Electromechanical Window and Spontaneous Ventricular Tachyarrhythmias in Takotsubo Syndrome

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QT interval prolongation is common in patients hospitalized with Takotsubo syndrome (TTS), however, only a minority experience ventricular tachyarrhythmias. Our aim was to characterize the electromechanical window (EMW) in patients with TTS and to evaluate its association with ventricular tachyarrhythmias. We preformed aretrospective analysis of 84 patients hospitalized with TTS in the Tel-Aviv Medical Center between 2013 and 2022. All patients underwent a comprehensive echocardiographic evaluation and the EMW was calculated by subtracting the QT interval from the QRS onset to the aortic valve closure obtained from a continuous-wave Doppler for the same beat. Of the 84 patients with TTS, 74 (88%) were female and the mean age was 70 ± 11 years. The mean left ventricular ejection fraction was 42 ± 8%. The EMW was negative in 81 patients (96%), and the mean EMW was −69 ± 50 ms. Ventricular tachyarrhythmias occurred in 7 patients (8%). The EMW of patients who experienced ventricular tachyarrhythmias was more negative than patients who did not (−133 ± 23 ms vs −63 ± 48 ms, p = 0.001). In the univariate analysis, EMW and QT were associated with ventricular tachyarrhythmias (univariate odds ratio [OR]$_{EMW}$ 1.03, 95% confidence interval [CI] 1.01 to 1.05, p = 0.003 and univariate OR$_{QTc}$ 1.02, 95% CI 1.01 to 1.03, p = 0.02); however, only EMW remained significant in the multivariate analysis (OR$_{EMW}$ 1.03 95% CI 1.03 to 1.05, p = 0.023). EMW was more effective than corrected QT interval in identifying patients who had ventricular tachyarrhythmias (AUC$_{EMW}$: 0.89, 95% CI 0.82 to 0.97 vs AUC$_{QTc}$ 0.77, 95% CI 0.61 to 0.93, p = 0.02), and a cut-off value of −108 ms was predictive of ventricular tachyarrhythmias with a sensitivity of 86% and a specificity of 79%. In conclusion, EMW is negative in patients with TTS and is associated with increased risk for ventricular tachyarrhythmias. The role of EMW in the risk stratification of patients with TTS warrants further investigation. **(Am J Cardiol 2024;210:100−106)**

Keywords: Takotsubo syndrome, EMW, ventricular tachyarrhythmias

Takotsubo syndrome (TTS), also known as stress-induced cardiomyopathy, is an acute cardiac syndrome typically characterized by chest pain, transient regional wall motion abnormalities, electrocardiographic changes, and a modest troponin increase in the absence of culprit obstructive epicardial coronary artery disease.[1] Acute complications can be severe, including cardiac arrest and a 4% to 5% in-hospital mortality rate.[2,3] Within the first 24 to 48 hours of presentation, most patients develop repolarization abnormalities, including diffuse T-wave inversions and QT interval prolongation, the latter often being quite pronounced.[4] These mechanisms can precipitate ventricular tachyarrhythmias in susceptible patients, although their exact contribution to arrhythmogenesis remains obscure.[5] Additional mechanisms, including electromechanical triggers, appear relevant; however, they are yet to be fully elucidated. A measure of electrical−mechanical interaction is the electromechanical window (EMW), defined as the difference between the interval from QRS onset to the aortic valve closure (QAoC), as determined by continuous-wave Doppler and the QT interval from the electrocardiogram (ECG), for the same beat (Figure 1).

In healthy subjects, repolarization is completed before the termination of mechanical systole, resulting in a positive EMW.[6] In contrast, patients with congenital long QT syndrome display a reversal of this sequence and repolarization is completed after mechanical systole, generating a negative EMW.[7] Such negative EMW has been associated with life-threatening arrhythmias,[8] and a correlation was also observed in patients with drug-induced long QT syndrome[9] and hypertrophic cardiomyopathy.[10]

Despite the increasing recognition of TTS as a cause of acquired long QT syndrome,[5,11] the EMW of patients with TTS had not been previously described, and its relation to ventricular arrhythmias remains largely unknown.

Our aim was to characterize the EMW in patients with TTS and to evaluate its association with ventricular tachyarrhythmias.

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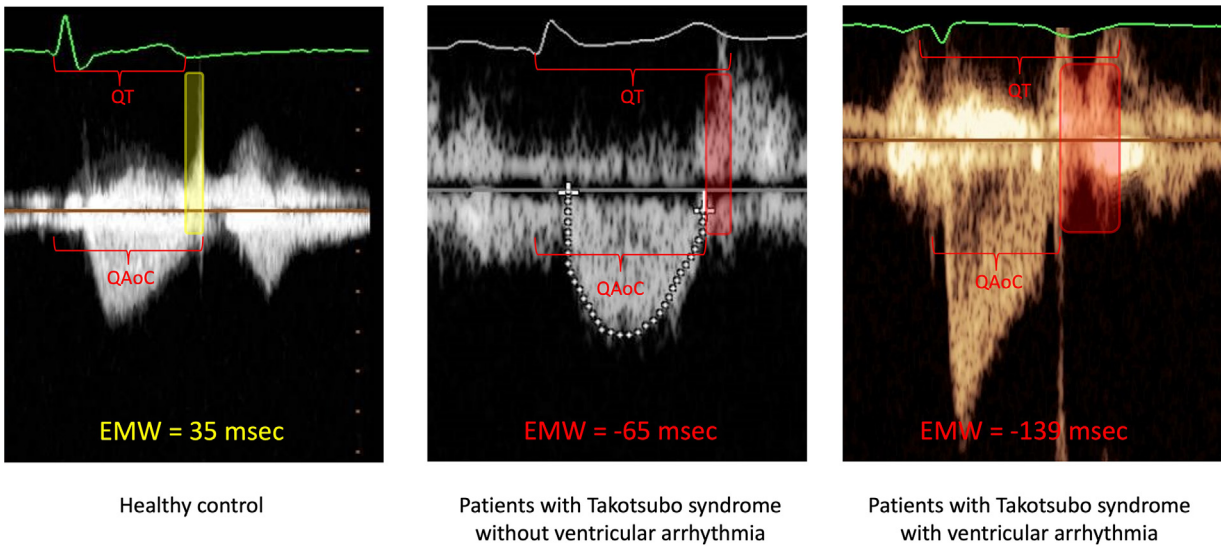


Figure 1. EMW calculation as derived from a continuous-wave Doppler image of the left ventricular outflow tract and a single-lead ECG for the same beat. EMW is positive in a healthy control (*left panel*). EMW turns negative in a patient with TTS without ventricular tachyarrhythmia (*middle panel*), and becomes more negative in a patient who experienced ventricular tachyarrhythmia during hospitalization (*right panel*).

Methods

We performed a retrospective analysis on 126 patients hospitalized with TTS at the Tel-Aviv Medical Center between June 2013 and January 2022. The diagnosis of TTS was made in accordance with the revised Mayo Clinic diagnostic criteria[12,13] and required patients to have (1) transient dyskinesia of the left ventricle extending beyond a single epicardial vascular distribution, (2) the absence of an obstructive coronary artery disease or absence of angiographic evidence of an acute plaque rapture, (3) new ECG abnormalities or modest troponin increase, and (4) the absence of pheochromocytoma and myocarditis. The ethics committee of the Tel-Aviv Medical Center approved the study (institutional review board number TLV-0323-21) as a deidentified retrospective analysis and voided the need for written informed consent.

Of the 126 patients with an initial diagnosis of TTS, 42 patients were excluded because of the following reasons: 3 patients had no angiography, 4 patients had no echocardiographic evaluation, and, in 35 patients, the single-lead ECG tracing recorded at the time of the echocardiographic evaluation did not allow a precise measurement of the QT interval, precluding EMW calculation. Thus, our final cohort included 84 patients with an established TTS diagnosis.

The baseline ECG tracings were recorded upon presentation to the emergency department or soon after symptom onset in already hospitalized patients. Follow-up ECG tracings were recorded daily throughout the course of hospitalization. QT was automatically calculated by the ECG software (Marquette 12 SL algorithm [GE Healthcare, Chalfont, United Kingdom] version 241 [150 Hz sampling rate] [MAC 5,500]). For quality assurance, the QT interval was manually measured in 17 ECG tracings (20%) by an electrophysiologist experienced in QT measurement using the tangent method.[14] This validation showed a high agreement between the QT intervals automatically obtained with those manually measured (Pearson correlation 0.92, p <0.01). To avoid over- and underestimation of corrected QT interval (QTc),[15] we used the Bazett formula[16] for patients with a heart rate ranging from 60 to 100 beats/min. For all other patients, the Fridericia formula[17] was used.

All patients underwent a comprehensive echocardiographic evaluation (CX 50, Philips Medical Systems, Bothell, Washington) performed by an echocardiography technician and analyzed by senior cardiologists experienced in echocardiography interpretation, in accordance with current guidelines.[18]

For the EMW calculation, we reviewed continuous-wave Doppler images of the left ventricular outflow tract recorded in the apical 5-chamber view and a concomitant single-lead ECG tracing. The EMW was calculated by subtracting the QT interval from the QAoC interval for the same beat. The QAoC and QT intervals were measured by 2 investigators who were blinded to the patient's outcomes. The intraobserver and interobserver correlation coefficients were 0.92 (95% confidence interval [CI] 0.90 to 0.94, p <0.001) and 0.91 (95% CI 0.86 to 0.94, p = 0.02), respectively.

Continuous variables were tested for normality using histograms, quantile-quantile plots, and the Shapiro−Wilk test. Normally distributed continuous variables were compared using the Student's *t* test and expressed as mean ± SD. Non-normally distributed continuous variables were compared using the Whitney−Mann test and expressed as the median (interquartile range). Categorial variables were compared using the Fisher's exact test and expressed as numbers and percentiles. To assess the independent association of EMW with ventricular tachyarrhythmias, a multivariate logistic regression model was used. With the exception of age that was forced into the model, variables with p <0.05 in a univariate analysis were selected for consideration for the multivariate regression model. To detect collinearity, correlation factor analyses were used, and variables were considered highly correlated if R >0.7. The results of the univariate and multivariate regression models

Table 1
Baseline characteristics

	n=84	No Ventricular arrhythmic events n=77	Ventricular arrhythmic events n=7	p
Demographics				
Age, mean±SD, years	70.3±10.7	70.3±11.2	72.6±6.1	0.609
Female gender, n (%)	74 (88.1)	69 (89.6)	5 (71.4)	0.194
BMI,mean±SD, Kg/m^2	24.78±3.6	24.8±3.6	23.7±3.3	0.438
Comorbidities				
Hypertension, n (%)	44 (52.4)	39 (50.6)	5 (71.4)	0.437
Hyperlipidemia, n (%)	29 (34.5)	28 (36.4)	1 (14.3)	0.413
Diabetes mellitus, n (%)	15 (17.9)	13 (16.9)	2 (28.6)	0.603
Smoker, n (%)	25 (29.8)	22 (28.6)	3 (42.9)	0.42
Obesity, n (%)	8 (9.5)	8 (10.4)	0 (0)	1
Ischemic heart disease, n (%)	14 (16.7)	11 (14.3)	3 (42.9)	0.087
Congestive heart failure, n (%)	2 (2.4)	1 (1.3)	1 (14.3)	0.161
Atrial fibrillation, n (%)	12 (14.3)	11 (4.3)	2 (28.6)	0.295
CVA/TIA, n (%)	6 (7.1)	6 (7.8)	0 (0)	1
Chronic renal failure, n (%)	4 (4.8)	3 (3.9)	1 (14.3)	0.299
Neurological disease, n (%)	3 (3.6)	2 (2.6)	1 (14.3)	0.232
Psychiatric disease, n (%)	13 (15.5)	12 (15.6)	1 (14.3)	1
Trigger				
None	25 (29.8)	25 (32.5)	0 (0)	0.098
Physical	26 (31)	20 (26)	6 (85.7)	0.003
Emotional	33 (39.3)	32 (41.6)	1 (14.3)	0.237
Laboratory at presentation				
Creatinine, median [IQR], mg/dL	0.83 [0.7-0.98]	0.83 [0.69-0.95]	1.27 [0.83-2.77]	0.012
Potassium, mean±SD, mmol/L	4.09±0.5	4.1±0.5	4.3±0.9	0.513
Magnesium, mean±SD, mg/dL	2.01±0.4	1.9±0.2	2.5±1.1	0.269
Calcium, mean±SD, mg/dL	8.95±0.81	8.9±0.8	8.7±0.8	0.453
Troponin-I, median [IQR], ng/L	1218 [317-2972]	1218 [332-2834]	2565 [74-9309]	0.784

BMI = body mass index; CVA = cerebrovascular accident; IQR = interquartile range; SD = standard deviation; TIA = transient ischemic attack.

are expressed as odds ratios (ORs) and the corresponding 95% CI. A receiver operating curve analysis was used to evaluate the predictive value of EMW for ventricular tachyarrhythmias. The optimal threshold value of EMW predictive of ventricular tachyarrhythmias was calculated using the Youden index. All statistical calculations were performed using SPSS version 28.0. The $p < 0.05$ were considered statistically significant.

Results

The baseline characteristics of the 84 patients with confirmed TTS included in the final analysis are listed in Table 1. The mean age was 70 ± 11 years and 74 the patients (88%) were women. Hypertension was the most common co-morbidity, followed by hyperlipidemia and a history of past or present smoking. An emotional trigger was identified in 33 patients (39%), a physical trigger in 26 patients (31%), and no trigger in 25 patients (30%).

The baseline ECG variables are listed in Table 2. Sinus rhythm was the presenting rhythm in 78 patients (93%) and the mean heart rate was 82 ± 19 beats/min. T-wave inversion in precordial leads was the most frequent abnormality, followed by left bundle branch block and ST elevation in leads V_1 to V_3 (37 [44%], 13 [15%], and 9 [11%], respectively). The mean QT interval was 412 ± 63 ms and the mean QTc interval was 473 ± 47 ms.

The median time to formal echocardiographic evaluation and EMW calculation was 1 day (1 to 2). The mean left ventricular ejection fraction was 42 ± 8% and the mean EMW was −68.9 ± 50.5.

A total of 7 patients (8%) experienced at least 1 ventricular tachyarrhythmia during hospitalization, of whom, 4 patients had Torsades de pointes, 2 patients had sustained monomorphic ventricular tachycardia, and 1 patient had ventricular fibrillation (Supplementary Table 1). In 4 patients, ventricular arrhythmia was the presenting symptom, whereas in the remaining 3, the arrhythmia occurred within 24 hours of admission. In-hospital mortality occurred in 4 patients (4.8%), although arrhythmia accounted for none of these deaths.

The patients' echocardiographic and electrocardiographic characteristics obtained during EMW calculation are listed in Figure 2, Table 3. No significant difference was observed between patients who experienced ventricular tachyarrhythmias to those who did not (448 ± 56 ms vs 452 ± 51). However, when corrected for heart rate (QTc), the interval was longer in patients with tachyarrhythmias (482 ± 53 ms vs 538 ± 62 ms, $p = 0.011$). Furthermore, patients who experienced arrhythmic events had a shorter QAoC (384 ± 43 ms vs 319 ± 46 ms, $p < 0.001$) and a more negative EMW (−63 ± 48 ms vs −133 ± 23, $p < 0.001$).

In-hospital mortality occurred in 4 patients. Although none of the mortalities was attributed to arrhythmia, a higher mortality rate was observed in patients who had arrhythmic events (3% vs 29%, $p = 0.033$). These patients also exhibited a higher incidence of cardiogenic shock, acute heart failure, and mechanical ventilation (Figure 3).

Table 2
ECG characteristics at presentation

Variable	n=84	No ventricular arhythmic events n=77	Ventricular arrhythmic events n=7	p
NSR, n (%)	78 (92.9)	73 (94.8)	5 (71.4)	0.076
Heart rate, mean±SD, beats/min	81.7±19.5	81.8±20	81±15.3	0.915
Atrial fibrillation, n (%)	6 (7.1)	4 (5.2)	2 (28.6)	0.076
QRS, mean±SD, msec	94.5±25.2	92.7±23	114.3±40	0.207
RBBB, n (%)	1 (1.2)	1 (1.3)	0 (0)	1
LBBB, n (%)	13 (15.5)	10 (13)	3 (42.9)	0.071
NSIVCD, n (%)	2 (2.4)	1 (1.3)	1 (14.3)	0.161
Anterior ST elevation, n (%)	9 (10.7)	9 (11.7)	0 (0)	1
Inferior ST elevation, n (%)	5 (6)	4 (5.2)	1 (14.3)	0.36
Lateral ST elevation, n (%)	6 (7.1)	6 (7.8)	0 (0)	1
ST depression, n (%)	2 (2.4)	2 (2.6)	0 (0)	1
T wave inversion, n (%)	37 (44)	33 (42.9)	4 (57.1)	0.694
QT, mean±SD, msec	412.2±63.3	408.8±58.8	463.9±85.7	0.025
QTc, mean±SD, msec	471.3±46.7	467.6±42.4	537.4±49.1	<0.001

LBBB = left bundle branch block; msec = milliseconds; NSICD = nonspecific intraventricular conduction delay; NSR = normal sinus rhythm; RBBB = right bundle branch block; SD = standard deviation.

On the receiver operating curve analysis (Figure 4), the EMW outperformed QTc in identifying patients with arrhythmic events (area under the curve$_{EMW}$ 0.89, 95% CI 0.82 to 0.97 vs area under the curve$_{QTc}$ 0.77, 95% CI 0.61 to 0.93, p = 0.02). The optimal EMW cut-off value predictive of ventricular tachyarrhythmias was −108 ms, with a sensitivity of 86% and a specificity of 79%.

The univariate logistic regression model showed that EMW and QTc are predictive of ventricular tachyarrhythmias (OR$_{EMW}$ 1.03, 95% CI 1.01 to 1.05, p = 0.003 and OR$_{QTc}$ 1.02, 95% CI 1.01 to 1.03, p = 0.02). In the multivariate analysis, only EMW remained a significant predictor for ventricular tachyarrhythmias (OR$_{EMW}$ 1.03, 95% CI 1.03 to 1.05, p = 0.023).

Discussion

To the best of our knowledge, this is the first study to describe the EMW in patients with TTS and evaluating its association with ventricular tachyarrhythmias. TTS is

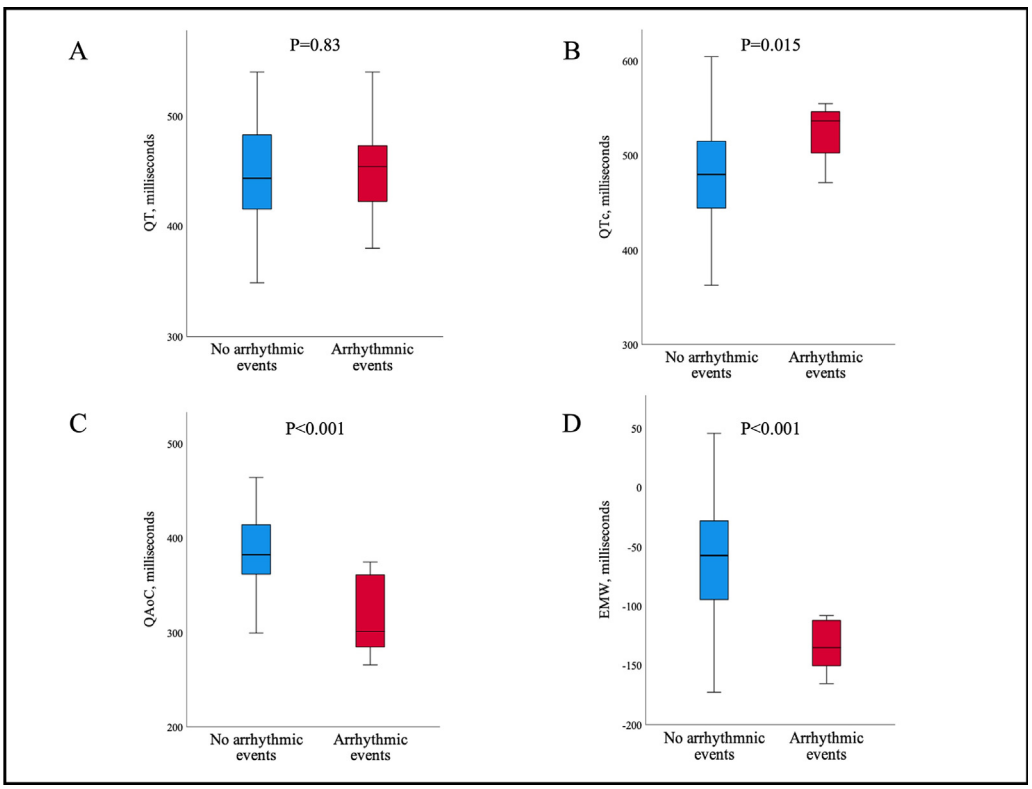


Figure 2. Comparison of QT (*A*), QTc (*B*), QAoC (*C*), and EMW in patients with and without ventricular tachyarrhythmias.

Table 3
Electrocardiographic and echocardiographic variables at time of EMW calculation

	No Ventricular arrhythmic events n=77	Ventricular arrhythmic events n=7	p
ECG			
RR, mean±SD, msec	879±186	717±157.6	0.028
QT, mean±SD, msec	448±56	452±51	0.833
QTc, mean±SD, msec	482±53	538±62	0.011
Echocardiography			
LVEF, mean±SD, %	42±8	41±12	0.701
QAoC, mean±SD, msec	384±43	319±46	<0.001
EMW, mean±SD, msec	-63±48	-133±23	<0.001

ECG = electrocardiography; EMW = electromechanical window; LVEF = left ventricular ejection fraction; msec = milliseconds; QAoC = QRS onset to aortic valve closure; SD = standard deviation.

associated with impaired left ventricular systolic function and repolarization abnormalities, manifested as marked QT interval prolongation.[4] We hypothesized that in patients with TTS, the physiologic left ventricular electromechanical sequence, in which the aortic valve closure occurs after repolarization completion, is reversed and that the uncoupling of the physiologic electromechanical sequence, expressed as a negative EMW, would be associated with ventricular tachyarrhythmias. The main findings of our study are the following: (1) ventricular tachyarrhythmias were a common complication in patients with TTS, occurring in 8.3% of patients, (2) EMW is negative in patients with TTS, (3) EMW negativity is associated with ventricular tachyarrhythmias, and (4) EMW is more effective than QTc in identifying patients who experienced ventricular tachyarrhythmias.

Recently, Del Buono et. Al[19] suggested a guideline-supported cut-off point of a QTc (Fridericia) of 460 ms as a reliable threshold for the identification of high-risk patients with TTS in predicting ventricular arrhythmic, with a sensitivity of 60% and a specificity of 77%, whereas, in our cohort, the same cut-off value yielded a 100% sensitivity and a 34% specificity. Although our study cannot account for this discrepancy in QTc diagnostic value, it is plausible that the using different methods for QTc correction have affected the observations.

The exact pathophysiology of TTS has not been completely elucidated, although several different mechanisms that result in myocardial damage from catecholamine excess have been suggested.[20] Catecholamine excess has a direct effect on cardiomyocyte function, resulting in arrythmias and irreversible cellular injury. This occurs by way of reactive oxidative species production, calcium overload, and mitochondrial dysfunction after the activation of β adrenoreceptor.[21,22]

Normally, the end of electrical systole occurs before the end of mechanical systole (closure of aortic valve), resulting in a positive EMW. A negative EMW occurs when there is a mismatch between the end of electrical and mechanical systole because of repolarization prolongation, shortening of mechanical systole, or both. Previous studies demonstrated that a negative EMW is associated with increased mortality in patients with coronary artery disease[23,24] and that a negative EMW is associated with increased ventricular tachyarrhythmias lability in patients with long QT syndrome.[8] The exact mechanistic link between a negative EMW and the increased risk of ventricular tachyarrhythmias is not clear. The predominant theory is that electrical−mechanical mismatch results from abnormalities in cell calcium control, with sustained or increased calcium

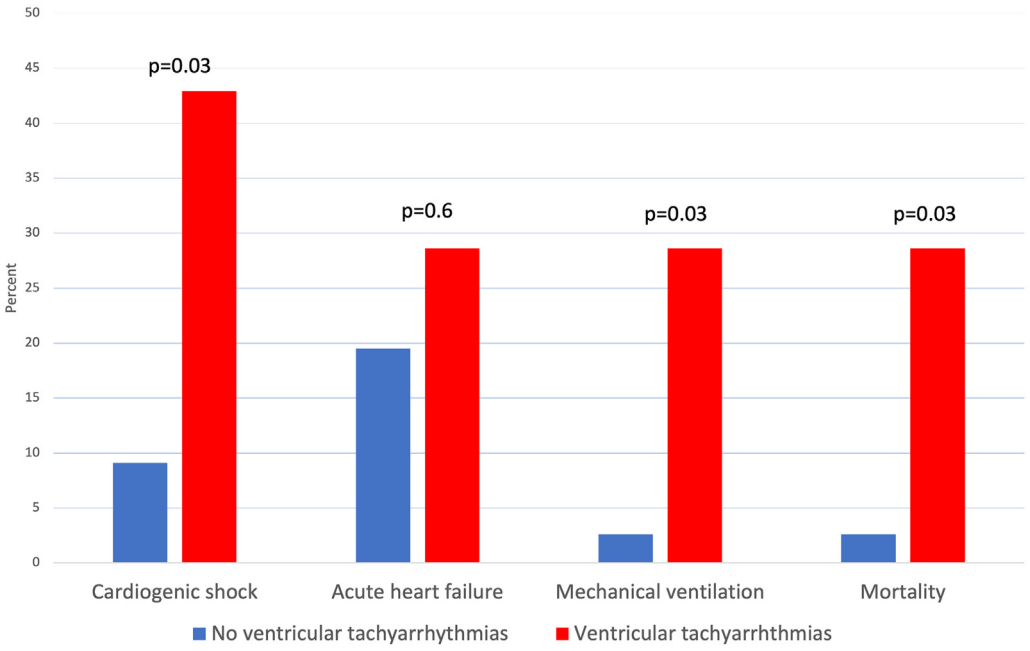
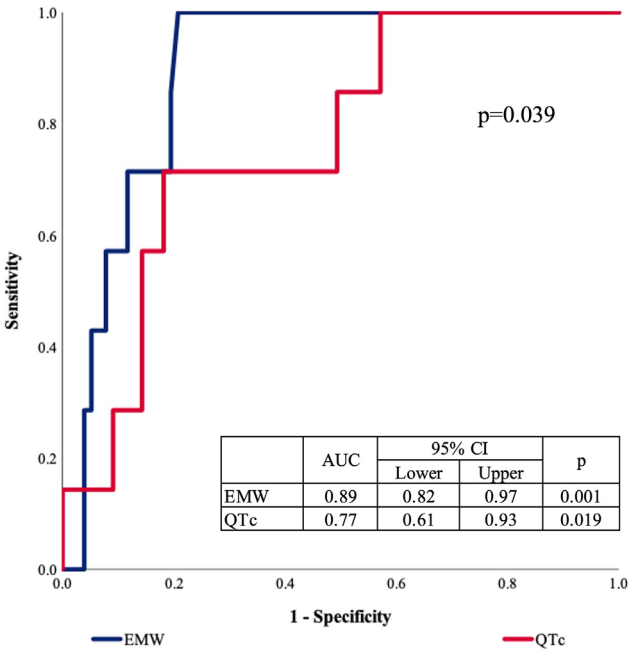


Figure 3. In-hospital events in patients with and without ventricular tachyarrhythmias.



	AUC	95% CI		p
		Lower	Upper	
EMW	0.89	0.82	0.97	0.001
QTc	0.77	0.61	0.93	0.019

Figure 4. ROC curve of EMW and QTc for ventricular tachyarrhythmias. ROC = receiver operating characteristic.

concentration.[7] After the ejection of blood and closure of the aortic valve, the muscle should be experiencing lusitropy. However, the ongoing calcium release caused by the prolonged action potential duration promotes after-depolarizations, which, in turn, may trigger arrhythmias.[25] The role of QT prolongation in ventricular arrhythmogenesis had been widely described,[26] recently also in patients with TTS.[19] Our study suggests that QT interval prolongation is not the sole factor involved in arrhythmogenesis and that shortening of the mechanical systole may also play a role. Additional potential arrhythmogenic factors include the dispersion of mechanical systole and myocardial contraction occurring after the closure of the aortic valve.[27]

Our study has several limitations. It is a single-center, retrospective analysis. Although all electronic files, ECGs, echocardiographic evaluations, and arrhythmic events were revised, biases inherent to our study design cannot be excluded. Our study cohort is small, with only 7 patients experiencing arrhythmic events. Hence, the comparisons made between patients who experienced ventricular tachyarrhythmias to those who did not and the results of the multivariate regression analysis should be interpreted cautiously. Circadian variation in the QT interval and beat-to-beat variation were not accounted for.

In conclusion, the EMW of patients hospitalized with TTS is negative, and EMW negativity is associated with the occurrence of ventricular tachyarrhythmias. Moreover, EMW is effective in identifying patients at risk for arrhythmic complications, and its role in risk stratification should be further explored.

Declaration of Competing Interest

The authors have no competing interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2023.10.016.

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