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Relationship between life threatening events and electromechanical window in patients with hypertrophic cardiomyopathy

- Electromechanical window in patients with hypertrophic cardiomyopathy-

비후성 심근병증 환자에서 생명을 위협하는 사건과 전기기계적 창의 관계

2021 년 8 월

서울대학교 대학원
임상의과학과
송미경

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지도 교수 배 은 정

이 논문을 의학박사 학위논문으로 제출함

2021 년 4 월

서울대학교 대학원

임상의과학과

송미경

송미경의 의학박사 학위논문을 인준함

2021 년 7 월

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Abstract

Relationship between life threatening events and electromechanical window in patients with hypertrophic cardiomyopathy

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Background: Hypertrophic cardiomyopathy (HCM) is a leading cause of sudden cardiac death (SCD) in young individuals, largely due to ventricular arrhythmias, which may be associated with electrical disturbances from the pathologic myocardial changes. However, the electromechanical relationship has not been studied in this population

Objectives: We investigated electromechanical mismatches in patients with HCM and the relationship between electromechanical mismatches and life-threatening events (LTEs).

Methods: We performed a retrospective study of patients diagnosed with HCM, ages 1–80 years old. Electromechanical mismatch was evaluated using the electromechanical window (EMW), defined as the interval between the Q wave and aortic valve closure minus the QT interval.

Results: We enrolled 458 patients (male, 66%) with a mean age of 52.4±18.8 years. When the EMW of patients with HCM was compared to that of age/sex-matched normal controls, the EMW was more negative in patients with HCM than in normal controls (-51±35 vs. 7±19 ms, $p<0.001$). LTEs occurred in 25 patients (5.5%). The

EMW was more negative in patients with LTEs than in those without (-77±33 vs. -42±31 ms, $p<0.001$). Decreased EMW was correlated with increased maximum left ventricular wall thickness, worse global strain, mitral E/A ratio, septal mitral tissue Doppler e', and decreased left ventricular outflow tract pressure gradient on echocardiography. The cut-off value of EMW to identify patients with a risk of LTEs development was -54 ms and c-index of EMW was 0.726. EMW<-54 ms, unexplained syncope, pediatric-onset, and extreme left ventricular hypertrophy were significant risk factors for LTEs on multivariate analysis.

Conclusions: EMW was more negative in patients with HCM than in healthy individuals, and profound EMW negativity was an independent risk factor for LTEs. EMW can be useful for the risk stratification of SCD in patients with HCM.

Keywords: cardiomyopathy, hypertrophic • death, sudden, cardiac • risk assessment • pediatric

Student Number : 2017-32936

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Chapter 1. Introduction

1.1. Study Background

Hypertrophic cardiomyopathy (HCM) is one of the most common hereditary heart muscle diseases and is a leading cause of sudden death in young athletes (1). Sudden cardiac death (SCD) in patients with HCM is usually attributable to ventricular arrhythmia. Severe ventricular wall hypertrophy and myocardial fibrosis are well-known risk factors for SCD, and some studies have shown that increased mechanical dispersion and decreased global longitudinal strain in HCM increase the risk of ventricular arrhythmia (2-4). Therefore, mechanical abnormalities affect electrical disturbances and ventricular arrhythmia in patients with HCM.

The electromechanical window (EMW) is characterized as the temporal difference between the QT interval (electrical systole) and left ventricle outflow ejection time (mechanical systole) (5). The duration of electrical systole is usually slightly shorter but parallels that of mechanical systole in healthy individuals at rest, resulting in a positive or zero EMW (6). However, in patients with long QT syndrome, the QT interval (electrical systole), is longer than the mechanical systole, producing a negative EMW, which is most profound in patients with a long QT interval and ventricular arrhythmia (7). Previous studies have shown that mechano-electrical coupling disturbances are more critical for the development of ventricular arrhythmia than the corrected QT interval (QTc) in patients with long QT syndrome (7,8). However, the relationship between electrical and mechanical disturbances, or electromechanical mismatch, has not yet been evaluated in patients with HCM.

1.2. Purpose of Research

We investigated electromechanical mismatch using EMW in patients with HCM and aimed to determine whether EMW negativity correlates with arrhythmic life-threatening events (LTEs).

We also studied the relationship between EMW and mechanical function parameters.

Chapter 2. Methods

We enrolled patients from Seoul National University Hospital who were diagnosed with HCM between 2007 and 2018 and were followed up for at least 6 months. Patient ranged in age from 1 to 80 years old. Demographic data, comorbidities, cardiac MRI data, echocardiography data, 24-hour Holter monitoring, resting electrocardiography (ECG) data, and genetic test results were retrospectively analyzed.

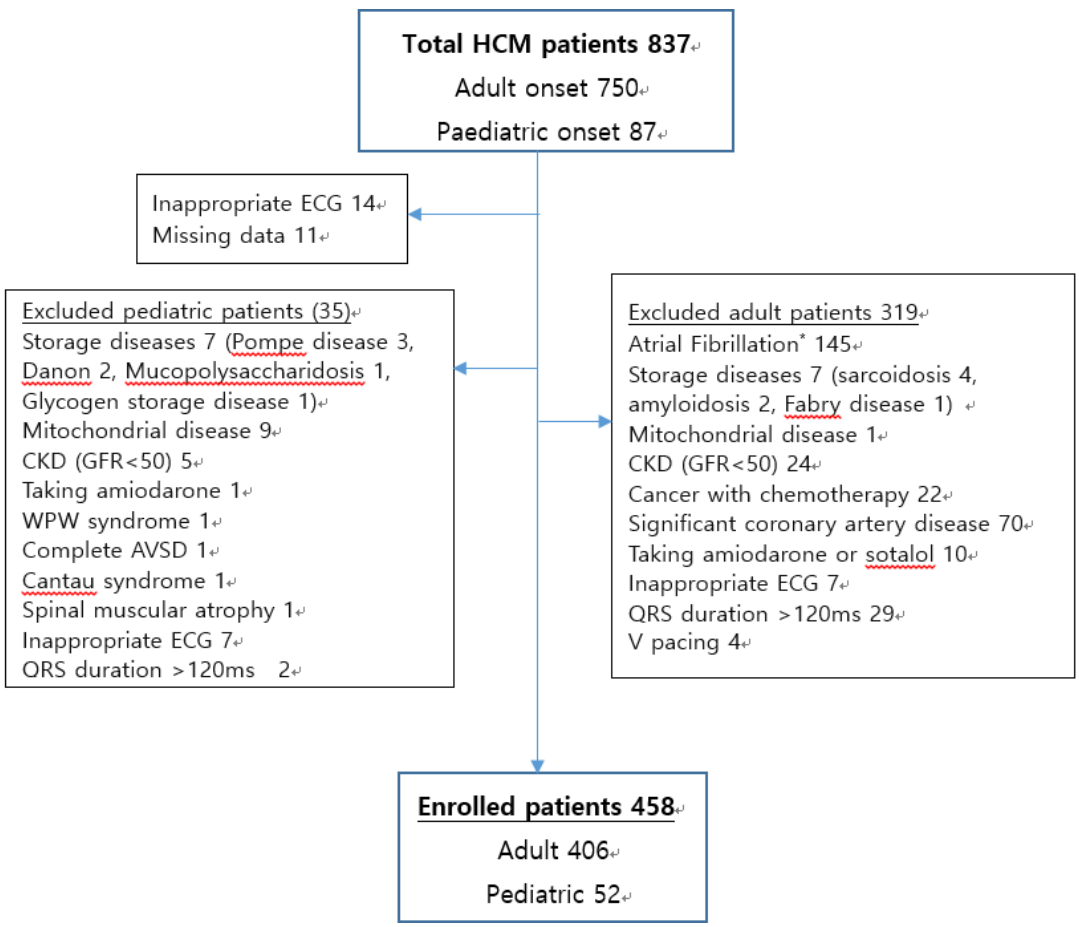
2.1. Definition

HCM was defined by a maximum left ventricular wall thickness (LVWT) more than 15 mm in adult patients and more than two standard deviations greater than the predicted mean in children that was not explained solely by loading conditions such as aortic stenosis and hypertension (9). LVWT was measured by echocardiography, and in pediatric patients, the maximum LVWT was expressed as a Z-score. Extreme left ventricular hypertrophy (LVH) was defined as an absolute maximal thickness ≥30 mm or a Z-score ≥6.0 in pediatric patients. Non-sustained ventricular tachycardia (VT) was defined as ≥3 consecutive beats at a rate of >120 beats/min for less than 30 seconds on 24-hour Holter monitoring. LTEs were defined as cardiac arrest, an appropriate shock by an implantable cardioverter-defibrillator, or VT.

2.2. Study population

A total of 837 patients with HCM were identified. Among them, 379 patients were excluded for a variety of reasons, and 458 patients, including 52 with pediatric-onset HCM, were enrolled. The mean follow-up duration was 8.6±6.1 years (3931.0 patient years). Patients with metabolic disease, patients diagnosed with atrial fibrillation before index echocardiography, patients whose QT interval was difficult to measure on stored echocardiography, patients with other myocardial loading conditions, and patients taking amiodarone or sotalol at the time of index echocardiography were excluded from this study (Figure 1).

<Figure 1> Study population

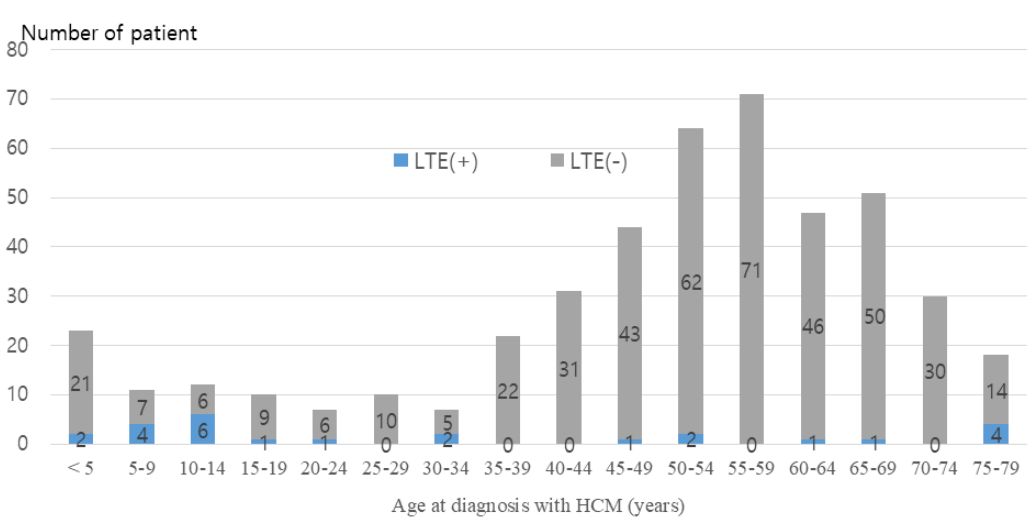


AVSD = atrioventricular septal defect; CKD = chronic kidney disease; ECG = electrocardiography; GFR = glomerular filtration rate

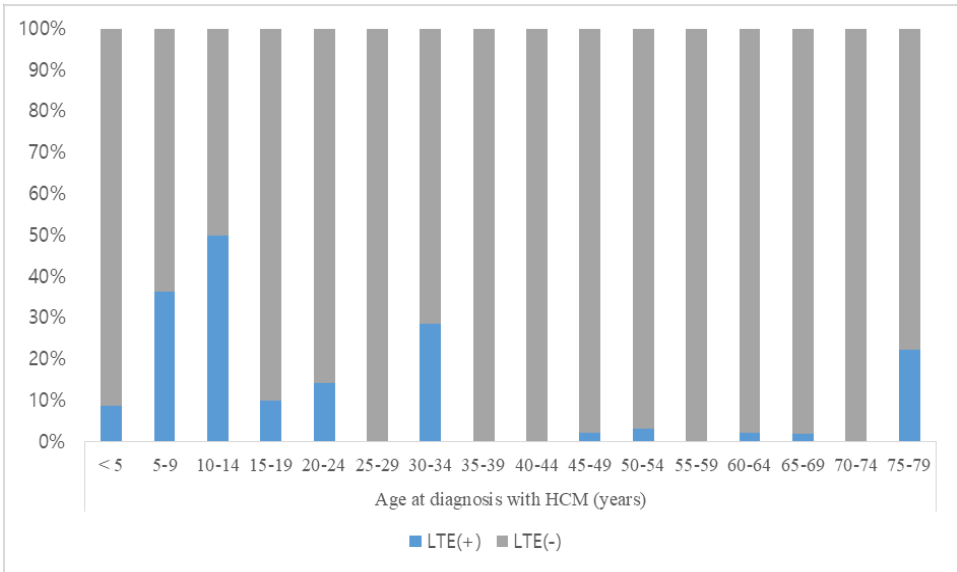
*Atrial fibrillation before index echocardiography.

Patients who were younger than 19 years of age at the time of HCM diagnosis were classified as having pediatric-onset HCM. The age distribution of enrolled patients is shown in Figure 2A and 2B. Healthy adults with normal echocardiography and normal ECG on general health check-ups and children visiting the center for the evaluation of general health check-ups and children visiting the center for the

< Figure 2A> Age Distribution at HCM diagnosis



< Figure 2B> Proportion of patients with LTEs according to HCM diagnosis age

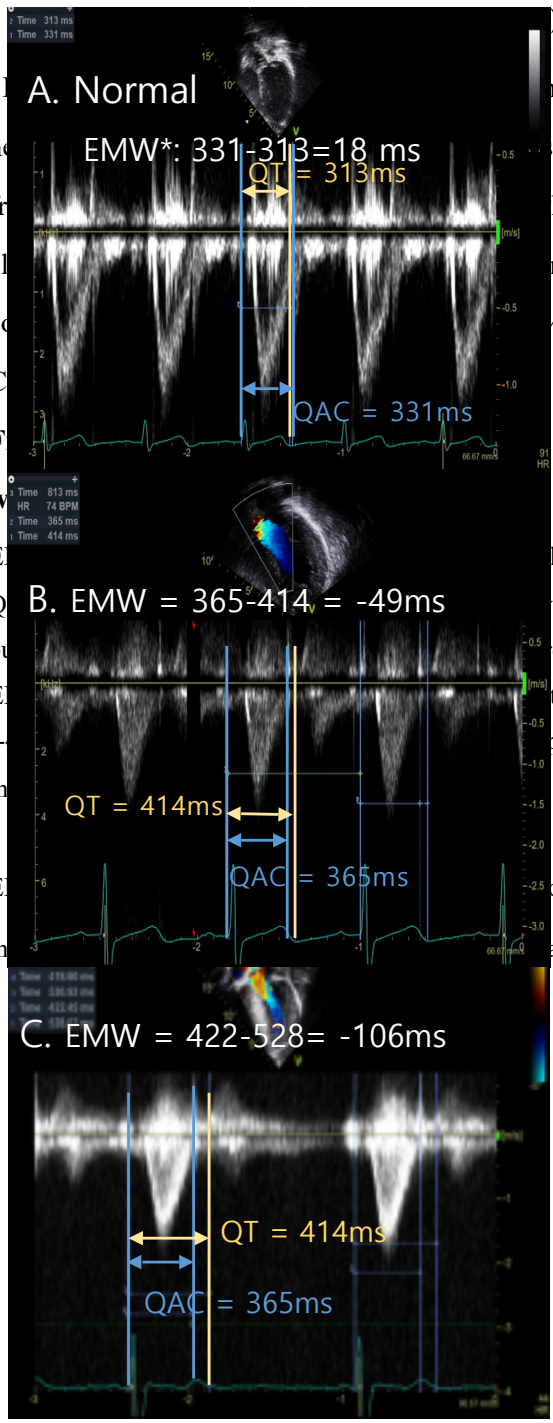


Evaluation of general health check-ups and children visiting the center for the evaluation of palpitations were initially selected as candidates for normal controls, of whom age- and sex-matched controls were selected. This study was approved by the Institutional Review Board of Seoul National University Hospital (No.1905-045-1031), and the requirement for written informed consent was waived owing to the retrospective nature of the study. The study complied with the Declaration of Helsinki.

2.3. Electromechanical window acquisition

EMW (ms) was defined as the time interval between Q wave and aortic valve closure (QAC) (ms) minus the QT interval for the same beat (ms) (Figure 1). QAC was measured using pulsed wave Doppler in the left ventricular outflow tract (LVOT) on a recorded apical 5-chamber view, and the QT interval was concurrently measured using 3-lead electrocardiography of echocardiography, which is the same as that of lead II (7) (Figure 1). We used the earliest echocardiographic recording images with measurable QAC and QTc. In subgroup

analysis with pediatric patients, we use corrected EMW which was defined as EMW divided by the square root of the RR interval, as pediatric patients' heart rates were variable.



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th HCM, the EMW value was negative

patients who experienced life-

ophic cardiomyopathy; LTE = life

ave and aortic valve closure

2.4. Echocardiography

Standard transthoracic echocardiographic examinations were performed with commercially available ultrasound machines (GE Vivid 7, E9/E95, Philips EPIQ7C, and Siemens SC2000) according to the guidelines (10,11). Diastolic function was evaluated by E and A from transmitral pulsed-wave Doppler and e', a', and s' from septal mitral annular tissue Doppler samplings (12). LVOT pressure gradients of blood flow were assessed at rest or using the Valsalva maneuver, and a gradient of ≥30 mmHg was defined as significant LVOT obstruction (6). Left atrial dimension was measured in the parasternal long-axis view and categorized into normal, mild, moderate, and severe dilatation to facilitate comparison between pediatric and adult patients (10).

2.5. Genetic testing

Genetic testing was performed using a targeted next-generation sequencing gene panel, including 31 genes associated with HCM in 121 patients. Patients with pathogenic or likely pathogenic mutation according to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (13) in the sarcomere genes were compared to those without sarcomere gene mutation to determine their risk of LTEs and relationship with EMW.

2.6. Statistical analysis

Data of continuous variables are expressed as mean ± standard deviation, or median and range as appropriate, and values were compared between the groups using Student's *t*-test. Categorical variables are expressed as frequency (percentage). Chi-square and Fisher's exact tests were used to compare categorical data between two or three groups. Bivariate Pearson correlation analysis was

conducted to evaluate the relationship between EMW and other continuous parameters. The Kaplan-Meier estimate was used to analyze the cumulative probability of freedom from LTEs. Multivariable analysis and univariate analysis using the Cox proportional hazards model was performed to evaluate the risk of LTEs using the stepwise selection method, with criteria for entry and exit at $p<0.05$ and $p<0.1$, respectively. Models met the proportional hazards assumptions and linear assumptions. These statistical analyses were performed using SPSS software (version 23.0, IBM Corporation, Armonk, NY, USA). A P-value of <0.05 was considered statistically significant.

The optimal cut-off value of EMW to identify patients with or without LTEs was determined using a minimal p-value approach based on log-rank test statistics and was validated with the help of two-fold cross-validation approach using SAS 9.4 (SAS Corporation Inc., Cary, NC) (14)·(15)**.** C-index using Uno's concordance statistic was used to evaluate the predictive power of EMW and corrected EMW for LTEs.

Chapter 3. Results

Baseline clinical characteristics of the 458 patients with HCM (66% male patients) are shown in Table 1. The mean age at index echocardiography was 52.4±18.8 (56.8, range 1.1–78.6) years, and the mean age at the diagnosis of HCM was 49.7±19.3 (53.9, range 0-78.2) years. Among all patients, those with pediatric-onset HCM accounted for 11% (52/458) with the mean age at diagnosis being 7.7±6.1 years.

Table 1. Baseline clinical characteristics of patients with HCM

Demographic data		Variables*
Age at echocardiography		52.4 ± 18.8 years
Diagnosis age of HCM		49.7± 19.3 years
Male		304 (66%)
≤ 18 years at HCM diagnosis		52 (11%)
Unexplained syncope		47 (10%)
Life threatening events		25 (6%)
HCM Class	apical	157 (34%)
	septal	161 (35%)
	mixed/diffuse	140 (31%)
Non-sustained VT		106/406 (26%)
Family history of SCD		51 (11%)
Family history of HCM		58 (14%)
LGE on MRI		267/318 (84%)
Genetic study		124
	sarcomere variant	48 (40%)
	Variant of known significance	41 (34%)

	No variant	17 (14%)
	Noonan syndrome	14 (12%)
LVOT obstruction		74 (16%)
Myectomy		12 (3%)
Mitral regurgitation>moderate		5 (1%)
AF during follow-up		40 (9%)
Body mass index (kg/m^2)		24.3 ± 3.7
Medications	none	276 (62%)
	Beta-blocker	104 (23%)
	Calcium channel blocker	57 (13%)
	Beta-blocker + calcium channel blocker	9 (2%)
Comorbidities	Hypertension	159 (35%)
	Diabetes	66 (14%)
	dyslipidemia	112 (25%)
	Cancer	36 (8%)

AF = atrial fibrillation; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; LGE = late Gadolinium enhancement; SCD = sudden cardiac death; VT = ventricular tachycardia

3.1. Comparison of EMW between normal controls and patients with HCM

One hundred sixty patients with HCM were randomly mathced and compared with 80 age/sex-matched normal controls (Table 2). The QAC of patients with HCM was slightly shorter than that of normal controls despite no differences in heart rate between the two groups (378±38 vs. 389±37, p=0.031), whereas the QTc interval of patients with HCM was longer than that of normal controls (441±36 vs. 394±24, p<0.001). The EMW of patients with HCM was more negative than that of normal controls (-51±35 vs. 7±19, p<0.001) (Figure 4).

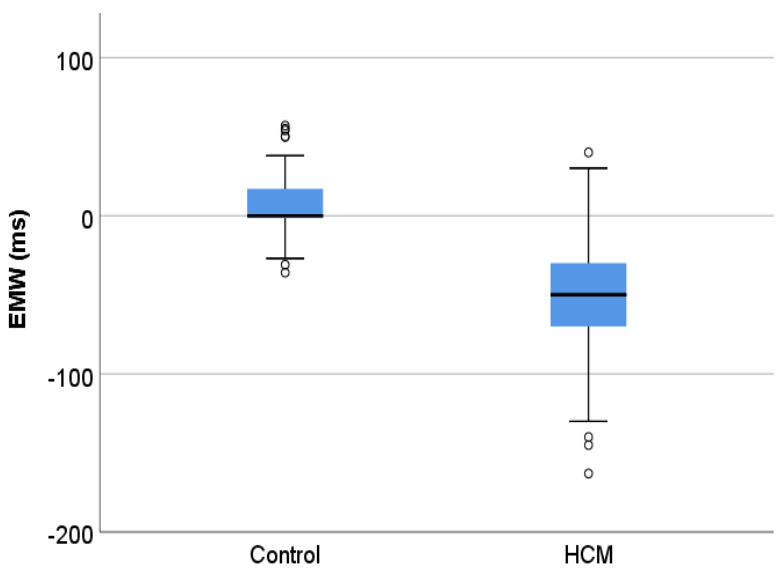
Table 2. Electromechanical window in normal control and patients with hypertrophic cardiomyopathy (age-sex matched ± 3yrs)

	HCM n=160	**Control** n=80	*p*
Age (years)	49.0±13.5	49.7±13.5	0.73
Sex (male)	124/160 (78%)	62/80 (78%)	1.0
QAC (ms)*	378±38	389±37	0.031
QT (ms)	428±48	382±35	<0.001
QTc (ms)	441±36	394±24	<0.001
EMW (ms)	-51±35	7±19	<0.001
Heart rate (/min)	65±12	65±13	0.787

EMW, corrected electromechanical window; HCM, hypertrophic cardiomyopathy

*QAC, time between Q wave and aortic valve closing

Figure 4. EMW in normal controls and patients with HCM



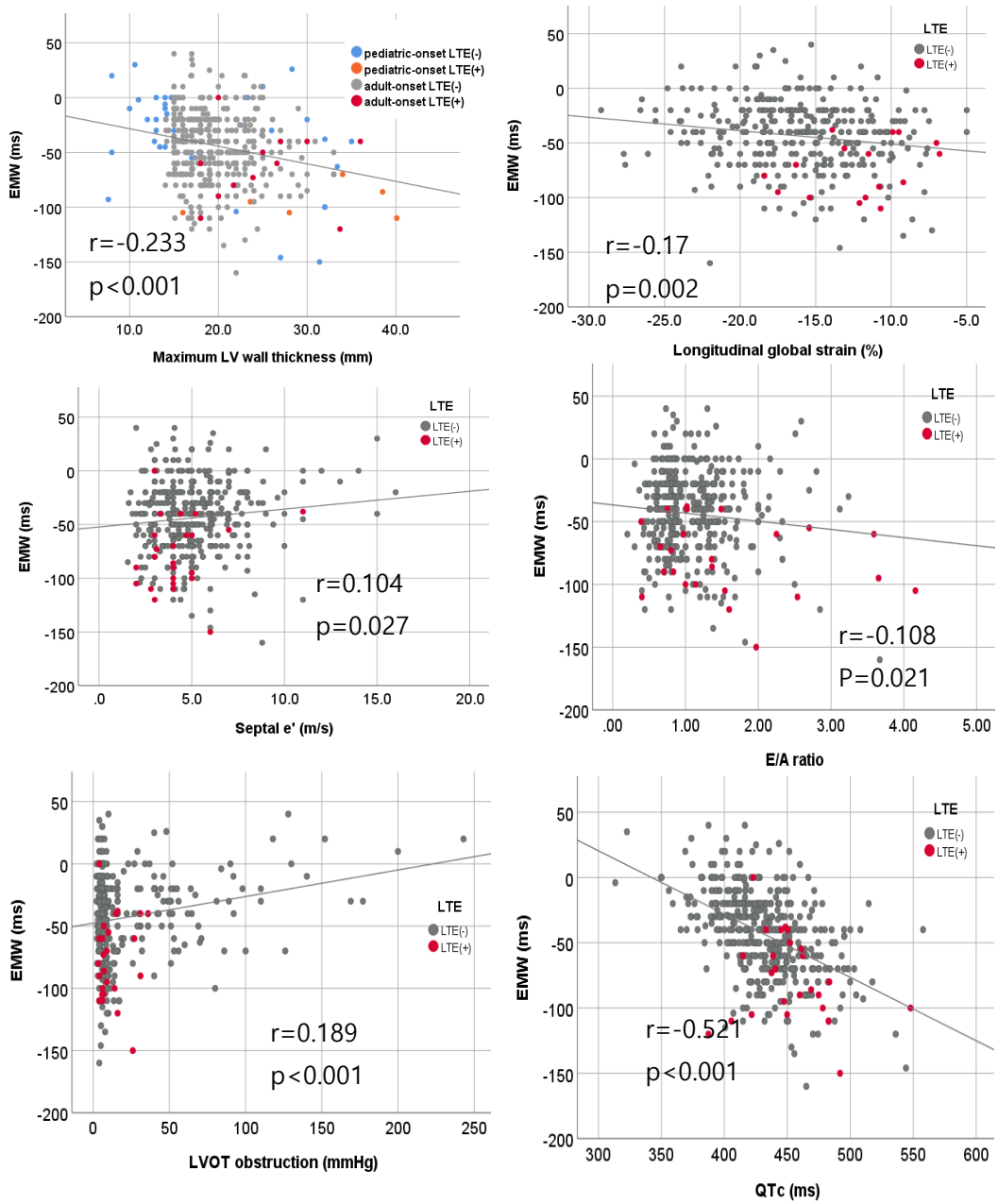
The EMW in patients with HCM had a more negative value than the EMW in normal controls (p<0.001).

3.2. EMW in 458 patients with HCM

The mean EMW in the 458 HCM patients was -44±33 ms. The mean QAC, QT, and QTc were 378±38 ms, 423±43, and 432±32 ms, respectively. The patients with extreme LVH had more negative EMW than those without (-66±40 ms vs. -43±31 ms, $p<0.001$). Decreased EMW was also significantly correlated with increased LVWT, worse left ventricular global longitudinal strain, decreased septal e', increased E/A ratio, lower LVOT peak pressure gradient on echocardiography and QTc (Figure 5). However, age, nonsustained VT, late gadolinium enhancement on magnetic resonance imaging, HCM subtype, hypertension, diabetes, atrial fibrillation during follow-up, sarcomere mutation positivity, and sex were not associated with EMW.

The optimal cutoff value of EMW to discriminate between patients with LTEs and those without LTEs was -54 ms. C-index of EMW was 0.726, indicating a good discriminatory power. The hazard ratio (HR) of EMW <-54 ms was 3.954 with a 95% CI of 1.511-10.350 ($p<0.001$).

Figure 5. Relationship between EMW and other parameters



The more negative EMW was correlated with increased maximum left ventricular wall thickness, worse left ventricular longitudinal global strain, decreased septal e', increased E/A ratio, decreased LVOT peak pressure gradient, and increased QTc.

LVOT=left ventricular outflow tract; EMW=electromechanical window

3.3. Life−threatening events

Twenty-five patients (5.5%) experienced LTEs. The characteristics of patients with LTEs are presented in Table 3. LTEs developed at the mean age of 36.0±22.6 years. Among patients with LTEs, seven had appropriate implantable cardioverter-defibrillator shock, eight had aborted sudden cardiac arrest, 10 had sustained VT, and five succumbed to sudden death.

Table 3. Clinical characteristics of patients with LTE and without LTE

Variables	LTE (n=25)	no LTE (n=433)
Age at diagnosis (year) *	27.8±21.3	51.0±18.5
Male	17 (68%)	287 (66%)
Apical HCM*	1 (4%)	156 (36%)
Non-sustained VT*	14 (56%)	92 (24%)
family history of SCD	5 (20%)	46 (11%)
Unexplained syncope*	10 (40%)	37 (9%)
LGE on MRI	14 (78%)	253 (84%)
QAC (ms)	374±37	379±38
QTc (ms) *	452±32	431±38
EMW (ms)*	-77±33	-42±31
Maximum LVWT (mm) *	26.7±7.0	19.3±4.2
LVOT obstruction①	3 (12%)	71 (16%)
<30mmHg	22	362
30-50 mmHg	3	27
>50 mmHg	0	44
Myectomy	2 (8%)	10 (2%)
Hypertension	5 (20%)	154 (36%)
Diabetes	2 (8%)	64 (15%)
Dyslipidemia*	2 (8%)	110 (26%)

① LVOT obstruction, left ventricular outflow obstruction with pressure gradient more than 30 mmHg.

AF	6 (24%)	36 (8%)
≥moderate LAE	13 (54%)	166 (38%)

Abbreviations as in Tables 1 and 2.

**p* value <0.05 on univariate analysis using Cox proportional hazard model.

Univariate analysis showed that LTEs occurred more frequently in patients diagnosed with HCM at a younger age and in those with non-apical HCM, unexplained syncope, increased QTc, decreased EMW, and extreme LVH (Table 4). EMW was more negative in patients with LTEs than in those without (-77±33 vs. -42±31, p<0.001, Figure 2B). QAC was not different between the two groups (374±37 vs. 379±38, p=0.578), but the QT and the QTc interval was longer in patients with LTEs than in those without LTEs (452±60 vs. 421±41, p=0.001, and 452±32 vs. 432±32, p=0.002, respectively). However, QT or QTc was not an independent risk factor when adjusted with other parameters whether or not including EMW. On multivariate analysis, EMW < -54ms, unexplained syncope, pediatric-onset HCM, and extreme LVH were significant risk factors for LTE.

On echocardiography, increased E/A ratio, decreased septal a', septal s', lower LVOT pressure gradient, and worse left ventricular global longitudinal strain emerged as risk factors for LTEs (Table 5).

When we combined EMW<-54 ms with the parameters of pediatric-onset, extreme LVH, syncope, and nonsustained VT, the HR were 17.1 (95% CI, 7.612-38.595), 12.9 (95% CI, 5.569-29.953), 7.1 (95% CI, 2.807-18.062), and 3.6 (95% CI, 1.581-8.166), respectively.

Medical treatment, such as beta-blockers or calcium channel blockers, was not associated with LTEs.

Table 4. Univariate and multivariate analysis of the risk factors for LTE

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*	HR	95% CI	*p* Value
Age at diagnosis	0.960	0.942-0.977	<0.001			
Pediatric-onset	8.717	3.948-19.244	<0.001	3.671	1.277-10.556	0.016
Male	1.063	0.458-2.464	0.887			
Non-Apical HCM	10.330	1.387-76.950	0.023			
Non-sustained VT	1.952	0.842-4.525	0.119			
FHx of SCD	1.520	0.561-4.119	0.410			
Unexplained syncope	4.964	2.211-11.144	<0.001	3.969	1.725-9.134	0.001
LGE on MRI	0.471	0.151-1.467	0.194			
QAC	0.997	0.987-1.007	0.575			
QTc	1.019	1.008-1.030	0.001			
EMW	0.984	0.973-0.963	<0.001			
EMW<-54ms	5.911	2.357-14.822	<0.001	3.954	1.511-10.350	0.005
Heart rate	1.006	0.976-1.037	0.703			
Extreme LVH*	10.299	4.617-22.974	<0.001	2.872	1.014-8.135	0.047
LVOT obstruction	0.995	0.975-1.016	0.646			
≥moderate LAE*	1.693	0.758-3.781	0.199			

AF = atrial fibrillation; EMW = electromechanical window; FHx = family history; HCM = hypertrophic cardiomyopathy; HR = hazard ratio; LAE = left atrium enlargement; LGE = late Gadolinium enhancement; LVOT = left ventricular outflow tract; LVWT = left ventricular wall thickness; QAC, time between Q wave and aortic valve closing; VT = ventricular tachycardia; SCD = sudden cardiac death

*Ventricular hypertrophy and left atrial enlargement were analyzed as categorical variables as this study included pediatric patients.

Table 5. Comparison of echocardiography parameters between patients with and without life threatening events

	LTE n=25	no LTE n=433	*p*
LV diastolic dimension (mm)	43.7±5.9	45.7±6.3	0.134
LV systolic dimension (mm)	26.8±6.4	27.0±5.0	0.824
Ejection fraction (%)	66.6±13.2	65.9±7.4	0.801
Deceleration time (ms)	200±85	215±73	0.324
E (m/s)	0.62±0.27	0.63±0.21	0.931
A (m/s)	0.47±0.19	0.65±0.23	<0.001
E/A	1.6±1.1	1.1±0.5	0.025
Septal e' (cm/s)	4.3±1.9	5.0±2.0	0.105
Septal a' (cm/s)	5.4±1.9	7.2±2.1	<0.001
Septal s' (cm/s)	5.5±1.2	6.6±1.5	0.001
E/e'	16.4±7.5	14±6.6	0.098
Global longitudinal strain (%)	-12.1±3.5	-16.1±4.4	<0.001
≥moderate LA enlargement*	44.7±9.0	43.0±7.3	0.379
LVOT peak pressure gradient (mmHg)	12.4±9.9	17.5±29.5	0.041

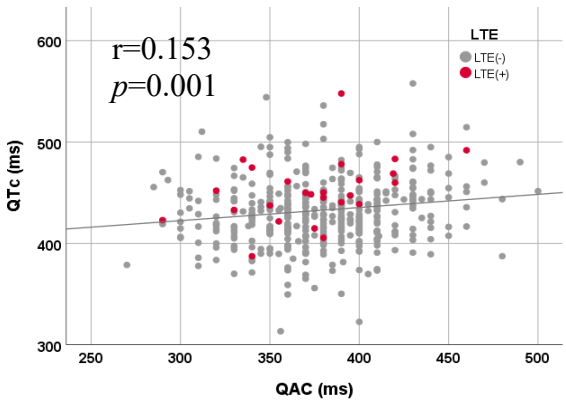
LTE = life threatening event; LA = left atrium; LV = left ventricle; LVOT = left ventricular outflow tract

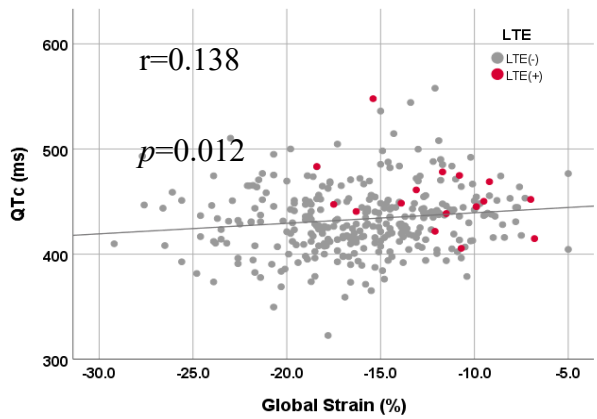
*left atrial enlargement were analyzed as categorical variables as this study included pediatric patients.

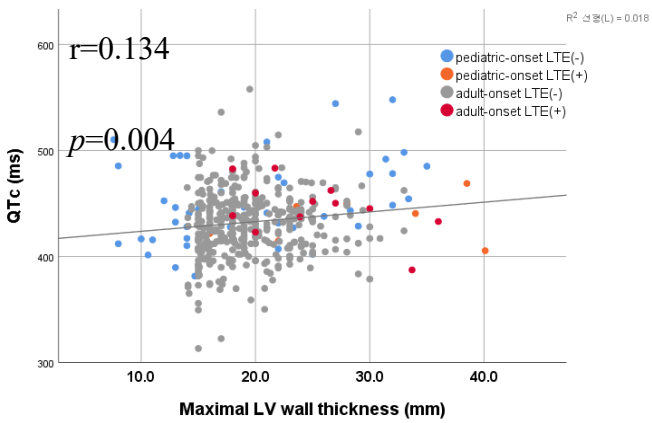
3.4. QTc and EMW as risk factors for LTEs

QTc was correlated with EMW, EMW, QAC, global strain, and maximum LV wall thickness (Figure 6).

<Figure 6> Relationship between QTc and QAC, global strain, and LV wall thickness







Increased QTc was associated with increased QAC, worse longitudinal global strain, and increased LVWT.

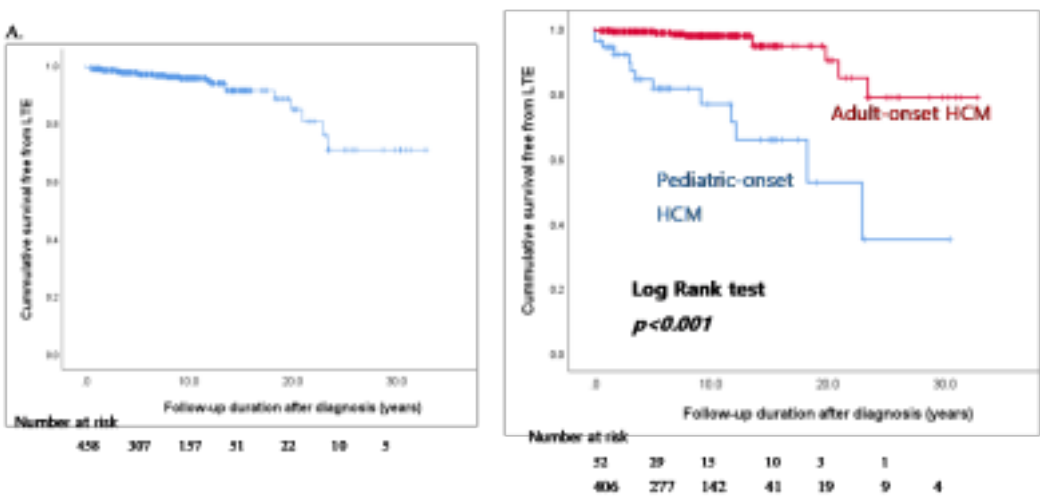
QTc was not associated with nonsusatined VT, late Gadolinium enhancement on MRI, syncope, family history of SCD, LVOT obstruction, E, A, E/A, E/e', and LA size.

QTc was a risk factor for LTE on univariate analysis (HR 1.019, 95% CI 1.008-1.030, p=0.001). However, on multivariate analysis with covariates of EMW and QTc, EMW was the only independent risk factor (HR 0.984, 95% CI 0.973-0.963, p<0.001).When we used QTc, EMW, QTc>450ms, EMW<-54ms as covariates on Cox proportional hazard model, EMW was the only independent risk factor for LTE (HR 0.973, 95% CI 0.963-0.984, p<0.001).

3.5. Subgroup analysis; pediatric-onset HCM vs. adult-onset HCM

Among the 25 patients with LTEs, 13 (52%) had pediatric-onset HCM. Patients with pediatric-onset HCM had a higher rate of LTEs than patients with adult-onset HCM (25% vs. 3%, p<0.001). Figure 8 shows the survival curve free from LTEs in all patients and according to time of diagnosis. Nine (17%) out of 52 patients with pediatric-onset HCM experienced SCD or aborted SCD. Non-apical HCM and severe LVH were more frequent in children than in adults (96% vs. 62%, p<0.001 and 40% vs. 2%, p<0.001, respectively). Non-sustained VT and late gadolinium enhancement on magnetic resonance imaging were more common in patients with adult-onset than pediatric-onset HCM (28% vs. 14%, p=0.026 and 86% vs. 63%, p=0.005, respectively). There was no difference between the two groups regarding EMW, sarcomere mutation, family history of SCD, LVOT obstruction, sex, or unexplained syncope.

<Figure 7> Kaplan-Meier estimate for free from life threatening events according to the onset age



Kaplan-Meier plot showing LTE-free survival during follow-up after HCM diagnosis in 458 HCM patients. B. Kaplan-Meier plot for LTE-free survival according to the onset age. Pediatric-onset HCM patients more frequently had LTEs (p<0.001).

In patients with pediatric-onset HCM (n=52), LTEs were associated with age at diagnosis, decreased EMW, non-sustained VT, unexplained syncope, and increased LVWT Z-score (Table 6). QTc, family history of SCD, late gadolinium enhancement on magnetic resonance imaging, and LVOT obstruction were not associated with LTEs. Patients with onset age at 5–14 years of age more frequently had LTEs than those with onset under 5 years of age (39% vs. 9%, p=0.019). Fourteen patients had genetically confirmed Noonan syndrome and had been diagnosed with HCM at a median age of 1.7 (range 0–9.4). One of them had appropriate implantable cardioverter-defibrillator shock, but Noonan syndrome was not associated with LTEs. In multivariate analysis, EMW <-54ms was the only risk factor for LTE in children (Table 8). C-index of EMW and corrected EMW by heart rate in pediatric-onset HCM were 0.738, and 0.832, respectively.

<Table 6> Risk factors for life threatening event in the pediatric-onset HCM patients.

	LTE n=13	no LTE n=39	total n=52	Hazard ratio (95% CI)	*p*
Age at diagnosis (year)	10.8±4.7	6.6±6.2	7.7±6.1	1.115 (1.019-1.220)	0.016
Age group * < 5 years	2 (9%)	20	29		
5-9 years	4 (36%)	7	11	6.378(1.126-36.127)	0.036
10-14 years	5 (42%)	7	12	6.879(1.308-36.187)	0.023
15-19years	2 (29%)	5	7	6.666(0.902-49.254)	0.063
Male	7 (54%)	28 (72%)	35 (67%)	0.345(0.103-1.15)	0.083
Apical HCM	0	2 (5%)	2 (4%)	0.047(0.000-)	0.731
NSVT	6 (46%)	1 (3%)	7 (14%)	3.499 (1.087-11.260)	0.036
Family history of SCD	2 (15%)	3 (8%)	5 (10%)	1.557(0.327-7.426)	0.578
Unexplained syncope	5 (39%)	2 (5%)	7 (14%)	5.840(1.811-18.828)	0.003

LGE on MRI	7 (64%)	10 (63%)	17 (63%)	0.733(0.205-2.617)	0.632
QAC (ms)[†]	384±30	367±39	371±38	1.004(0.990-1.019)	0.571
QTc	458±37	449±39	451±38	1.005(0.991-1.019)	0.527
EMW	-90±29	-33±38	-47±43	0.982(0.969-0.995)	0.006
EMW<-54ms	12 (92%)	8 (21%)	20(39%)	16.034(2.056-125.047)	0.008
corrected EMW (ms)	-85±23	-37±41	-49±43	0.981(0.9687-0.995)	0.008
LVWT Z-score	6.1±1.2	4.9±2.0	5.2±1.9	1.217(0.925-1.603)	0.161
Extreme LVH[‡]	9 (69%)	12 (31%)	21 (40%)	2.615(0.796-8.586)	0.113-
LVOT peak pressure gradient (mmHg)	11.6±8.3	16.1±18.7	15.0±16.8	0.978(0.949-1.019)	0.294
Myectomy	2 (15%)	3 (8%)	5 (10%)	1.261(0.274-5.793)	0.766
AF	1 (8%)	2 (5%)	3 (6%)	0.358(0.039-3.324)	0.366
GLS (%)	-12.5±3.2	-15.8±5.3	-14.7±4.9	1.056(0.885-1.261)	0.546
≥moderate LAE	3 (23%)	9 (23%)	12 (23%)	1.304(0.344-4.935)	0.696
Noonan syndrome	1 (8%)	13 (33%)	14 (27%)	0.176(0.023-1.353)	0.095

AF = atrial fibrillation; EMW = electromechanical window; HCM = hypertrophic cardiomyopathy; LAE= left atrium enlargement; LGE = late Gadolinium enhancement; LTE = life threatening event; LVOT = left ventricular outflow tract; LVWT = left ventricular wall thickness; MR = mitral regurgitation; NSVT = nonsustained ventricular tachycardia; SCD = sudden cardiac death;

[*] Onset age of 1-5 years was used as reference to compare the risk of LTEs between HCM onset age groups.

[†]QAC, time between Q wave and aortic valve closing

[‡] Extreme LVH was defined as an absolute maximal thickness Z-score ≥ 6.0.

In patients with adult-onset HCM (n=406), LTEs were associated with unexplained syncope, EMW, more than moderate left atrial enlargement, increased LVWT, and atrial fibrillation during follow-up (Table 7). In multivariate analysis, more than moderately enlarged left atrium, increased LVWT, and EMW <-54 ms were risk factors for LTEs in adults (Table 7). The C-index of EMW was 0.676 with adult-onset HCM.

<Table 7> Risk factors for life threatening event in the adult-onset HCM patients

	LTE n=12	no LTE n=394	total n=406	Hazard ratio (95% CI)	*p*
Age at diagnosis (year)	46.3±15.7	55.4±12.5	55.1±12.7	0.983(0.939-1.029)	0.459
Male	10 (83%)	259 (66%)	269 (66%)	2.738(0.598-12.532)	0.194
Apical HCM	1 (8%)	154 (39%)	155 (38%)	0.205(0.026-1.626)	0.134
NSVT	8 (67%)	91 (27%)	99 (28%)	2.520(0.699-9.080)	0.158
Family history of SCD	3 (25%)	43 (11%)	46 (11%)	1.815(0.479-6.883)	0.381
Unexplained Syncope	5 (42%)	35 (9%)	40 (10%)	4.858(1.511-15.621)	0.008
LGE on MRI (291)	7 (100%)	243 (86%)	250/291 (86%)	24.547(0.000-)	0.575
Myectomy	0	7 (2%)	7 (2%)	0.049(0.000-)	0.837
QAC	364±42	380±38	380±38	0.991(0.976-1.005)	0.213
QTc	446±26	430±31	430±31	1.018(0.999-1.036)	0.057
EMW	-64±33	-43±31	-44±31	0.981(0.964-0.998)	0.031
EMW<-54ms	7 (58%)	132 (34%)	139 (34%)	2.904 (0.917-9.199)	0.070
Maximal LVWT	25.0±5.9	19.3±3.7	19.5±4.0	1.184(1.079-1.300)	<0.001
LVOTO (>=30mmHg)	2 (17%)	64 (16%)	66 (16%)	1.401(0.300-6.536)	0.668
LVOT peak pressure gradient (m/s)	13.3±11.8	17.7±30.4	17.5±30.0	0.999(0.974-1.025)	0.949
≥moderate LAE	10 (83%)	159 (40%)	169 (42%)	6.458(1.413-20.511)	0.016
AF during follow-up	5 (42%)	32 (8%)	37 (9%)	3.682(1.118-12.130)	0.032
≥moderate MR	0	3 (1%)	3 (1%)	0.049(0.0-)	0.916
Hypertension	5 (42%)	154 (39%)	159 (39%)	1.055(0.331-3.362)	0.928
Diabetes	2 (18%)	63 (16%)	65 (16%)	1.314(0.275-6.294)	0.732
Dyslipidemia	2 (17%)	109 (28%)	111 (27%)	0.451(0.099-2.062)	0.305
Cancer	0	36 (9%)	36 (9%)	0.039(0-80.258)	0.405

Abbreviations as in Tables 6.

<Table 8> Multivariate analysis for the risk of LTE by subgroup

Pediatric-onset HCM

Multivariate analysis	Hazard ratio	95%C.I.	*p*
EMW<-54ms	15.042	1.908-118.562	0.010

Adult-onset HCM

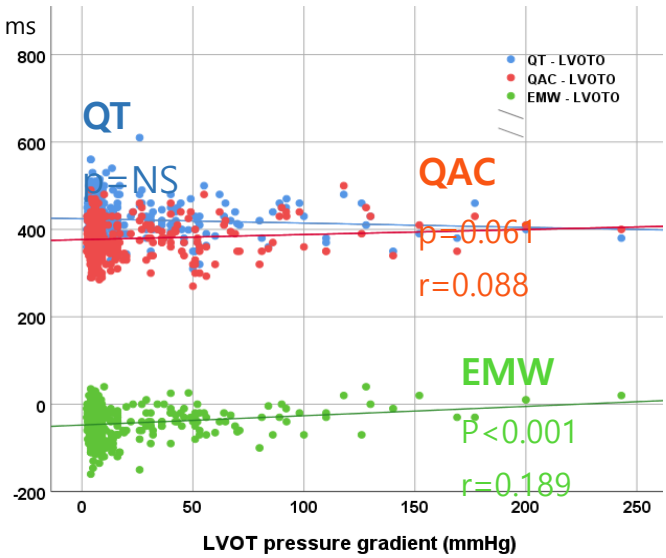
Multivariate analysis	Hazard ratio	95%C.I.	*p*
Moderate LAE	6.056	1.305-28.104	0.021
Maximal LVWT	1.185	1.071-1.310	0.001
EMW<-54ms	3.817	1.088-13.387	0.036

Abbreviations as in Tables 1.

3.6. LVOT obstruction and EMW

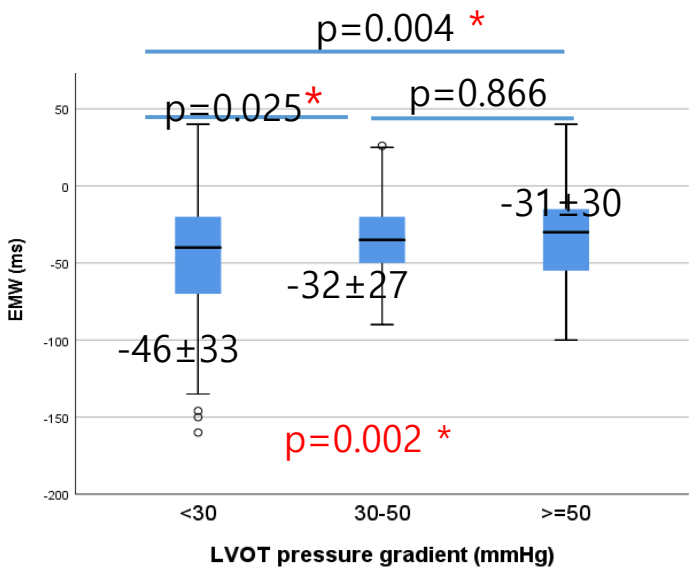
There were 71 patients (16%) with significant LVOT obstruction (LVOT peak pressure gradient >30mmHg). Among them, 44 patients had severe LVOT obstruction (peak pressure gradient >50mmHg). LVOT obstruction was associated with increased EMW ($p<0.001$) and increased tendency of QAC, although the correlation between LVOT obstruction and QAC did not reach statistical significance ($p=0.061$). On the other hand, QT interval was not related to LVOT pressure (Figure 9). LVOT obstruction was not associated with LTEs.

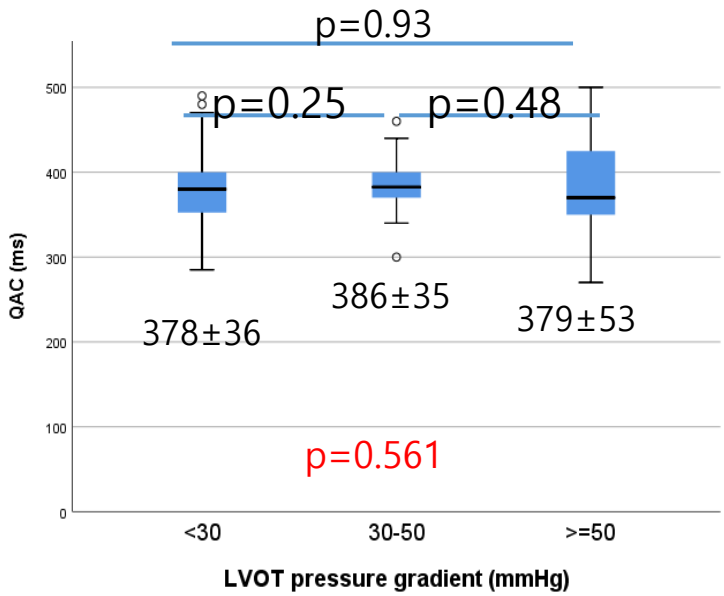
<Figure 8> QT, QAC, and EMW changes with LVOT obstruction



LVOT obstruction was associated with increased EMW (p<0.001). Increased LVOT pressure gradient had a tendency to be correlated with increased QAC, but it did not reach statistical significance (p=0.061).

<Figure 9> EMW and QAC according to the degree of left ventricular outflow tract obstruction





**p* value <0.05

Patients without LVOT osbtruction had significantly lower EMW than those with severe LVOT obstruction (LVOT pressure gradient >50mmHg) (p=0.002). QAC of patients without LVOT obstruction was lower than those with severe LVOT obstruction, but it did not reach statistical significance.

3.7. Results of genetic test

Of a total of 121 patients undergoing genetic testing, 49 (MYBPC3 in 28 patients, MYH7 in 7, TTN in 4, TNNI3 in 4, and others in 6) had pathogenic or likely pathogenic sarcomere gene mutation, 41 had variants of unknown significance, 17 had no mutation, and 14 had Noonan syndrome. EMW and QTc did not differ according to gene mutation type. Severe LVH was more frequent in patients with Noonan syndrome than the others (28% in patients with Noonan, 12% in patients with pathogenic sarcomere variants, 5% in patients with variant of unknown significance, and 0 in patients without mutation, p=0.032). Nonsustained

VT, family history of SCD or HCM were more common in patients with sarcomere mutation than in the others (40% vs. 22% (p=0.038), 23% vs. 9% (0.027), and 37% 8% (<0.001), respectively). Among the 121 patients who underwent genetic testing, patients with sarcomere mutation had a higher prevalence of LTEs than the others (17% vs. 1%, HR 12.8, 95% CU 1.598-102.665, p=0.016).

Chapter 4. Discussion

This study revealed that EMW has a negative value in patients with HCM, which was in clear contrast to that in normal controls. Furthermore, EMW was more negative in HCM patients with LTEs and EMW<-54 ms was an independent risk factor for LTEs with a hazard ratio of 5.9. These novel findings suggest that the increased arrhythmogenicity observed in HCM is associated with altered electromechanical coupling. EMW was also associated with extreme LVH, E/A ratio, septal e', and longitudinal global strain. Thus, it is conceivable that EMW reflects pathological changes in the myocardium that are associated with arrhythmic LTEs in patients with HCM.

EMW is the difference between the duration of electrical systole and mechanical systole. It was first introduced in the 1980s, and mechanical systole was measured indirectly by the time interval between the Q wave and the second heart sound (QS_2) at that time (6,16). In normal individuals, the QT interval is shorter than mechanical systole (QS_2), showing positive EMW. However, this relationship is inverted in patients with long QT syndrome (7,17), and negative EMW is related to mortality in patients with coronary artery disease and mitral leaflet prolapse (16,18).

QT prolongation is known as a risk factor for SCD in HCM (19,20). However, in this study, QTc was not an independent risk factor in multivariate analysis. van der Linde et al. studied the predictive value of EMW for arrhythmic events in a canine model (5). EMW decreased from 90 to 5 ms by beta-adrenoceptor stimulation, and in combination with potassium blockers, a large negative EMW (-109 ms) and torsades de pointes were induced. They observed

that during the short period of complete mechanical systole and incomplete electrical systole (during the window), aftercontractions were noted on LV pressure signal, followed by torsades de pointes. Torsades de pointes was prevented by atenolol or verapamil; however, this was mainly due to increased EMW, not QT interval reduction. Mechanical aftercontractions can cause myocardial afterdepolarization, and once above the threshold, afterdepolarizations trigger a premature ventricular complex resulting in the development of torsades de pointes (21,22).

This electrophysiologic mechanism suggests that profound negative EMW rather than QT prolongation is a significant risk factor for ventricular arrhythmia, as noted in this study. Even in the study of EMW in patients with long-QT syndrome, EMW was a better discriminator in patients with previous arrhythmic events than resting QTc (AUC of EMW 0.78 vs. AUC of QTc 0.70) (7,8).

Long QT syndrome is a primary electrical disease, but it also has altered ventricular mechanics (23). HCM is a myocardial disease, but it also involves electrophysiological disturbances, which can result in lethal ventricular arrhythmia (24). Recent studies suggested the central role of I_{NaL} in patients with HCM (18,24). I_{NaL} (late sodium current) functions during the plateau of the cardiac action potential. Generally, the magnitude of I_{NaL} is small, but in patients with HCM, the magnitude increased by 2- to 3-fold. It causes cytosolic Ca^{2+} overload and prolonged action potential duration and exacerbates susceptibility to triggered arrhythmias (25).

Patients with LTE had significantly lower LVOT pressure gradients in this study (12.4 vs. 17.5 mmHg, p=0.041). This finding differs from those reported in previous studies, which showed that severe LVOT obstruction is associated with sudden death (26). Furthermore, higher LVOT pressure gradients were associated with increased EMW, and patients with LVOT pressure gradient <30 mmHg had

more negative EMW than patients with pressure gradient >30 mmHg (-46±32ms vs. -32±29ms, $p<0.001$). Increased LVOT pressure gradient has a tendency to be correlated with increased QAC by Pearson correlation analysis, although it did not reach statistical significance ($p=0.061$), whereas QT was not correlated with LVOT obstruction ($p=0.164$ and $p=0.891$, respectively). We thereby speculated that increased mechanical systolic time (QAC) in patients with LVOT obstruction might increase EMW and lower the risk of ventricular arrhythmia. In more recently published multicenter studies of pediatric patients with HCM, patients without significant LVOT obstruction had an increased risk of SCD compared to that in those with stenosis, showing an inverse relationship (27,28), similar to our findings. The relationship between LVOT obstruction and EMW regarding SCD risk might require further investigation.

Sarcomeric mutation was significantly associated with SCD in patients with HCM compared to the mutation negative in previous studies (27,29), which was consistent in this study. However, genetic testing was mainly conducted in patients with severe LVH or family history of SCD or HCM. So these patients population who underwent genetic testing could have a selection bias.

Beta-blocker and calcium channel blocker were associated with a less negative EMW and prevented torsades de pointes in a canine model of drug-induced long QT syndrome (21). Beta-blocker treatment in patients with long QT syndrome also showed association with longer QAC and similar QT/QTc, resulting in reduced EMW negativity (7). However, in this study, beta-blocker treatment was not associated with a less negative EMW. Since this study was a retrospective study with medical records, it is thought that it is not clear whether the prescribed drug was taken at the time of echocardiography especially in a case with poor drug compliance.

HCM is a leading cause of SCD in young individuals, including competitive athletes. Previous studies have reported that children and young adults with HCM have an increased risk of SCD compared to that in adult patients (29-31), which was also true in this study. Patients with pediatric-onset HCM had several differences from adult patients in risk factors for LTEs as well as in the rate of LTEs in this study. Diffuse- or septal-type HCM and severe LVH were more frequent in children; however, non-sustained VT and late gadolinium enhancement on magnetic resonance imaging were more common in adults. Increased LA size and increased LVWT were significant risk factors for SCD in adults but not in children in this study. Pediatric patients with LTEs had more strongly related with EMW. When EMW was corrected by heart rate, c-index of corrected EMW was as high as 0.832 whereas c-index of EMW in adult patients was 0.676. Pediatric-onset HCM might have distinct differences from adult-onset HCM, and it has a poor prognosis, although the mechanism remains to be determined.

Clinical implications

Several risk factors for SCD have been identified, such as maximal LVWT ≥30 mm, non-sustained VT, family history of SCD, unexplained syncope, and delayed enhancement on cardiac magnetic resonance imaging (3), and there have been many studies on the risk stratification of SCD in HCM. The 2014 European Society of Cardiology proposed a risk prediction model for the primary prevention of SCD and provided the HCM Risk-SCD calculator to estimate the 5-year risk of SCD (9). However, these risk stratifications have limitations for discrimination between low- and high-risk patients for SCD (32,33), and in children and adolescents, only extreme LVH was consistently associated with lethal arrhythmic events, and others were not (28,34).

EMW was an independent risk factor for SCD on multivariate analysis in both pediatric-onset and adult-onset HCM patients as well as in the entire patient group. The cut-off value of EMW to identify patients with LTEs was -54ms with a hazard ratio of 5.9 and prediction power of EMW was as high as 0.738 of c-index. Furthermore, in patients with pediatric-onset HCM, corrected EMW had further increased prediction power.

EMW is a novel predictor of SCD in patients with HCM, and it is relatively easy to measure. Therefore, it can be a useful marker for risk stratification. However, further validation of EMW for SCD prediction in patients with HCM is necessary in the future.

Limitations

This study was limited by its retrospective nature. The QT interval was measured retrospectively in only one lead. Although there is a possibility of a longer QT interval in other leads, lead II is typically used as a reference lead for QT interval evaluation; hence, we used the QT interval of lead II in all patients and controls to calculate EMW.

This study could also have had selection bias, as it was based on tertiary referral center data, and it may not have included patients with mild symptoms or mild disease. Gene studies were conducted in only 27% of patients, and there may have been selection bias because only patients with severe disease phenotypes underwent genetic testing. Therefore, sarcomere mutation was not included in multivariate analysis for the SCD risk.

Chapter 5. Conclusion

This study showed EMW was a significant risk factor for the life threatening arrhythmic events in patents with HCM as well as its negativity in the patients with HCM, unlike normal individuals. EMW was also associated with extreme LVH, diastolic/systolic dysfunction

An EMW of <-54 ms was an independent risk factor for LTEs in patients with HCM. The EMW is a novel predictor of SCD in patients with HCM, and it is relatively easy to measure. Therefore, it can be a useful marker for risk stratification for SCD.

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요약

배경: 비후성 심근병증 (hypertrophic cardiomyopathy, HCM) 은 젊은 사람에서 급성심장사를 일으키는 주요 원인 질환으로 잘 알려져 있다. 이는 주로 심실 빈맥과 관련이 있는 것으로, 병리적인 심근변화가 전기생리학적 장애를 야기하는 것과 관련이 있을 것으로 생각된다.

목적: 본 연구에서는 비후성 심근병증 환자에서 전기-기계불일치 특성과 생명을 위협하는 사건 발생 (life threatening events, LTEs)과 전기-기계 불일치와의 관계를 규명하고자 하였다.

방법: 비후성 심근병증으로 진단받고 6 개월 이상 추척 관찰 중에 있는 1 세에서 80 세까지 환자에서 전기기계창 (electromechanical window, EMW) 을 구하여 평가하였으며, 전기기계창은 [Q 파 시작점 ~ 대동맥 판막 폐쇄시간]-QT 간격으로 구하였다.

결과: 평균 52.4±18.8 세의 458 명이 연구에 등록되었다. HCM 환자군의 EMW 를 나이/성별로 무작위적으로 짝지은 정상군의 EMW 와 비교하였을 때, 환자군의 EMW 가 더 음의 값을 보였다 (-51±35 vs. 7±19 ms, $p<0.001$). LTEs 는 25 명에서 발생하였으며 LTE 가 발생한 환자군의 EMW 가 LTE 가 발생하지 않은 환자군의 EMW 보다 음의 값을 보였다 (-77±33 vs. -42±31 ms, $p<0.001$). LTE 의 발생여부를 구분하는 EMW 의 cutoff 값은 -54ms 였으며 EMW 의 C-index 는 0.739 였다. 다변수 분석에서 LTEs 발생의 중요한 위험인자는 EMW-54ms, 실신, 소아연령 진단, 그리고 심한 심실비대였다.

결론: EMW 는 건강인에서 보다 HCM 환자에서 의미있는 음의 값을 보였으며, 환자군내에서 LTEs 가 발생한 환자들이 더 심한 음의 값을 보였다. EMW 는 비후성 심근병증 환자에서 급성 심장사를 예측하는 데에 유용하게 쓰일 수 있을 것으로 전망된다.