Portrait® ECG apparatus (Mortara Instrument, WI, USA). The choice of a 5 min recording from the possible 2 to 60 min range, was taken considering this time short enough for subject comfort and compliance, and long enough to allow the analysis of almost all ECG predictors of risk[8]. The standard position for the 10 ECG electrodes was used for 12-lead extended length ECG recordings. To reduce muscle noise, the arm leads were placed on the acromion of the shoulder blade, and the leg leads on the anterior superior iliac crest. Data of 8 ECG leads (I, II, V_1 through V_6) were acquired at a sampling rate of 1000 Hz/s per lead (5000 Hz for the signal averages). All ECG data were acquired and stored at a voltage resolution of 16 bits. The 5 min recording generates a data file of 5.24 megabytes in size. The Portrait® ECG apparatus has a built-in PCMCIA card slot that can accommodate compact flash cards holding up to 64 megabytes of data. After acquisition, the data were transferred from the flash card to the hard disk of a desktop PC. Custom software analyzed the 5 min of data for the 8 parameters listed below. Leads III, aVR, aVL and aVF were calculated from leads I and II using standard formulas[9].

The following parameters were calculated:

• resting heart rate: it was calculated as the averaged RR interval in the 5 min ECG recording;

• QRS duration: QRS duration was measured in all leads from the earliest onset to the latest offset and the median value was calculated. The resolution was 1 ms and the filter range was 0.05 to 300 Hz;

• heart rate variability: the parameter used was SDNN[10];

• signal-averaged ECG: signal-averaged ECG was measured on a vector magnitude signal derived from 8 leads, rather than from the Frank XYZ leads. Twenty-five and 40 Hz were used as high-pass filters. The three measured parameters were: 1) fQRS, 2) LAS, and 3) RMS_{40}[11];

• QT interval: the third longest value of the QT interval among the 8 recorded leads was used as the global QT interval. Heart rate-corrected QT (QTc) was evaluated by using the Bazett [$QTc = QT/(R\text{-}R)^{1/2}$], Fridericia [$QTc = QT/(R\text{-}R)^{1/3}$], Framingham [$QTc = QT + 1.54 \times (1 - RR)$], Hodges [$QTc = QT + 1.75 \times$ (heart rate - 60)] formulas[12];

• QT interval dispersion: this parameter was determined by subtracting the shortest from the longest QT value among 8 leads, chosen as follows according to the recommendations of de Bruyne et al.[13]: the 6 precordial leads, the extremity lead with the shortest QT, and the extremity lead with the median QT;

• T-wave complexity index: this method is based on principal component analysis applied to 12 leads as opposed to the many leads used during body surface mapping[14,15]. Compared with other methods available to characterize the QT interval, this method does not require identification of the end of the T wave. The analysis allows the identification of a set of 8 values that represent the relative magnitude of the spatial components of repolarization. The evaluation of the relative contribution of these components provided an estimate of the spatial complexity of repolarization. The T-wave complexity index utilized in this study was calculated[15] as the ratio of the second value to the first multiplied by 100, thus expressed in percentage. Such an approach should allow a comparison between the morphology of the T wave across the 12 leads and the quantification of T-wave abnormalities in an observer-independent way[15];

• ARI dispersion: ARI is defined as the time from the most negative dV/dt during the QRS complex (the intrinsic deflection) to the most positive dV/dt during the T wave[16]. This parameter was measured only in the precordial (V_1-V_6) leads. ARI dispersion is the difference between the longest ARI minus the shortest one.

Statistical analysis. Data are reported as mean ± standard error. Comparisons between the hypertrophy

group and healthy subjects were performed by unpaired Student's t-test after Levene's test for equality of variances. Comparisons among the subgroups with hypertensive hypertrophy and HCM and healthy subjects were performed by ANOVA followed by Bonferroni t-test. Previously reported[17] sex differences for RR interval, QRS duration, ARI dispersion and fQRS were separately analyzed. Since age differences for SDNN, T-wave complexity and QT dispersion were previously reported in normal subjects, controls were grouped by age decades between 30 and 50 years of age and > 50 years in order to perform comparisons with HCM and hypertensive hypertrophy patients, respectively. SDNN and T-wave complexity (TWC) were normalized for RR interval of 1 s as previously described [SDNNc = SDNN + 0.0816 × (1 - RR) and TWCc = TWC - 0.0158 × (1 - RR). Correlations with left ventricular mass index and ECG parameters were analyzed by Pearson's r. Data were analyzed by SPSS statistical package for Windows 10.0 (SPSS Inc., Chicago, IL, USA).

Results

Table I shows the clinical characteristics of all subjects included in the study (healthy subjects, patients with hypertensive LVH and patients with HCM). Hypertensive hypertrophic patients were significantly older than HCM patients ($p < 0.001$); sex distribution was not different. All patients with hypertensive hypertrophy included in the study had 2nd and 3rd degree hypertensive disease. Therefore the degree of myocardial hypertrophy in hypertensive LVH was comparable with that of HCM. However hypertensive LVH was characterized by higher values of diastolic left ventricular diameter, posterior wall thickness, left ventricular mass and mitral E-wave deceleration time, while interventricular septum thickness, mitral E/A ratio and isovolumic relaxation time were higher in HCM. No patient in the hypertensive group reported a history of syncope or significant ventricular arrhythmias while in the HCM group 5 patients were symptomatic for syncope, in 2 of them ventricular tachycardia was recorded on 24-hour ECG monitoring, and one was resuscitated from sudden cardiac arrest.

As depicted in table II, the RR interval was similar in the hypertrophic group and healthy subjects, without differences between subgroups. QRS duration and QT interval were longer in the hypertrophic group without any significant difference between hypertensive LVH and HCM (Table III). QT Bazett, QT Fridericia, QT Framingham, and QT Hodges were longer in the hypertrophic group (439 ± 5 vs 409 ± 3 ms, 431 ± 4 vs 399 ± 3 ms, 430 ± 4 vs 400 ± 2 ms, 430 ± 4 vs 398 ± 2 ms, $p < 0.0001$ for all correction formulas) without any differences between subgroups.

QT dispersion was greater in the hypertrophic group than in healthy subjects (Table III); it was the greatest in HCM when a comparison among age-matched groups was performed (Table IV).

Table II. RR interval, QRS duration, QT interval, T-wave complexity index, activation-recovery interval (ARI) dispersion in healthy subjects and in patients with left ventricular hypertrophy (LVH).

	Healthy subjects	Patients with LVH	p
RR interval (ms)	881 ± 13	912 ± 20	NS
QRS duration (ms)	85 ± 1	96 ± 3	< 0.001
QT interval (ms)	382 ± 3	417 ± 5	< 0.001
QT dispersion (ms)	40 ± 3	56 ± 6	0.010
SDNN (ms)	61 ± 2	65 ± 6	NS
T-wave complexity index (%)	14 ± 1	30 ± 3	< 0.001
ARI dispersion (ms)	83 ± 3	62 ± 6	0.002

SDNN = standard deviation of all RR intervals.

Table I. Clinical and echocardiographic characteristics of the study population.

	Healthy subjects	LVH		p (hypertensive LVH vs HCM)
		Hypertensive	HCM	
No. patients	105	29	28	
Age (years)	42.5 ± 1.5	66.8 ± 1.8*	44.4 ± 2.8	< 0.001
Sex (M/F)	51/54	19/10	14/14	NS
LVDD (mm/m^2)	28.4 ± 0.1	32.0 ± 0.7*	25.8 ± 0.2*	< 0.001
IVSTh (mm)	8.7 ± 0.1	17.5 ± 0.3*	19.0 ± 0.6*	0.001
PWTh (mm)	8.8 ± 0.1	17.6 ± 0.3*	9.7 ± 0.3**	< 0.001
LVM (g/m^2)	69.5 ± 0.9	181.5 ± 6.2*	116.6 ± 25.9*	< 0.001
FS (%)	40.9 ± 0.4	36.1 ± 0.8*	37.1 ± 1.6*	NS
E/A ratio	1.22 ± 0.04	0.89 ± 0.12**	1.36 ± 0.11	< 0.001
DT (ms)	156.4 ± 2	201.0 ± 5.2*	162.0 ± 13.0	< 0.001
IVRT (ms)	70.9 ± 0.7	86.9 ± 3.1*	111.0 ± 4.3*	< 0.001

DT = deceleration time; FS = fractional shortening; HCM = hypertrophic cardiomyopathy; IVRT = isovolumic relaxation time, IVSTh = interventricular septum thickness; LVDD = left ventricular diastolic diameter; LVH = left ventricular hypertrophy; LVM = left ventricular mass; PWTh = posterior wall thickness. * $p < 0.001$; ** $p < 0.01$.

Table III. RR interval, QRS duration, QT interval, T-wave complexity index, activation-recovery interval (ARI) dispersion in healthy subjects and in the two subgroups of patients with left ventricular hypertrophy (LVH) included in the study.

	Healthy subjects	Patients with LVH		p (hypertensive LVH vs HCM)
		Hypertensive	HCM	
RR interval (ms)	881 ± 13	896 ± 24	929 ± 32	NS
QRS duration (ms)	85 ± 1	96 ± 4*	96 ± 4*	NS
QT interval (ms)	382 ± 3	411 ± 8**	422 ± 6**	NS
QT dispersion (ms)	40 ± 3	54 ± 9	57 ± 7*	NS
SDNN (ms)	61 ± 2	65 ± 10	64 ± 7	NS
T-wave complexity index (%)	14 ± 1	28 ± 4**	31 ± 4**	NS
ARI dispersion (ms)	83 ± 3	62 ± 8*	62 ± 8*	NS

HCM = hypertrophic cardiomyopathy; SDNN = standard deviation of all RR intervals. * $p < 0.05$; ** $p < 0.001$.

Table IV. RR interval, QRS duration, QT interval, T-wave complexity index, activation-recovery interval (ARI) dispersion in age-matched subgroups of subjects included in the study.

	Healthy subjects (n = 49)	Hypertrophic cardiomyopathy (n = 28)	Healthy subjects (n = 31)	Hypertensive LVH (n = 29)
QT dispersion (ms)	36 ± 4	57 ± 7*	50 ± 6	54 ± 9
SDNN (ms)	60 ± 2	64 ± 7	55 ± 3	65 ± 10
T-wave complexity index (%)	14 ± 2	31 ± 4**	16 ± 2	28 ± 4***

LVH = left ventricular hypertrophy; SDNN = standard deviation of all RR intervals. * $p < 0.05$; ** $p < 0.001$; *** $p < 0.01$.

SDNN did not differ between hypertrophic patients and healthy subjects and no differences among hypertrophic subgroups were found even when comparisons were performed in age-matched groups (Table IV).

T-wave complexity was greater in the hypertrophic group but no differences were observed between patients with hypertensive hypertrophy and HCM. These results were confirmed by repeating the analysis in age-matched groups (Table IV).

ARI dispersion was lesser in the hypertrophic group with no differences in the two subgroups (Tables III and IV).

Table V shows the values of signal-averaged ECG in healthy subjects and in hypertrophic patients. fQRS at 25 and 40 Hz was greater in the hypertrophic group showing a trend toward higher values in the hypertensive subgroup.

LAS at 25 Hz had a trend toward lower values in the hypertrophic group being lesser in HCM, while LAS at 40 Hz, RMS_{40} at 25 and 40 Hz showed no difference between healthy subjects and hypertrophic patients.

Finally, echocardiographic left ventricular mass index in the hypertrophy group was not correlated with any of the above-mentioned parameters (QRS duration, QT duration, fQRS at 25 and 40 Hz, LAS at 25 Hz, ST SD/amplitude ratio, QT dispersion, ARI, SDNN, T-wave complexity).

Discussion

In the present investigation we evaluated different electrophysiologic parameters in patients with LVH with respect to healthy subjects by means of a multiparametric simultaneous non-invasive analysis of surface ECG. All parameters but SDNN were statistically different between hypertrophic patients and controls (some values were, however, within the normalcy range), but only few (ARI dispersion, fQRS and LAS_{25}) were sensitive to the type of hypertrophy (hypertensive hypertrophy vs HCM).

Heterogeneous recovery of ventricular refractory periods is an important factor for arrhythmia development. Since the interlead variability of the QT interval on the surface ECG (i.e., QT dispersion defined as the difference between maximal and minimal QT interval duration) is a measure of non-homogeneity of ventricular repolarization[18-21], QT interval measurements remain a reliable tool to quantify ventricular repolarization[14] despite the well-known methodological limitations. In patients with LVH, QT interval has been reported to be prolonged only slightly[22-24] or not at all[25]. Recently Wolk et al.[26] evaluated changes in the T_{peak}-T_{end} interval (an index of transmural dispersion of repolarization) in hypertensive patients with LVH and reported that the T_{peak}-T_{end} interval was not affected by LVH, while there was an increase in QT_{peak} dispersion

Table V. Signal-averaged ECG in healthy subjects and in patients with left ventricular hypertrophy (LVH).

	Healthy subjects	Patients with LVH	Hypertensive LVH	HCM	p (hypertensive LVH vs HCM)
fQRS 25 Hz (ms)	97 ± 1	109 ± 3*	113 ± 5*	104 ± 4	NS
fQRS 40 Hz (ms)	94 ± 1	105 ± 3*	109 ± 5*	100 ± 4	NS
LAS 25 Hz (ms)	32 ± 1	27 ± 2*	28 ± 2	26 ± 2**	NS
LAS 40 Hz (ms)	34 ± 1	33 ± 2	36 ± 3	30 ± 3	NS
RMS_{40} 25 Hz (μV)	50 ± 3	50 ± 5	28 ± 5	38 ± 7	NS
RMS_{40} 40 Hz (μV)	41 ± 3	40 ± 3	33 ± 3	46 ± 5	NS

fQRS = filtered QRS duration; HCM = hypertrophic cardiomyopathy; LAS = low amplitude signal duration (< 40 μV) in the terminal portion of the fQRS; RMS = root-mean-square voltage of the last 40 ms of the fQRS. * $p < 0.001$; ** $p < 0.05$.

which resulted from an increase in the maximum QT_{peak} interval without any change in the minimum QT_{peak} interval. The authors concluded that the effect of LVH was to prolong the QT interval (and, by implication, the action potential duration) although this prolongation is probably heterogeneous and aspecific. Our results are well in keeping with these data; further, they indicate that the QT interval is insensitive to the type of LVH, being its prolongation comparable in patients with hypertension and in patients with HCM.

QT dispersion is increased in patients with LVH due to hypertension and isolated aortic stenosis, without any significant differences between the two etiologies[27,28]. In our study QT dispersion was abnormally greater in the population of patients with LVH, being higher in those with HCM. However, QT dispersion did not correlate with left ventricular mass in hypertrophic patients: this is in keeping with the data by Zoghi et al.[29] who documented no increase in QT dispersion in endurance athletes despite an increase in left ventricular mass. Besides, the lack of correlation between QT dispersion and left ventricular mass was previously described in an unselected hypertensive population[30] and in patients with hypertrophic obstructive cardiomyopathy[31]. Our results suggest that QT interval and QT dispersion cannot be considered as a sensitive and specific ECG method for LVH detection, while independently of the left ventricular mass they have the ability to unmask repolarization alteration.

The ARI has been proposed as a measure of local repolarization duration[32] and in animal studies, it showed a close correlation with action potential duration recorded from the cells underlying the recording electrode[33] under conditions of varying cycle length and adrenergic stimulation[32]. Previous studies have suggested that ARI is a good estimate of the underlying action potential in surface leads as well[34]. Interestingly, in our study ARI dispersion was lesser in patients with LVH than in control subjects; furthermore, this parameter was sensitive to the type of LVH, being lesser in hypertensive LVH. Probably the structural characteristics of septal hypertrophy modulate inhomogeneity of repolarization and therefore modulate ARI dispersion.

T-wave complexity index is a newly-developed parameter recently introduced from 12-lead ECG and from 12-lead digital Holter recordings which was shown to differentiate normal subjects from patients with the long QT syndrome[35] and arrhythmogenic right ventricular dysplasia[36]. In the present study, patients with LVH showed increased T-wave complexity with respect to control subjects, in keeping with previous data in HCM[15]. T-wave complexity, however, seems unable to distinguish patients with hypertensive LVH from those with HCM.

Heart rate variability is considered as a non-invasive marker of the autonomic nervous system function[37], and a low heart rate variability (as inferred by low values of SDNN) has been shown to have prognostic value in the general population[38] and in patients with myocardial infarction[39]. Although a decreased heart rate variability is a risk factor for arrhythmic events, it lacks by itself the positive predictive accuracy to stratify the risk in a clinical setting. We have recently documented[17] the relation between SDNN and both age and sex, confirming previous data[40,41]. In the present paper, SDNN corrected for heart rate was not able to distinguish between healthy subjects and patients with LVH nor the type of LVH influenced the parameter.

The value of late potentials as a prognostic indicator of the occurrence[42] of ventricular tachycardia and sudden cardiac death has been reported in patients with coronary heart disease, as well as in non-ischemic dilated cardiomyopathy[43]. While RMS_{40} was not different in our controls and LVH patients and was insensitive to the type of LVH, both fQRS and LAS_{25} differed between healthy subjects and patients and were able to distinguish patients with hypertensive LVH from those with HCM. In HCM patients the simultaneous evaluation of T-wave complexity, QRS dispersion and LAS_{25}, unable by itself to hold a predictive value, yielded high accuracy in predicting cardiogenic syncope[44].

In conclusion, the inability of QT interval, of QT dispersion, of ARI dispersion, and of T-wave complexity to identify the type of hypertrophy and to separate patients with hypertensive LVH from those with HCM suggests that ventricular repolarization parameters, as

evaluated by means of multiparametric analysis of the ECG, are affected by the presence of LVH, not by its type. Thus a prognostic role of multiparametric analysis of ECG indexes in LVH patients has not emerged so far; perhaps further longitudinal studies, performed in larger cohorts of patients are needed to add new insights.

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