RESEARCH LETTER

Repolarization parameters and ventricular arrhythmias in Takotsubo syndrome: A substudy from the RETAKO national registry

Ravi Vazirani, MD,* Eduardo Martínez, MD,* Aitor Uribarri, MD, PhD,† Emilia Blanco-Ponce, MD, PhD,‡ Manuel Martínez-Sellés, MD, PhD,§ Miguel Corbí-Pascual, MD,|| Alessandro Sionis, MD, PhD,¶ Jorge Salamanca, MD,** Oscar Vedia, MD,* Iván J. Núñez-Gil, MD, PhD,†††‡‡ on behalf of the RETAKO researchers

*From the *Instituto Cardiovascular, Hospital Clínico San Carlos, Madrid, Spain, †Servicio de Cardiología, Hospital Universitario Vall d'Hebron, Barcelona, Spain, ‡Servicio de Cardiología, Hospital Universitario Arnau de Vilanova, Lérida, Spain, §Servicio de Cardiología, Hospital General Universitario Gregorio Marañón, Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares, Universidad Europea de Madrid, Universidad Complutense de Madrid, Madrid, Spain, ||Servicio de Cardiología, Hospital Universitario de Albacete, Albacete, Spain, ¶Unidad de Cuidados Intensivos Cardiológicos, Servicio de Cardiología, Hospital de Sant Pau, Instituto de Investigación Biomédica Sant Pau, Barcelona, Spain, **Servicio de Cardiología, Hospital de la Princesa, Madrid, Spain, ††Cardiology Department, Hospital Clínico San Carlos, Madrid, Spain, and ‡‡Faculty of Biomedical and Health Sciences, Universidad Europea de Madrid, Villaviciosa de Odón, Spain.*

Ventricular arrhythmias (VAs) occur in about 10% of Takotsubo syndrome (TTS) patients[1] and comprise ventricular tachycardia (monomorphic or polymorphic and ventricular fibrillation). All of them have been linked to reduced survival in TTS.

Electrocardiographic (ECG) abnormalities such as the lengthening of the QT interval corrected for heart rate (QTc) using Bazett's formula and prolongation of the T-wave peak point–T-wave end point (Tpe) interval have also been associated with major adverse cardiovascular events and worse prognosis,[2] although some studies do not report a definite association with VA.[3,4]

Our purpose was to investigate whether there is an association between electrocardiographic repolarization parameters and VA in 106 patients with TTS in the REgistro nacional multicéntrico sobre síndrome de TAKOtsubo (RETAKO) registry. TTS definition and the diagnostic protocol have been previously described[5]: transient hipo/akinesia of the ventricle with typical or atypical patterns, new ECG abnormalities or modest elevation in cardiac troponin, and coronary angiography without significant obstructive lesions and recovery of the contractility abnormalities and ejection fraction, with absence of pheochromocytoma or myocarditis.

KEY FINDINGS

- The T-wave peak point–T-wave end point (Tpe) interval is greater in subjects with Takotsubo syndrome (TTS) and ventricular arrhythmias (VAs) compared with those without VAs.
- The Tpe interval has a better area under the curve for predicting VAs in TTS than the QT interval corrected for heart rate, a classical measurement reported.
- The longest Tpe interval in the precordial leads appears to be an easier and more reliable measurement than the classical QT interval corrected for heart rate for the prediction of VAs in TTS.

For this analysis we used the first ECG obtained upon admission was used. The exclusion criteria were pacemaker rhythm and left or right bundle branch block.[2] We produced 2 groups. The case group included 13 consecutive patients with at least 1 VA during the hospital stay. The control group was composed of 65 patients without VA. The mean QTc measured across all leads was used. The QT-d was calculated as the difference between the maximum and the minimum QT interval. The Tpe interval was measured in precordial leads from the peak to the end of the T-wave. The longest interval obtained in all precordial

KEYWORDS ECG; Takotsubo; Arrhythmias; Repolarization; Electrocardiogram
(Heart Rhythm O2 2023;4:517–519)

Address reprint requests and correspondence: Dr Iván J. Núñez Gil, Cardiology, Hospital Clínico San Carlos, C/ Profesor Martin Lagos s/n, Madrid, Spain. E-mail address: ibnsky@yahoo.es; Twitter: @DrRaviVazirani

2666-5018/© 2023 Heart Rhythm Society. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

https://doi.org/10.1016/j.hroo.2023.06.008

Table 1 Prevalence and electrocardiographic measurements of life-threatening arrhythmias in Takotsubo syndrome

	All patients (N = 79)	Case (n = 13)	Control (n = 66)	*P* value
Clinical characteristics				
Male	10 (12.82)	5 (38.5)	5 (7.6)	.02
Age, y	N/A	65.92 ± 17.94	68.88 ± 11.20	.577
Syncope on arrival	4 (5.1)	3 (23.1)	1 (1.5)	.01
Killip IV on arrival	10 (12.82)	5 (38.5)	5 (7.7)	.01
Onset ECG ST-segment elevation	56 (70.9)	6 (7.6)	50 (63.3)	.032
Onset ECG ST-segment depression	15 (19)	1 (1.3)	14 (17.7)	.443
Left ventricular ejection fraction on arrival, %	N/A	41.12 ± 15.93	45.12 ± 12.96	.346
1-y mortality	4 (5.1)	2 (15.4)	2 (3)	.063
1-y recurrence	1 (1.3)	0 (0)	1 (1.5)	.431
Ventricular arrhythmias				
Monomorphic ventricular tachycardia	8 (10.3)	8 (61.5)	N/A	N/A
Polymporphic ventricular tachycardia	2 (2.6)	2 (16.7)	N/A	N/A
Ventricular fibrillation	3 (3.8)	3 (21.1)	N/A	N/A

Values are n (%) or mean ± SD. The table shows the clinical status on arrival and the type of ventricular arrhythmias. Each patient contributed only once to the prevalence of ventricular arrhythmias in case various types of arrhythmias occurred in the same patient.

ECG = electrocardiography; N/A = not applicable; QTc = QT interval corrected for heart rate.

leads was used. SPPS version 24 (IBM Corporation, Armonk, NY) was used for statistical comparisons.

The measurements were carried out by 2 cardiologists (RV and EM) to the presence of VA, with intra- and interobserver variability using Cohen's kappa of 1 in both cases.

Clinical and electrocardiographic characteristics are depicted in Tables 1 and 2, respectively. Compared with control subjects, VA cases consulted more frequently for syncope, and had a higher prevalence of cardiogenic shock on arrival.

The longest Tpe interval (170 ms vs 103 ms; $P < .001$) and the Tpe interval corrected both by heart rate (179.93 ms vs 109.65 ms; $P < .001$) were higher in VA cases.

The QTc and QTc dispersion were also higher in the VA case group. The areas under the receiving-operating characteristic curve for the longest Tpeak-Tend in the precordial leads were 0.946 (95% confidence interval 0.885–1.0) and 0.732 (95% confidence interval 0.565–0.899) for the QTc.

Two patients from the case group received de novo treatment with amiodarone for the VA: one of them was excluded due to bundle branch block and the other one had normal QTc and Tpe interval. Two patients from the case group received vasoactive support and had prolonged QTc and Tpe interval. None of the patients had prior treatment with beta-blockers. None of the patients had previous VAs or predisposing factors.

There was greater prevalence of monomorphic over polymorphic ventricular tachycardia, even in the setting of prolonged QTc and Tpe interval. This could be due to focal gadolinium enhancements,[1] which might represent a substrate for VAs. There was a greater prevalence of ST-segment elevation in the control group as well ($P = .032$).

This study sheds light into the usefulness of the ECG repolarization parameters for predicting VAs in TTS. The Tpe interval corresponds with transmural dispersion of repolarization in the ventricular myocardium, likely corresponding to an extended vulnerable period that could increase the risk of ventricular arrhythmogenesis. The longest Tpe interval in the precordial leads appears to be an easier and more reliable measurement than the classical QTc for the prediction of VAs in TTS. This could be of paramount importance to make therapeutic decisions or prolong monitorization.

Table 2 ECG repolarization analysis

Electrocardiographic characteristics	Case	Control	AUC (95% CI)	*P* value
Heart rate	78 ± 18.27	84.50 ± 23.82	0.348 (0.203–0.493)	.326
QTc in V3	528.20 ± 108.64	424.28 ± 51.40	0.710 (0.540–0.880)	<.001
QTc in III	461.23 ± 50.12	430.55 ± 45.00	0.673 (0.483–0.863)	<.001
QT dispersion	91.6 ± 51	62.71 ± 30.91	0.674 (0.524–0.825)	<.001
Mean QTc	495.18 ± 79.92	429.95 ± 44.77	0.732 (0.565–0.899)	<.001
Longest Tpe interval	170.77 ± 34.51	102.94 ± 23.05	0.946 (0.885–1.000)	<.001
Heart rate–corrected Tpe interval	179.93 ± 58.55	109.65 ± 31.51	0.870 (0.782–0.959)	<.001
QTc-corrected Tpe interval	0.296 ± 0.09	0.242 ± 0.06	0.771 (0.637–0.906)	<.05

Values are mean ± SD. The AUC for the occurrence of ventricular arrhythmias is provided for each parameter.

AUC = area under the curve; CI = confidence interval; QTc = QT interval corrected for heart rate; Tpe = T-wave peak point–T-wave end point.

Further evaluation of these repolarization parameters in different populations and other prospective studies is needed.

Funding: The registry webpage was funded by an AstraZeneca nonconditioned grant and by FIC (Fundación Interhospitalaria para la Investigación en Cardiología).

Disclosures: The authors have no conflicts to disclose.

Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent: All patients provided written informed consent.

Ethics Statement: The research protocol used in this study was approved by the institutional review board and adhered to the Helsinki Declaration guidelines.

References

1. Möller C, Eitel C, Thiele H, Eitel I, Stiermaier T. Ventricular arrhythmias in patients with takotsubo syndrome. J Arrhythm 2018;34:369–375.
2. Braschi A, Frasheri A, Lombardo RM, et al. Association between Tpeak-Tend/QT and major adverse cardiovascular events in patients with Takotsubo syndrome. Acta Cardiol 2021;76:732–738.
3. Mugnai G, Vassanelli F, Pasqualin G, et al. Dynamic changes of repolarization abnormalities in takotsubo cardiomyopathy. Acta Cardiol 2015; 70:225–232.
4. Matsuoka K, Okubo S, Fujii E, et al. Evaluation of the arrhythmogenecity of stress-induced "takotsubo cardiomyopathy" from the time course of the 12-lead surface electrocardiogram. Am J Cardiol 2003;92:230–233.
5. Núñez Gil IJ, Andrés M, Almendro Delia M, et al. Characterization of Tako-tsubo cardiomyopathy in Spain: results from the RETAKO national registry. Rev Esp Cardiol (Engl Ed) 2015;68:505–512.