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Temporal variability of the electromechanical window in long-QT syndrome and drug-induced QT prolongation: Value for enhanced arrhythmia-risk assessment

Peter M. Deissler, MD,[1] Ann-Kathrin Rahm, MD,[1,2] Anat Berkovitch, MD,[3] Mara Elena Müller, MD,[2] Maurits Sikking, MD,[1] Stephane Heymans, MD, PhD,[1,4,9] Benedikt Langenberg, PhD,[5] Maximilian Moersdorf, MD,[6] Marina Rieder, MD,[7] Saranda Nimani, MD, PhD,[7] Katja E. Odening, MD,[7] Wolfgang Dichtl, MD, MSc,[8] Avi Sabbag, MD,[3] Paul G.A. Volders, MD, PhD,[1,9] Rachel M.A. ter Bekke, MD, PhD[1,9]

ABSTRACT

BACKGROUND Arrhythmia-risk assessment in congenital long-QT syndrome (LQTS) and drug-induced QT prolongation (diQTP) is primarily based on clinical, genetic, and electrical parameters. Electromechanical window (EMW) (aortic-valve closure time minus QT interval) assessment outperformed heart rate–corrected QT interval (QTc) as a predictor of symptomatic status in LQTS.

OBJECTIVE The study aimed to investigate the relationship between temporal QTc and EMW dynamics, and ventricular tachyarrhythmia (VT) timing in LQTS and diQTP.

METHODS 47 patients with LQTS/−VT, 18 patients with LQTS/+VT, 9 patients with diQTP/+VT, and 26 controls were included. QTc and EMW were obtained from standard 12-lead electrocardiograms and electrocardiogram-echocardiograms at 2 or 3 time points. Patients with +VT were included if EMW/QTc assessments were performed within 2 weeks before or after VT.

RESULTS In control subjects, EMW remained stably positive over time. In patients with LQTS/−VT, EMW was negative without significant variation. In patients with LQTS/+VT and diQTP/+VT, transient accentuations of EMW negativity were observed at the time point closest to VT (2 days [1–7] to arrhythmia), regardless of whether measured before or after VT. Temporary EMW negativity accentuation was driven by foreshortening of the mechanical systole despite concurrent QT prolongation. EMW recovery after VT was similar for patients with or without beta-blocker therapy. Multiple logistic regression analysis identified EMW negativity and EMW dynamics (ΔEMW) as independent predictors of imminent VT in LQTS. An EMW of −75 ms and a ΔEMW of −39 ms were optimal cutoffs to predict emergent arrhythmic deterioration in the LQTS cohort.

CONCLUSION Temporary accentuation of EMW negativity is a marker of impending VT in patients with LQTS and diQTP.

KEYWORDS Risk stratification; Long-QT syndrome; Drug-induced QT prolongation; Electromechanical window; Sudden cardiac death; Echocardiography

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From the [1]Department of Cardiology, Cardiovascular Research Institute Maastricht, Maastricht University Medical Center+, Maastricht, The Netherlands, [2]Department of Cardiology, Heidelberg Center for Heart Rhythm Disorders, Medical University Hospital Heidelberg, Heidelberg, Germany, [3]Leviev Heart Center, Sheba Medical Center, Affiliated with Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel, [4]Centre for Molecular and Vascular Biology, Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium, [5]Department of Methodology and Statistics, Maastricht University, Maastricht, The Netherlands, [6]Herz- und Diabeteszentrum Nordrhein-Westfalen, Universitätsklinik der Ruhr-Universität Bochum, Klinik für Elektrophysiologie–Rhythmologie, Bad Oeynhausen, Germany, [7]Translational Cardiology, Department of Cardiology, Inselspital, Bern University Hospital, Institute of Physiology – University of Bern, Bern, Switzerland, and [8]Department of Internal Medicine III, Cardiology and Angiology, Innsbruck Medical University, Innsbruck, Austria.

[9]Stephane Heymans, Paul G.A. Volders, and Rachel M.A. ter Bekke are members of the European Reference Network for Rare, Low Prevalence, and Complex Diseases of the Heart.

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Sudden cardiac death accounts for approximately half of all cardiac deaths and is primarily caused by ventricular tachyarrhythmia (VT) and fibrillation (VF).[1] Inherited channelopathies, such as congenital long-QT syndrome (LQTS), account for 5%–10% of sudden cardiac death cases; however, the annual arrhythmia risk in patients with LQTS is relatively low at 0.47%.[1–3] Drug-induced QT prolongation (diQTP) occurs more commonly and can be found in ~6% of patients treated with repolarization-delaying cardiac or noncardiac compounds. Less than 5% of patients with diQTP develop VT.[4]

Risk stratification in LQTS is primarily based on electrocardiogram (ECG) characteristics (prolongation of heart rate–corrected QT interval [QTc] and T-wave dynamics), torsades de pointes (TdP), syncope, sex, genotype, and family history.[5–7] Serial ECG assessment may further enhance risk stratification, given that QTc values in patients with LQTS fluctuate over time.[8,9]

The electromechanical window (EMW) is an ECG-echocardiographic parameter that indicates the relationship between repolarization duration and left ventricular (LV) contraction duration.[10] Previous studies have demonstrated that a single measurement of EMW outperforms the QTc in predicting the symptomatic status of patients with LQTS.[10–12] Patients with LQTS with a remote history of sudden cardiac arrest or TdP had a more negative EMW than those without, even for the same QT interval.[10–12] In addition, in a case report, profound EMW negativity was associated with life-threatening arrhythmic events in diQTP.[13] Whether accentuated EMW negativity in patients with LQTS/diQTP reflects an increased imminent risk of VT remains unknown. Here, we investigated the temporal variability of EMW in a large group of patients with LQTS and diQTP with documented VT, hypothesizing that EMW is more negative during episodes of electrical instability and arrhythmia. In addition, we examined whether accentuated EMW negativity and its change over time (ΔEMW) are associated with the timing of VT, to assess their potential for improving arrhythmia-risk prediction.

Abbreviations

AUC: area under the curve

diQTP: drug-induced QT prolongation

EMW: electromechanical window

ICD: implantable cardioverter-defibrillator

LCSD: left cardiac sympathetic denervation

LQTS: long-QT syndrome

QAoC: QRS-onset to aortic-valve closure time

TdP: torsades de pointes

VF: ventricular fibrillation

VT: ventricular tachyarrhythmia

Methods

Study design and criteria

Subjects were enrolled retrospectively from 6 centers across 5 countries, with a written informed consent obtained following the Declaration of Helsinki. Control subjects were recruited after cardiac abnormalities were excluded. LQTS was diagnosed according to the European Society of Cardiology Guidelines for the Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death,[1] and diQTP as transient QT prolongation during treatment with known repolarization-delaying drugs (https://crediblemeds.org/). Arrhythmic events (VT) were defined as documented TdP, VT, or VF. Patients with LQTS/diQTP/+VT were only included if echocardiography was performed less than 14 days before or after VT (Figure 1A). ECG and echocardiographic characteristics were assessed at 2 or 3 time points. According to this study design, the reference time point was set as the first time point for controls and LQTS/−VT and the time point closest to VT for LQTS/+VT and diQTP/+VT. Parameter changes between time points (Δ) were calculated as the mean of the change between available time points (see results section for details). Data will be shared by the corresponding author upon reasonable request.

QTc, QRS-onset to aortic-valve closure time, and EMW calculation

The QT time was determined from the single-lead ECG traces (usually lead II), which were recorded during apical aortic-valve Doppler echocardiography, and the tangent method was used to standardize QT assessment.[10] The QRS-onset to aortic-valve closure time (QAoC) was measured from the onset of the QRS complex to the center of the aortic-valve closure artifact. EMW was calculated by subtracting the QT time from the QAoC of the same heartbeat.[10] For EMW, no heart-rate correction was performed, given that EMW is heart rate independent.[10,14] For comparability of QT and QAoC over time, these parameters were rate corrected using Bazett's formula. Data were analyzed by 1 investigator (P.D.) and blindly reanalyzed in part by P.D. and R.t.B., showing high EMW intraobserver (0.99 [0.97–1.0]) and interobserver agreements (0.99 [0.96–1.0]).

Statistical analysis

Statistical analysis was performed with GraphPad Prism (GraphPad Software Inc, version 10.0.1) and R (version 4.4.1 [2024-06-14]). In Table 1, continuous data are presented as mean ± standard deviation or median (interquartile range). Statistical comparisons were performed using 1-way analysis of variance with Tukey's post hoc correction or the Kruskal–Wallis test with Dunn's post hoc comparison. Binary variables are shown as frequencies and percentages, and an omnibus Fisher's exact test, followed by pairwise Fisher's exact test with Bonferroni correction, was used. In Figure 1, a normal distribution of variables was assumed,[15] and a linear mixed model with random intercept analysis and Tukey post hoc correction was used. In Figure 2, the association between absolute time to event and EMW was assessed based on a linear mixed-effects model with a random intercept. Kruskal–Wallis test with Dunn's correction was used for comparisons of group Δ's. Single and multiple logistic regression were based on the "glm2" R-package, and the "pROC" package was used for area under the curve (AUC) and receiver operating characteristic analysis. A 2-sided $P < .05$ was considered

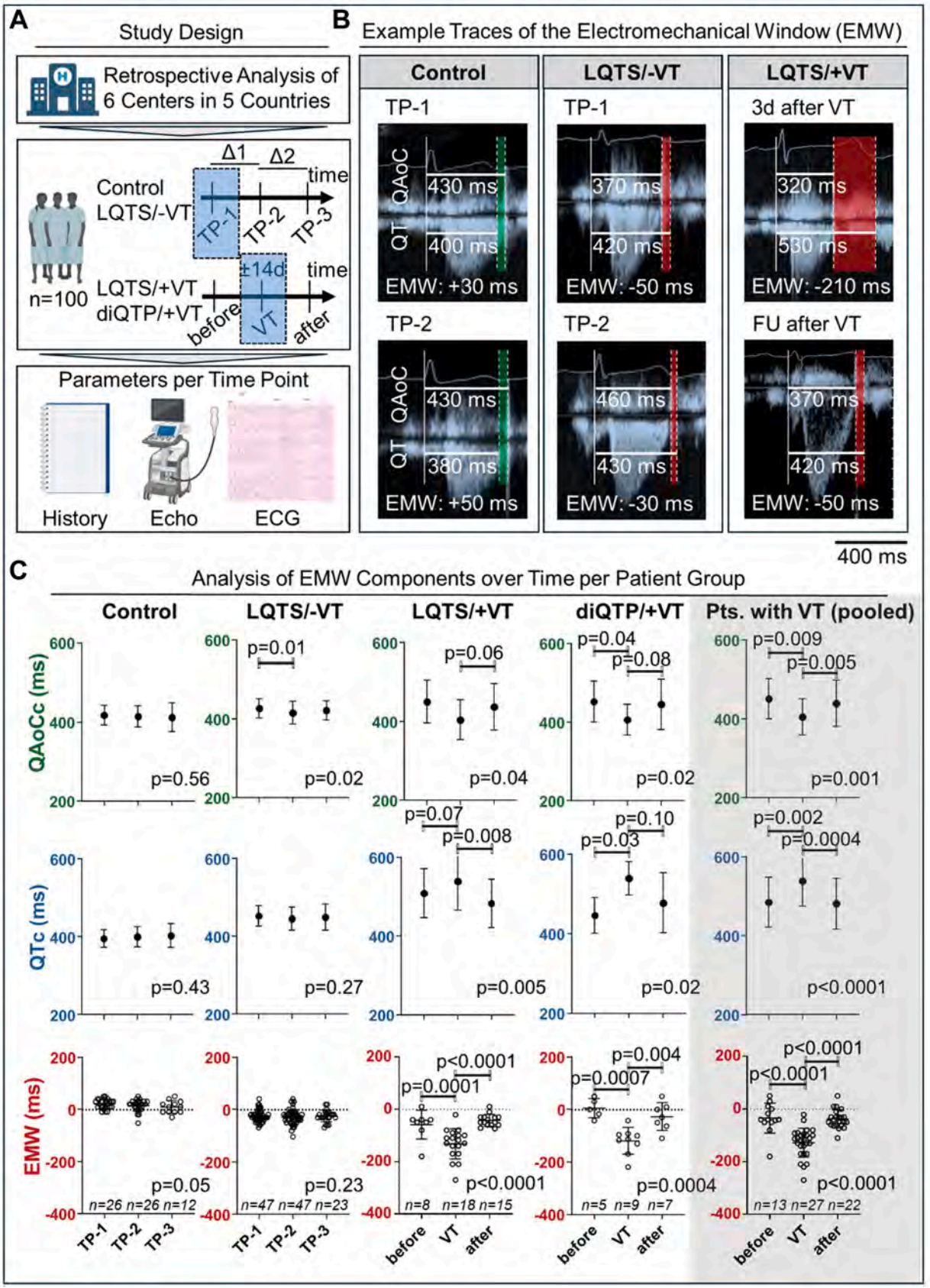


Figure 1

Temporal variability of the EMW and its components. **A:** Study design, FU scheme with up to 3 study TPs, and parameters assessed. Per patient, a minimum of 2 TPs were assessed, and parameter changes between TPs (ΔQAoCc, ΔQTc, and ΔEMW) were defined as the mean of Δ1 and Δ2. The reference time points are highlighted in *light blue*. **B:** For controls, patients with LQTS without VT during FU (LQTS/−VT), and patients with LQTS with VT during FU (LQTS/+VT), 2 representative

Table 1 Patient characteristics

	Controls	LQTS/−VA	LQTS/+VA	di-LQT/+VA
Number of patients	26	47	18	9
Age, ± y	44 ± 89	39 ± 14	40 ± 15	62 ± 16*,†,‡
Female sex, n (%)	18 (69)	30 (64)	15 (83)	7 (78)
Genotype, n (%)	n/a	LQT1: 18 (38) LQT2: 10 (21) LQT3: 17 (36) LQT7: 0 (0) Negative: 2 (4)	LQT1: 3 (17) LQT2: 5 (28) LQT3: 4 (22) LQT7: 3 (17) Negative: 3 (17)	n/a
ICD at first TP, n (%)	0 (0)	4 (9)	3 (17)	0 (0)
Prev. symptomatic at first TP, n (%)	0 (0)	19 (40)*	11 (61)*	1 (11)
AAD therapy at any TP, n (%)	3 (12)	29 (62)*	13 (72)*,†	6 (67)
β-blocker, n (%)	2 (8)	29 (62)*	13 (72)*	4 (44)
other, n (%)	1 (4)	3 (6)	2 (11)†	5 (56)†
QT-prolonging drugs at any TP, n (%)	0 (0)	0 (0)	5 (28)*,†	9 (100)*,†,‡
ECG				
RR interval, ms	909 ± 136	953 ± 183	842 ± 144	863 ± 170
QRS interval, ms	86 (82–91)	86 (80–95)	80 (75–92)	98 (84–105)
QT interval, ms	392 ± 27	439 ± 43*	524 ± 92*,†	492 ± 78*
QTc, ms	414 ± 22	454 ± 29*	570 ± 84*,†	516 ± 73*,†,‡
Echocardiography				
LVEF, %	63 (59–65)	61 (56–65)	60 (53–65)	42 (31–56)*,†
RR interval, ms	940 (788–1063)	910 (849–1020)	854 (750–1050)	781 (735–920)
QAoC interval, ms	400 (388–420)	400 (400–428)	376 (350–403)†	360 (325–415)†
QAoCc, ms	418 ± 25	427 ± 24	406 ± 50	407 ± 39
QT interval, ms	379 ± 32	435 ± 34*	512 ± 55*,†	487 ± 65*,†
QTc, ms	398 (390–408)	452 (434–461)*	541 (494–617)*,†	521 (506–587)*,†
EMW, ms	25 (10–33)	−30 (−40 to −10)*	−124 (−170 to −98)*,†	−113 (−150 to −94)*,†
Follow-up				
Total, d	1772 (1102–2512)	1906 (910–3114)	1613 (533–3056)	251 (38–1070)*,†
Time to VT, d	n.a.	n.a.	3 (1–9)	1 (1–7)

Clinical characteristics of the patients at the reference TP, if not specified otherwise. Data are shown as n (%), mean ± SD, or median (25th to 75th percentile). For controls and LQTS/−VT, the reference is defined as the first echocardiographic evaluation (TP-1 in Figures 1 and 2), for LQTS/+VT and diQTP/+VT, the reference is defined as the TP closest to VT (VT in Figures 1 and 2). For patients with VT during follow-up, the time elapsed from the reference point to VT is indicated under follow-up. Continuous data are shown as mean ± SD or median (IQR), and 1-way analysis of variance with Tukey post hoc test or Kruskal–Wallis test with Dunn's comparison was used. Binary variables are shown as frequencies and percentages, and an omnibus Fisher's exact test followed by pairwise Fisher's exact test with Bonferroni correction was used.

AAD = antiarrhythmic drug; diQTP = drug-induced QT prolongation; ECG = electrocardiogram; di-LQT = drug-induced long QT; EMW = electromechanical window; ICD = implantable cardioverter-defibrillator; IQR = interquartile range; LQT1 = LQTS type 1; LQT2 = LQTS type 2; LQT3 = LQTS type 3; LQT7 = LQTS type 7; LQTS = long-QT syndrome; LVEF = left ventricular ejection fraction; n/a = not available; QAoC = QRS-onset to aortic-valve closure time; QAoCc = rate-corrected QAoC by Bazett's formula; QTc = heart rate–corrected QT interval; SD = standard deviation; TP = time point; VA = ventricular arrhythmia; VT = ventricular tachyarrhythmia.

*$P < .05$ vs controls.

†$P < .05$ vs LQTS/−VT.

‡$P < .05$ vs LQTS/+VT.

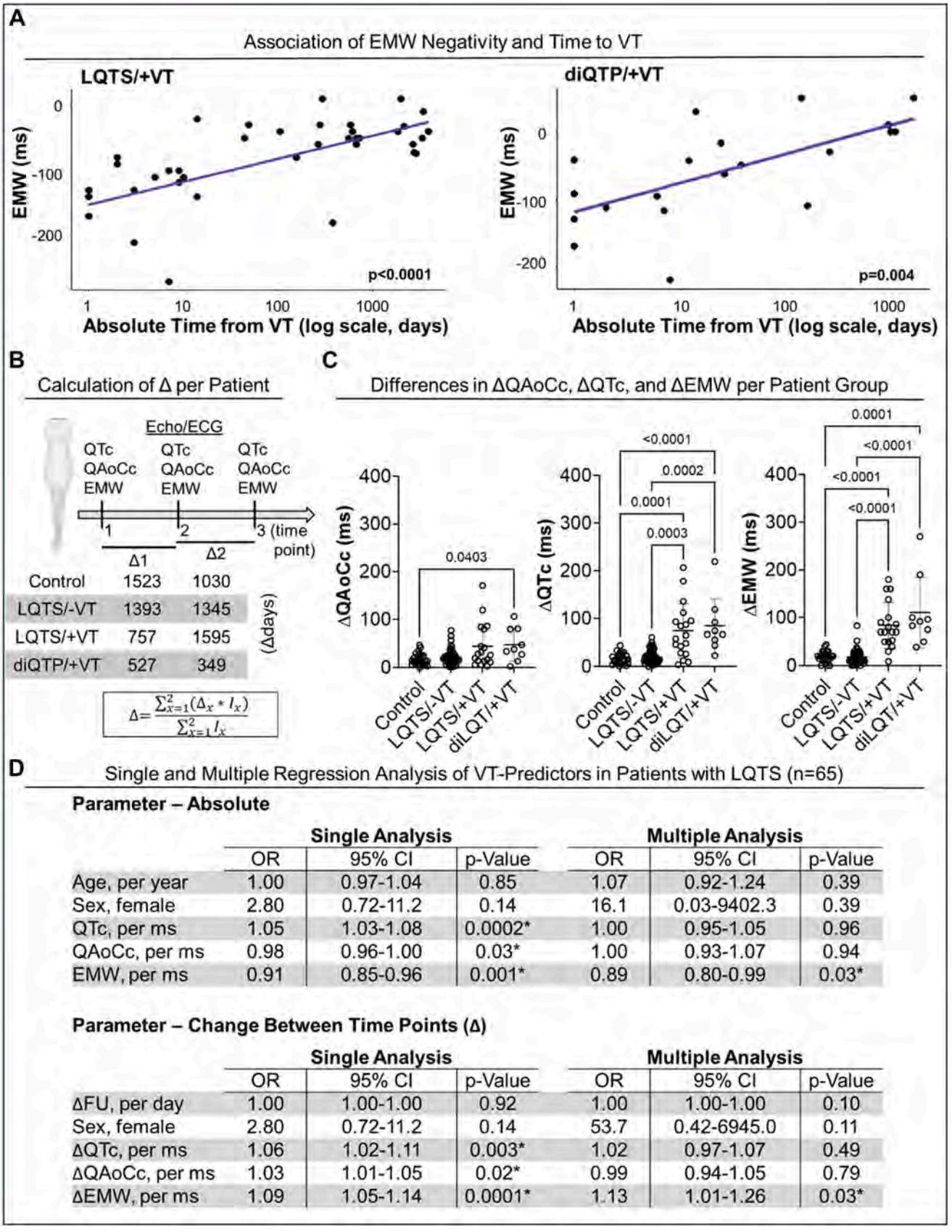
statistically significant. Additional details on the methods and statistical analyses are provided in the Online Supplement.

Results

The EMW differs between controls and patients with LQTS or diQTP, depending on symptomatic status

A total of 100 patients and control subjects with a median age of 42 years (interquartile range 27–57) and mean ± SD follow-up duration of 1869 ± 1360 days were included: 26 controls, 47 patients with LQTS without VT (LQTS/−VT), 18 patients with LQTS with VT (LQTS/+VT), and 9 patients with diQTP with VT (diQTP/+VT). 70% of all patients were female, and LQTS types 1–3 (LQT1–3) were the most common genotypes in LQTS/−VT (LQT1 38%; LQT2 21%; LQT3 36%; LQTS type 7 [LQT7] 0%; genotype-negative 4%) and LQTS/+VT (LQT1 17%; LQT2 28%; LQT3 22%; LQT7 17%; genotype-negative 17%). Overall, beta-blockers were used in 8% of

consecutive EMW measurements are depicted. EMW is calculated by subtracting the QT interval (lower *line*) from the QAoC interval (upper *line*). Note that the EMW is relatively stable in controls and LQTS/−VT, but shows exaggerated negativity in patients with LQTS/+VT close to VT, and becomes less negative again during FU. **C:** QAoCc and QTc are shown alongside EMW for each patient group. In patients with symptomatic diQTP/LQTS, exaggerated EMW negativity close to VT was composed of both a shortened mechanical systole (QAoCc↓) and a prolonged repolarization duration (QTc↑). The pooled analysis discussed in the text is highlighted in *light gray*. Data are shown as mean ± SD. diQTP = drug-induced QT prolongation; ECG = electrocardiogram; EMW = electromechanical window; FU = follow-up; LQTS = long-QT syndrome; QAoC = QRS-onset to aortic-valve closure time; QAoCc = rate-corrected QAoC; QTc = heart rate–corrected QT interval; SD = standard deviation; TP = time point; VT = ventricular tachyarrhythmia.



D Single and Multiple Regression Analysis of VT-Predictors in Patients with LQTS (n=65)

Parameter – Absolute

	Single Analysis			Multiple Analysis		
	OR	95% CI	p-Value	OR	95% CI	p-Value
Age, per year	1.00	0.97-1.04	0.85	1.07	0.92-1.24	0.39
Sex, female	2.80	0.72-11.2	0.14	16.1	0.03-9402.3	0.39
QTc, per ms	1.05	1.03-1.08	0.0002*	1.00	0.95-1.05	0.96
QAoCc, per ms	0.98	0.96-1.00	0.03*	1.00	0.93-1.07	0.94
EMW, per ms	0.91	0.85-0.96	0.001*	0.89	0.80-0.99	0.03*

Parameter – Change Between Time Points (Δ)

	Single Analysis			Multiple Analysis		
	OR	95% CI	p-Value	OR	95% CI	p-Value
ΔFU, per day	1.00	1.00-1.00	0.92	1.00	1.00-1.00	0.10
Sex, female	2.80	0.72-11.2	0.14	53.7	0.42-6945.0	0.11
ΔQTc, per ms	1.06	1.02-1.11	0.003*	1.02	0.97-1.07	0.49
ΔQAoCc, per ms	1.03	1.01-1.05	0.02*	0.99	0.94-1.05	0.79
ΔEMW, per ms	1.09	1.05-1.14	0.0001*	1.13	1.01-1.26	0.03*

Figure 2
Time dependence and regression analysis of electromechanical parameters. **A:** EMW negativity correlates with the absolute time from VT in patients with LQTS and diQTP during longitudinal FU in a linear mixed model with a random intercept. **B:** To determine parameter changes between time points, the ΔQAoCc, ΔQTc, and ΔEMW were calculated according to the depicted formula ("I" being the indicator of whether the Δ is available for this time interval or not). Mean Δdays are shown

controls (for hypertension), 62% of patients with LQTS/−VT, 72% of patients with LQTS/+VT, and 44% of patients with diQTP/+VT at any time point (Table 1). In the +VT group, 21 of 27 patients experienced TdP, 3 of 27 (bidirectional) VT, and 3 of 27 VF based on medical records or implantable cardioverter-defibrillator (ICD) readouts. EMW at the reference time point was 25 ms (10–33) in controls, −33 ms (−40 to −10) in LQTS/−VT, −124 ms (−170 to −98) in LQTS/+VT, and −113 ms (−150 to −94) in diQTP/+VT. For details, see Supplemental Figure 1.

The EMW is stable in controls and −VT patients, but dynamically rendered more negative in +VT patients close to arrhythmic events

Over time, the EMW remained stable and positive in controls and stable but negative in patients with LQTS/−VT (Figure 1B and 1C). In line with this, rate-corrected QAoC (QAoCc) and QTc remained unchanged between time points. In LQTS/−VT, QAoCc showed a small variation over time with stable QTc, which, however, did not result in significant EMW variability. In contrast, in patients with LQTS/+VT and diQTP/+VT, EMW became transiently and significantly more negative when assessed within days before or after VT (Figure 1B and 1C). In a pooled analysis of all patients with +VT, QTc (baseline 485 ± 63 ms; 555 days [1294–65] before VT) had prolonged significantly 2 days (1–7) after VT (545 ± 63 ms; $P = .002$) and returned to a baseline level during follow-up (482 ± 64 ms; $P = .0004$), 627 days (151–2677) after VT. In the same period, QAoCc (baseline 452 ± 51 ms) had dropped significantly close to VT (406 ± 46 ms; $P = .009$), returning to baseline (440 ± 59 ms; $P = .005$) in the follow-up period. Consequently, the EMW (baseline −35 ± 57 ms) became most negative close to VT (−128 ± 55 ms; $P < .0001$), returning to baseline values at follow-up (−38 ± 35 ms; $P < .0001$). When analyzing the LQTS/+VT and diQTP/+VT study groups separately, both showed similar changes in the electrical and mechanical components of EMW near the time of VT (see Online Supplement for details). In addition, at time points remote from VT, patients with LQTS/+VT had more negative EMW values than patients with LQTS/−VT (before VT [−584 days {−1543 to −212}] −45 [−73 to −40] vs −30 ms [−40 to −10]; $P = .009$; follow-up after VT [+722 days {276–2864}] −50 [−60 to −30] vs −30 ms [−40 to −10]; $P = .003$). Temporal EMW variability was similar for patients with LQTS with LQT1–3, patients with Andersen-Tawil syndrome (LQT7), or genotype-negative patients. Interestingly, absolute time from VT and EMW negativity was significantly associated for patients with LQTS/+VT ($P < .0001$) and diQTP/+VT ($P = .004$) (Figure 2A).

EMW restitution after VT is independent of beta-blocker therapy

In patients with LQTS/+VT (n = 4) not treated with beta-blockers before the event nor during follow-up, QAoCc was significantly shorter close to VT than at follow-up (391 ± 34 vs 416 ± 34 ms; $P = .03$). QTc was numerically longer close to VT than during follow-up (505 ± 54 vs 463 ± 49 ms; $P = .12$), and consequently, the EMW was more negative close to VT than during follow-up (−110 ± 26 vs −43 ± 14 ms; $P = .01$). Thus, EMW normalization during follow-up also occurred in the absence of beta-blocker therapy.

In the next step, we compared the 4 beta-blocker-naive patients with LQTS/+VT with 7 patients with LQTS/+VT who were initiated on beta-blocker therapy after the arrhythmic event (5 of 7 propranolol, 2 of 7 metoprolol). QAoCc, QTc, and EMW were similar between groups close to VT and during follow-up (2-way repeated measures analysis of variance with Sidak correction; see Online Supplement and Supplemental Figure 2).

Absolute EMW and EMW dynamics (ΔEMW) are independently associated with VT status in LQTS

Mean QAoCc, QTc, and EMW changes between time points (Δ) were quantified for every patient according to the formula shown in Figure 2B. In general, ΔQTc and ΔEMW were significantly larger in patients with LQTS/+VT and diQTP/+VT than in controls or patients with LQTS/−VT (Figure 2B and 2C). Patients with +VT of both LQTS and diQTP groups showed similar ΔQAoCc (27 [13–81] vs 38 ms [21–80]; $P = .99$), ΔQTc (62 [28–99] vs 67 ms [50–106]; $P = .99$), and ΔEMW (70 [50–110] vs 92 ms [63–145]; $P = .99$, respectively) (Figure 2C). A single logistic regression model (Figure 2D) for the patients with LQTS/−VT and LQTS/+VT (n = 65 patients) revealed that EMW ($P = .001$), QTc ($P = .0002$), and QAoCc ($P = .03$) were associated with VT status, but only EMW ($P = .03$) remained significant after multiple regression analysis. In a second model investigating parameter changes (Δ) over time, ΔEMW ($P = .0001$), ΔQTc ($P = .003$), and ΔQAoCc ($P = .02$) were predictors of VT status, but only ΔEMW ($P = .03$) remained significant after multiple regression analysis (Figure 2D). In a receiver operating characteristic analysis for identifying patients with LQTS/+VT, an AUC of 0.97 (confidence interval 0.89–1.00) for EMW was found, with a cutoff EMW of −75 ms (sensitivity 0.94; specificity 1.00). For ΔEMW, an AUC of 0.93 (confidence interval 0.82–1.00) was

for all groups. **C:** The analysis of Δ parameters per patient group revealed pronounced dynamicity in patients with VT during FU, especially for ΔQTc and ΔEMW (Kruskal–Wallis test with Dunn's comparison). **D:** 2 logistic regression models were created for the analysis of VT predictors in the LQTS cohort, one including the absolute parameter values measured at the reference time points (defined in Table 1) and the other including the mean Δ per parameter measured (defined in Figure 2B). These models only included the data from the LQTS cohort (47 patients with LQTS/−VT and 18 patients with LQTS/+VT). The analysis revealed that both the time-point value of QAoCc, QTc, and EMW and the Δ of values of these parameters were associated with the VT status in respective single logistic regression analyses. However, only the EMW and ΔEMW remained significant predictors of VT status in multiple logistic regression analysis. CI = confidence interval; diLQT = drug-induced long QT; diQTP = drug-induced QT prolongation; EMW = electromechanical window; FU = follow-up; LQTS = long-QT syndrome; OR = odds ratio; QAoCc = rate-corrected QRS-onset to aortic-valve closure time; QTc = heart rate–corrected QT interval; VT = ventricular tachyarrhythmia.

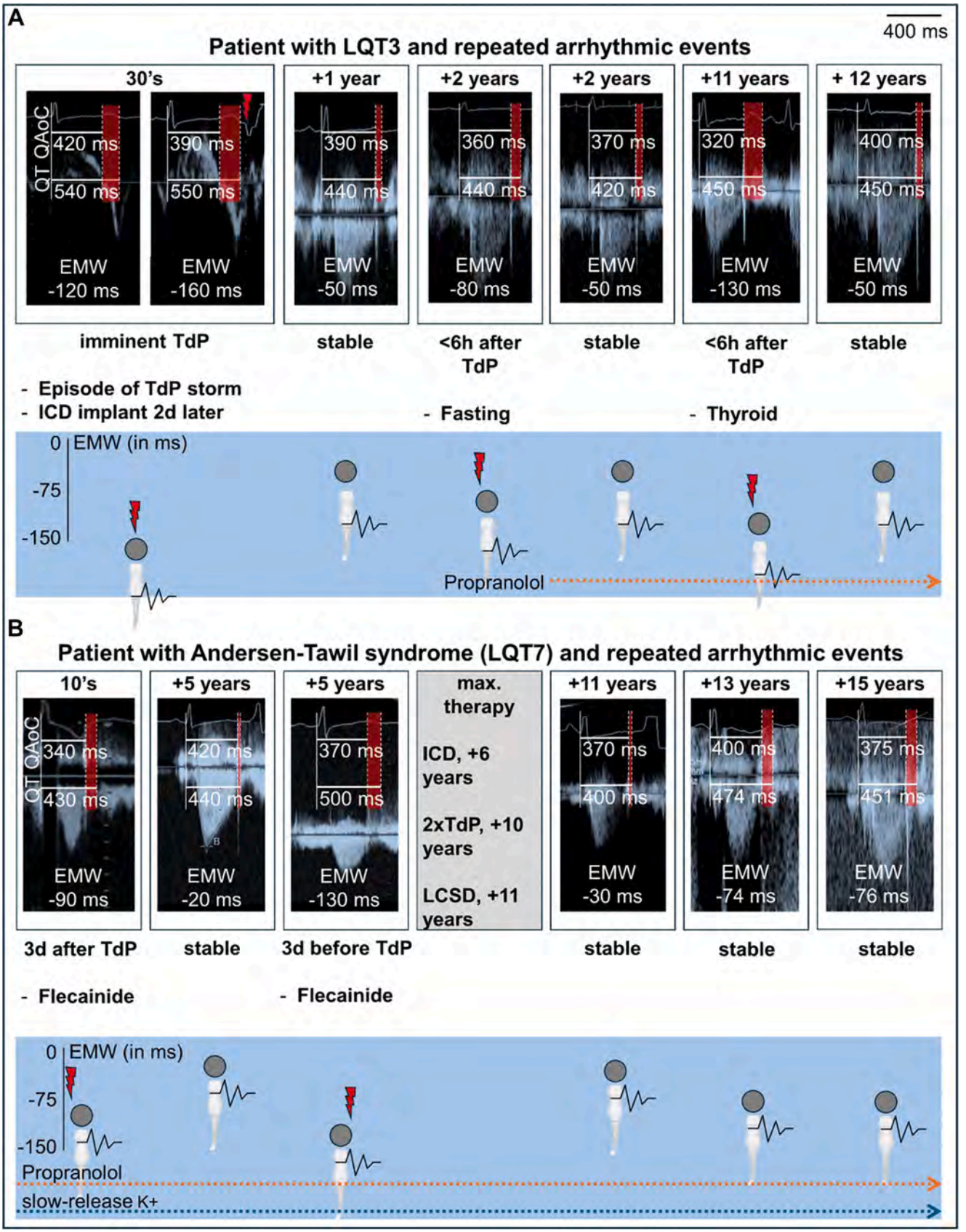


Figure 3

Examples of EMW temporal variability around moments of TdP in patients with highly symptomatic LQTS. **A:** In this patient with LQT3, TdP storm occurred, and TdP onset was coincidentally recorded with tissue-Doppler echocardiography, revealing a markedly negative EMW right before TdP induction (first panel: both 10 minutes before [left] and in the beat immediately preceding TdP onset [right]). During follow-up of >12 years, the patient experienced 2 adequate ICD shocks in the

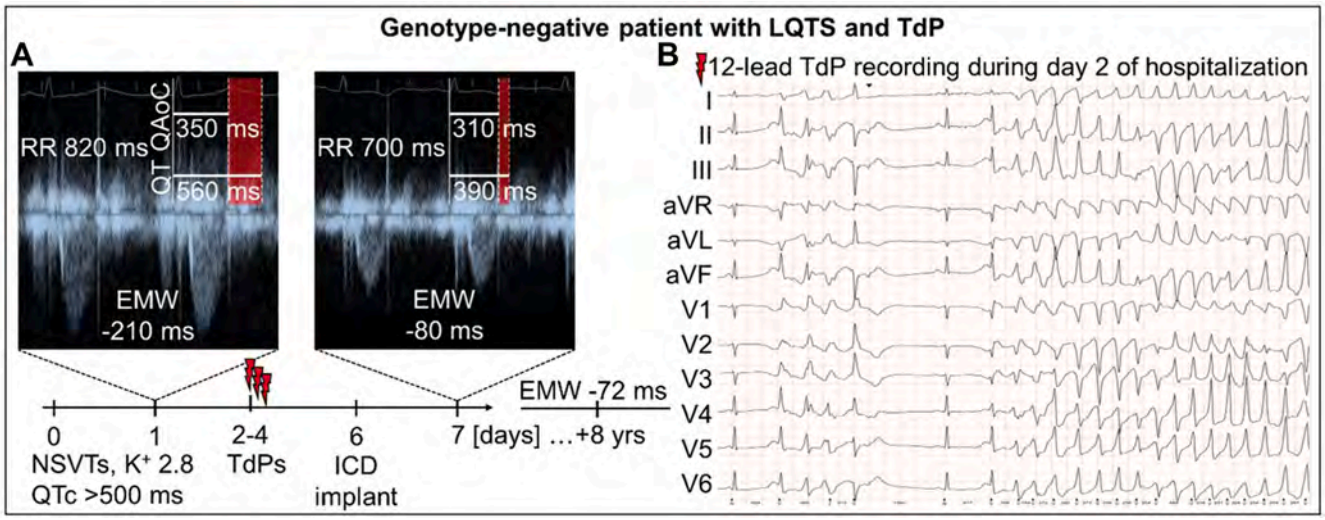


Figure 4
Transient EMW negativity preceding torsades de pointes in a patient with genotype-negative LQTS. **A:** In this patient with genotype-negative LQTS, EMW was −210 ms on admission to our center (day 1). During the following days (2–4), the patient experienced repeated episodes of nonsustained and sustained TdP. After clinical stabilization, the EMW had returned to significantly less negative values (day 7, −80 ms) and remained in this range during 8 years of follow-up without another arrhythmic episode. **B:** Classical TdP induction with a short-long-short sequence was observed during 12-lead electrocardiogram surveillance. This case demonstrates a clear correlation between exaggerated EMW negativity before TdP and EMW "recovery" during electrical stabilization. EMW = electromechanical window; ICD = implantable cardioverter-defibrillator; LQTS = long-QT syndrome; NSVT = nonsustained ventricular tachycardia; QTc = heart rate–corrected QT interval; TdP = torsades de pointes.

found, with a cutoff of −39 ms (sensitivity 0.89; specificity 0.96).

Representative cases with a high arrhythmic burden illustrate temporarily accentuated EMW negativity just before TdP

In a patient with LQT3 with VT storm and a history of major adverse cardiac events, TdP onset was coincidentally recorded with ECG-echocardiography, revealing a markedly negative EMW of −120 ms approximately 10 minutes before TdP onset in the absence of ventricular ectopy and an EMW of −160 ms in the last sinus-rhythm beat before TdP. The latter may have been accentuated by a preceding short-long sequence (Figure 3A, Supplemental Figure 3).[10] Years later, this patient experienced 2 appropriate ICD shocks for TdP, each coinciding with another transient exaggeration of EMW negativity. During clinically stable periods, EMW was consistently less negative at −50 ms (Figure 3A).

In a case of a patient with symptomatic LQT7 with a high burden of premature ventricular complexes (PVCs) and repeated episodes of nonsustained VT, flecainide therapy was started. The patient was admitted shortly thereafter with recurrent episodes of TdP, prompting flecainide discontinuation. The EMW was assessed 3 days later (−90 ms) and returned to more positive values during follow-up (Figure 3B). Several years later, ajmaline provocation testing demonstrated effective PVC suppression, and flecainide was restarted. 1 month later, routine ECG-echocardiography showed an LV ejection fraction of 45%, with again a markedly negative EMW (−130 ms). 3 days afterward, the patient developed polymorphic VT and TdP, leading to the discontinuation of flecainide and ICD implantation. After 2 additional arrhythmic events years later, the patient underwent left cardiac sympathetic denervation, which led to a substantial reduction in PVC burden and complete suppression of TdP. The patient has remained free from TdP or any sustained VT, and LV ejection fraction remained at >50% thereafter (Figure 3B). During event-free survival, the EMW gradually became more negative, approaching the values measured close to the first TdP episode. However, ΔEMW was much lower during this stable period (2–44 ms) than surrounding the episodes of TdP (70–110 ms), which supports our contention that, apart from absolute EMW negativity, temporal EMW dynamics also provide important information about the underlying arrhythmia risk.

Finally, a patient with genotype-negative LQTS in their 40s was admitted to a peripheral hospital (day 0) and transferred to our center for further evaluation. ECG-echocardiography revealed an extremely negative EMW of

context of a fasting period and hyperthyroidism, both coinciding with transient exaggeration of EMW negativity measured on the day of the event. **B:** In this teenager patient with LQT7, flecainide therapy was initiated twice for premature ventricular complex suppression. Flecainide therapy led to a transient exaggeration of EMW negativity, and polymorphic VT/TdP occurred. Interestingly, a markedly negative EMW was found 3 days before TdP occurred. *Gray circles* indicate EMW value at the time of measurement; ECG/echocardiography icons indicate points of EMW assessment, whereas the *lightning icon* marks the occurrence of TdP/VT relative to ECG-echocardiography. Both examples demonstrate that accentuated EMW negativity develops before VT and is not a post hoc phenomenon occurring in the aftermath of severe arrhythmia. CI = confidence interval; ECG = electrocardiography; EMW = electromechanical window; ICD = implantable cardioverter-defibrillator; LCSD = left cardiac sympathetic denervation; LQT3 = LQTS type 3; LQT7 = LQTS type 7; LQTS = long-QT syndrome; OR = odds ratio; QAoC = QRS-onset to aortic-valve closure time; TdP = torsades de pointes; VT = ventricular tachyarrhythmia.

−210 ms (day 1) (Figure 4A). Subsequently, the patient experienced multiple nonsustained and sustained TdPs (days 2–4), of which one also deteriorated into VF (day 4; see example 12-lead ECG TdP onset of the patient in Figure 4B). Electrical stabilization of the patient coincided with a rapid EMW increase to −80 ms (day 7), and EMW remained within this range during 8 years of event-free follow-up (last EMW −72 ms).

Discussion

In the setting of ventricular repolarization prolongation, TdP occurs under dynamic rather than static conditions. Electrical instability and emergent ventricular ectopy precede sustained arrhythmia.[16,17] This study demonstrates that transient mechanical changes (QAoCc↓) parallel electrical alterations (QTc↑), and mark pending VT in patients with LQTS and diQTP. Consequential temporary accentuation of EMW negativity is an independent marker for imminent VT in patients with LQTS and is superior to QTc or its long-term variability (ΔQTc). These findings suggest that periodic noninvasive EMW monitoring to detect these changes provides significant added value for arrhythmia-risk stratification beyond the repeated determination of QTc.

Mechanical abnormalities in patients with LQTS were first described by Nador et al[18] in the 1990s, who observed an abnormal systolic contraction phase in patients with LQTS, which was attributed to abnormal intracellular Ca^{2+} handling.[19,20] In addition, an abnormal relationship between electrical and mechanical systole was found in patients with LQTS, which was accentuated by exercise testing, indicating the central role of the autonomic nervous system.[21] Apart from the overall EMW assessment,[11,12] exercise-induced variability in EMW has been observed in patients with LQTS, particularly in those who were previously symptomatic.[22]

The interplay of multiple (partially concealed) factors that align at a critical moment to provoke arrhythmic events may also lead to accentuated EMW negativity. Although acute drivers of arrhythmic instability are often unknown in patients with congenital LQTS, drug-mediated rapid delayed rectifier potassium current block serves as a dominant factor in patients with diQTP, whether or not against a background of repolarization lability by other causes.[23] To improve arrhythmia prediction in patients with LQTS and diQTP, the change of EMW (ΔEMW) around moments of TdP was investigated. Our analysis demonstrates that ΔEMW is an independent predictor of imminent arrhythmia risk, with an optimal cutoff of −39 ms over time, yielding a sensitivity of 0.89 and a specificity of 0.96. Interestingly, patients with LQTS and diQTP with pending TdP, VF, and/or bidirectional VT showed remarkable similarity in the temporal variability of the EMW and its components. This suggests that the mechanisms driving EMW negativity and arrhythmogenesis partly overlap. These drivers likely involve electromechanical reciprocity, meaning that transient changes in both electrics and mechanics can influence each other.[2] For example, early and delayed afterdepolarizations may lead to mechanical abnormalities such as postsystolic shortening, aftercontractions, and dispersion of contraction,[24,25] whereas primary mechanical abnormalities (eg, acute afterload increases during exercise) may, in turn, precipitate repolarization instability in susceptible myocardium.[2,26] In addition, episodes of increased sympathetic activity and pause-dependent potentiation may transiently accentuate electromechanical dispersion. Such episodes may vary among individuals, as exemplified by interindividual differences in adrenergic responsiveness and neural regulation of the heart, even among patients harboring the same pathogenic gene mutation.[27] Experimental work in a canine drug-induced LQT1 model showed that left-stellate ganglion stimulation led to accentuated EMW negativity (and TdP initiation) owing to divergent autonomic effects on electrics (QT) and mechanics (QAoC).[10,28] Conversely, beta-blocker treatment and left-stellate ganglion denervation rendered EMW less negative in patients with LQTS, reducing TdP occurrence.[10,11,29] Our results suggest that EMW normalization during follow-up cannot be solely attributed to the initiation of beta-blocker therapy after ventricular arrhythmia, given that a comparable reduction in EMW negativity was observed in beta-blocker-naive patients, albeit with different absolute values. Furthermore, electrolyte imbalance (eg, hypokalemia, hypomagnesemia) can impair electromechanical stability.[1,2] Finally, abnormal gene regulation, or proarrhythmic drug effects influencing ion-channel function and/or trafficking, may further aggravate electromechanical instability in susceptible patients, ultimately facilitating TdP.[23,30] Quantifying this accumulation or coincidence of transient functional abnormalities in the heart is challenging, which further highlights the need for integrated parameters such as the EMW for dynamic risk assessment.

In the present study, EMW was assessed within 2 weeks of the arrhythmic event (median 2 days [1–7] to arrhythmia), given that ECG-echocardiography was typically performed during the clinical workup after TdP. This raises 2 questions: (1) Is EMW negativity a cause or consequence of ventricular arrhythmia? (2) What is the timescale of the EMW change? To address the first issue, we have carefully reviewed cases with ECG-echocardiography just before the occurrence of VT (Figures 3 and 4), revealing that pronounced EMW negativity precedes the arrhythmia, confirming experimental data.[12,26] Therefore, accentuated EMW negativity may add to the substrate for TdP. Regarding the second question, changes in autonomic tone or short-long-short sequences may modulate the EMW within seconds to minutes,[22,31] whereas myocardial remodeling associated with disease progression influences EMW over longer timescales.[32,33] Although unknown for LQTS and diQTP, significant EMW negativity was already observed 79 days (21–192) before VT occurred in ICD carriers with mostly ischemic or dilated cardiomyopathy.[33]

Ultimately, the findings of the present study raise the question of whether—and, if so, which—preventive measures should be implemented when a large EMW drop is

found in a patient with LQTS or other susceptible patients. Although prospective trials are needed to answer this question, it seems reasonable to speculate that this finding should trigger a thorough investigation of potential underlying and addressable causes (eg, electrolyte imbalance, new [QT-prolonging] medication, insufficient beta-blocker adherence). In addition, prospective trials should investigate which methods of continuous EMW monitoring (eg, photoplethysmography combined with repolarization monitoring) provide further insights into electromechanical dynamics under various conditions.[10]

Limitations

The patient number in this retrospective study was relatively small, and follow-up intervals varied among subjects, limiting the assessment of the speed of change of the parameters, which would be available in a prospective study. However, given that repeated ECG-echocardiographic analyses are not routinely performed in patients with LQTS in most clinics, our dataset provides unique insights into the temporal variability of EMW. Although the number of 9 patients with diQTP/+VT was low, we have established the presence of exaggerated and dynamic EMW negativity for the first time, indicating that EMW assessment besides classic 12-lead ECG testing may provide additional insights into the arrhythmic risk of this patient category.

Conclusion

While temporal stability characterizes the EMW of control subjects and patients with asymptomatic LQTS, EMW negativity is temporarily accentuated in patients with LQTS/diQTP with pending VT, and this is driven by both electrical and mechanical changes. Noninvasive EMW monitoring outperforms QTc in determining recent arrhythmia occurrence in patients with LQTS and diQTP and may improve the prediction of imminent TdP, thus facilitating preventive management.

Data availability

Data will be shared upon reasonable request and after legal assessment by the corresponding author (R.t.B.).

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this manuscript, the authors occasionally used ChatGPT (chatgpt.com) for language editing. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article. Figures were partially created with a licensed version of BioRender.com.

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Appendix

Supplementary data

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Address reprint requests and correspondence: Dr Rachel ter Bekke, Department of Cardiology, Cardiovascular Research Institute Maastricht, Maastricht University Medical Center+,

P.O. Box 5800, 6202 AZ Maastricht, The Netherlands. E-mail address: rachel.ter.bekke@mumc.nl

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