

Malignant ventricular arrhythmias in patients with implantable cardioverter-defibrillators: electrical signals which are predictors of recurrence

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Acronyms

f-QRS: fragmentation of QRS

ICD: implantable cardioverter-defibrillators

LQTS: long QT syndrome

MVA: malignant ventricular arrhythmias

QTd: abnormal QT interval dispersion

SCD: sudden cardiac death

Tp-Te: Tpeak-Tend interval

Tp-Ted: abnormal Tp-Te interval dispersion

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ABSTRACT

Introduction: There is a growing number of patients with implantable cardioverter-defibrillators. Recurrences are frequent and electrical shocks are the main factor affecting the quality of life.

Objective: To identify the electrocardiographic predictors of the recurrence of malignant ventricular arrhythmias in these patients.

Method: From a universe of 76 patients, who had undergone cardioverter-defibrillator implantation, 46 patients were selected and two groups were formed. Group A consisted of 27 patients with at least one episode of malignant ventricular arrhythmias after device implantation; and group B consisted of 19 subjects without recurrences. Measurements (prolonged QTc, abnormal QT dispersion, Tpeak-Tend interval and its abnormal dispersion) were averaged over three consecutive heartbeats in each lead, manually, by two independent observers.

Results: In group A, there was a predominance of structural heart disease and an ejection fraction less than 35%. The fragmentation of the QRS complex, bimodal T wave and early repolarization pattern were also present. There were significant differences in the mean values of the QT interval (428 vs. 390 ms), $p=0.004$; the corrected QT (476 vs. 436 ms), $p=0.011$; and Tpeak-Tend interval (108 vs. 87 ms), $p=0.006$. There were no significant differences in QT dispersion (51 vs. 48 ms), the Tpeak-Tend dispersion (35 vs. 27 ms), or QRS duration (121 vs. 105 ms).

Conclusions: QT, QTc and Tpeak-Tend intervals are electrocardiographic predictors of the recurrence of ventricular arrhythmias in patients with implantable cardioverter-defibrillators.

Key words: Implantable cardioverter-defibrillator, Electrical predictors, Recurrence, Malignant ventricular arrhythmias

Arritmias ventriculares malignas en pacientes con cardiodesfibrilador implantable: signos eléctricos predictores de recidivas

RESUMEN

Introducción: Existe un número creciente de pacientes con cardiodesfibriladores, las recidivas son frecuentes y los choques eléctricos constituyen el principal factor reductor de la calidad de vida.

Objetivo: Identificar los predictores electrocardiográficos de recidivas de arritmias ventriculares malignas en estos sujetos.

Método: De un universo de 76 pacientes a los que se les había implantado un cardiodesfibrilador automático implantable, se seleccionaron 46 y se confeccionaron dos grupos. El A estuvo constituido por 27 pacientes, con al menos un episodio de arritmias ventriculares malignas tras el implante del dispositivo; y el B, por los 19 sujetos sin recurrencias. Las mediciones (QTc prolongado, dispersión anormal del QT, T_{pico}-T_{final} y su dispersión anormal) se promediaron en tres latidos consecutivos en cada derivación, de forma manual, por dos observadores independientes.

Resultados: En el grupo A predominó la cardiopatía estructural y la fracción de eyección inferior a 35 %. Estuvieron igualmente representados la fragmentación del complejo QRS, la onda T bimodal y el patrón de repolarización precoz. Hubo diferencias significativas en los valores medios del intervalo QT (428 vs. 390 ms), $p=0.004$; del QT corregido (476 vs. 436 ms), $p=0.011$; y del intervalo T_{pico}-T_{final} (108 vs. 87 ms), $p=0.006$. No existieron en la dispersión del QT (51 vs. 48 ms), la dispersión del T_{pico}-T_{final} (35 vs. 27 ms), ni en la duración del QRS (121 vs. 105 ms).

Conclusiones: Los intervalos QT, QTc y T_{pico}-T_{final} son predictores electrocardiográficos de recidivas de arritmias ventriculares en pacientes con cardiodesfibriladores.

Palabras clave: Cardiodesfibrilador implantable, Predictores eléctricos, Recidivas, Arritmias ventriculares malignas

INTRODUCTION

Repeated electric shocks are among the main problems faced by patients with implantable cardioverter-defibrillators (ICD). There are numerous markers associated with this phenomenon; many are complex in their production and reproducibility. Surface electrocardiogram may show signals that reflect alterations in the processes of ventricular depolarization and repolarization. Identifying them would help to establish a more accurate individual risk stratification, define a therapeutic strategy and prevent complications in patients at high arrhythmic risk. The aim of this study was to identify electrocardiographic signals which are predictors of recurrence of malignant ventricular arrhythmias (MVA) in the clinical monitoring of patients with ICD.

METHOD

The universe consisted of 76 patients, who were treated at the Arrhythmia and Pacing Department of the Institute of Cardiology and Cardiovascular Surgery, aged between 15 and 80 years, of both sexes, with demonstrable structural heart disease or not, who had undergone ICD implantation as a secondary or primary

(one case) prevention of MVA. The sample was defined by the study period (from February 2007 to February 2009) and the inclusion criteria (to have a baseline electrocardiogram near the moment of the arrhythmic event or device implantation, without the use of antiarrhythmic drugs), and consisted of 46 patients, 34 men (73.9%), aged between 40 and 70 years

Two groups were formed. Group A consisted of 27 patients with at least one episode of MVA after implantation of the device, and group B, consisting of 19 subjects without recurrence.

The first episode of MVA after implantation of the device was defined as relapse. To be included in the group B, it was necessary two or more years of follow-up without MVA.

Measurements were averaged over three consecutive heartbeats in each lead, manually, by two independent observers. The results were compared, and the greatest value was considered valid. If the differences were greater than 20 ms, one was chosen by mutual agreement, or a third expert was consulted.

The following concepts were used^{1,2}:

- Prolonged QTc: greater than 460 ms
- Abnormal QT interval dispersion (QTd): greater

- than 65 ms
- Prolonged Tpeak-Tend interval (Tp-Te): equal to or greater than 100 ms
 - Abnormal Tp-Te interval dispersion (Tp-Ted): greater than 20 ms.

The mean, standard deviation and percentage were calculated for comparison of the descriptive summary measures. Pearson's chi-square test for qualitative variables was used for determining the association of variables, and t-test was used to compare the means between groups. Survival of patients was assessed according to the values of Tp-Te, by analyzing the Kaplan-Meier curve³.

RESULTS

Age and sex were distributed similarly in both groups (**Table 1**). Structural heart disease (66.7 %) predo-

minated in patients with recurrences, including dilated cardiomyopathy (37%). Primary electrical disease predominated in group B (57.8 %).

Qualitative electrocardiographic parameters (QRS fragmentation, bimodal T wave and early repolarization pattern) were distributed similarly in both groups, although fragmentation of QRS (f-QRS) was slightly predominant in group A (**Table 2**).

Quantitative electrocardiographic variables are shown in **Table 3**. There were statistically significant differences in the mean values of QT, QTc and Tp-Te between the groups. It was not so with the other values; which showed a similar behavior (QTd, Tp-Ted and QRS duration).

QRS duration in patients with recurrences, who had electrical storms, showed significantly prolonged mean values (128.3 ± 38.6 ms), compared with the group without recurrence (105.7 ± 17.7 ms), $p = 0.045$.

Table 1. Demographic characteristics, underlying disease and follow-up time.

Group	Diagnosis	Nº	Sex		Age (Years)	Follow-up (Months)
			F	M		
GROUP A With recurrences	Dilated cardiomyopathy	10	2	8	50,3	2,4
	Primary electrical disease	9	2	7	41,6	11,9
	Ischemic heart disease	7	1	6	66,2	7,1
	Ebstein's disease	1	1	0	19,0	5,0
	Subtotal	27	6	21	52,2	6,9
GROUP B Without recurrences	Dilated cardiomyopathy	1	0	1	53,0	72,0
	Primary electrical disease	11	4	7	40,0	50,7
	Ischemic heart disease	4	0	4	66,0	45,0
	Hypertrophic cardiomyopathy	1	0	1	60,5	65,0
	Mitral valve replacement	2	2	0	50,0	29,0
	Subtotal	19	6	13	50,0	49,1
TOTAL		46	12	34	51,3	50,7

Table 2. Fragmentation of QRS and bimodal morphology of the T wave.

Signal	With recurrences (A)						Without recurrences (B)						p
	Yes		No		Total		Yes		No		Total		
	Nº	%	Nº	%	Nº	%	Nº	%	Nº	%	Nº	%	
f-QRS	10	37.0	17	62.9	27	100	5	26.3	14	73.6	19	100	0.445
Bimodal T wave	8	29.6	19	70.3	27	100	5	26.3	14	73.6	19	100	0.806

f-QRS: fragmentation of QRS

Table 3. Distribution of quantitative variables.

Parameter		Mean (ms)	SD	p
QT	Recurrences	428,14	42,70	0.004
	No recurrences	390,52	40,75	
QTc	Recurrences	476,29	54,15	0.011
	No recurrences	436,42	43,24	
QTd	Recurrences	51,11	22,41	0.718
	No recurrences	48,42	27,74	
Tp-e	Recurrences	108,88	27,36	0.006
	No recurrences	87,36	20,23	
Tp-Ted	Recurrences	35,55	16,94	0.122
	No recurrences	27,36	17,99	
QRS	Recurrences	121,11	35,76	0.092
	No recurrences	125,26	68,18	

SD: Standard deviation
 QTc: corrected QT interval
 QTd: QT interval dispersion
 Tp-Te: Tpeak-Tend interval
 Tp-Ted: Tpeak-Tend interval dispersion
 ms: milliseconds

In this study, 58.7 % of patients had recurrences, a high figure compared to another study at the same hospital (115 ICD recipients with 31.3 % MVA recurrence)⁵. Another study⁴ showed a 74.6% recurrence in 67 patients who were resuscitated from sudden cardiac death (SCD), without demonstrable structural abnormality. Some international studies on ICD recipients report recurrences between 50 and 70 % in the first two years⁶⁻⁹. Its frequency is a reality and a problem to be resolved.

It is striking the early appearance of recurrences, as all of them occurred in the first year of follow-up, and 37 % during the first three months. This could be explained because, in general, after implantation, antiarrhythmics are suspended, and only later, if necessary, they are administered again. Issues that are inherent in the device have also been described¹⁰.

The f-QRS did not show a statistically significant difference between the two groups, (it was found in both, in 1 of the 8 patients with Brugada syndrome). Morita *et al*¹¹, in 115 subjects with that channelopathy, found f-QRS in 43%, with the highest incidence in those with a history of ventricular fibrillation. This marker prevailed in patients diagnosed with ischemic

dilated and non-dilated cardiomyopathy, as it has been described in the literature¹².

There was no difference between the two groups with regard to the presence of bimodal T wave, this parameter has been described in patients with long QT syndrome (LQTS)¹³. It was found in 2 out of 5 patients with this disease, and in 6 patients with structural heart disease.

The early repolarization pattern in inferolateral leads has been described as a predictor of MVA by other authors¹⁴⁻¹⁶; however, it was not detected in this series.

The mean values of QT were within normal limits in both groups, with significant differences between those who had recurrences and those who did not have them (**Table 3**). The mean values of QTc (Bazett) were slightly prolonged in group A and showed significant differences with group B.

Prolongation of the QT interval is associated with an increased risk of MVA and SCD in various clinical conditions including congenital and acquired LQTS, myocardial infarction, hypertrophic cardiomyopathy, hypertension, patients who underwent surgery for tetralogy of Fallot, ventricular dysfunctions, and even in apparently healthy subjects^{17,18-22}. The MADIT II study found an association between QT prolongation and the occurrence of spontaneous ventricular tachycardia and fibrillation²⁰. Other studies have argued that the abnormal QT prolongation is an independent predictor of arrhythmic death in postinfarction patients²³⁻²⁵.

The QT dispersion values above 60 ms are considered a prolonged dispersion and risk markers for SCD due to MVA²²⁻²⁵. The average values of this series were normal in both groups, without significant differences. This may be justified by the variability of the parameters reflecting the dispersion of repolarization in a single patient at different times. If several baseline electrocardiograms had been measured in each one, maybe higher numbers would have been found.

The mean values of Tp-Te interval showed significant differences between groups A and B (**Table 3**). The Tp-Te interval reflects the transmural dispersion of repolarization and the consequent risk of MVA. This parameter has been studied as a predictor of malignant ventricular tachyarrhythmias in patients with Brugada syndrome², congenital and acquired LQTS, hypertrophic cardiomyopathy and ischemic heart disease²⁶⁻²⁸.

In this study, 100 ms was used as the cutoff value of the Tp-Te interval². Survival analysis (Kaplan-Meier) showed a statistically significant difference between the curves of patients with Tp-Te interval ≥ 100 ms and those with lower values. Most patients with equal or greater values had a “lower survival”, that is, they received shocks because of MVA. Most subjects with Tp-Te interval less than 100 ms did not require this type of therapy (**Figure 1**).

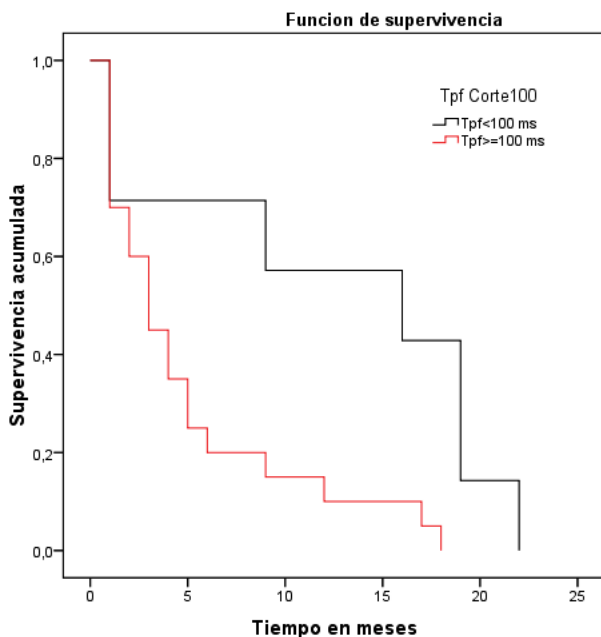


Figure 1. Survival curve (Kaplan Meier) Tp-Te.

There were no statistically significant differences between the dispersion of the Tp-Te interval in the recurrence group and the no recurrence group; however, the mean values of both groups were above 27 ms. The dispersion of Tp-Te interval reflects changes in transmural repolarization and is a parameter that has been little studied. Castro *et al*² demonstrated, in patients with Brugada syndrome, that a cutoff point higher than 20 ms was predictive of recurrence. Our sample included high-risk patients (secondary prevention of SCD), which justifies the presence of high values in both groups

The mean QRS duration was 121 ms in group A and 105 ms in group B, with no statistical difference. However, it differentiated significantly the electrical storm subgroup (mean values above 120 ms) from those who

did not have recurrences, reflecting an abnormal transmural activation. Several studies in subjects with and without structural heart disease have noted the role of QRS prolongation as a marker for risk of SCD^{29,31}.

MVA recurrences in patients with ICD are very common. Risk stratification is extremely difficult: the signals that have been described lack absolute accuracy in terms of sensitivity and specificity; its variability is common; the actual boundary between “innocent” and arrhythmogenic findings is not known; the analysis of electrical sequences would be necessary. In addition, there is the fundamental fact of the great complexity of arrhythmic events.

In this research, quantitative electrocardiographic signals, such as QT, QTc and Tp-Te intervals, identified a subgroup of patients with ICD who were at very high risk of recurrence of MVA, allowing an appropriate course of action: a more aggressive treatment of the underlying disease, selection of the antiarrhythmic drug, device reprogramming and closer monitoring.

CONCLUSIONS

The QT, QTc and Tp-Te intervals are electrocardiographic predictors of the recurrence of MVA in patients with implantable cardioverter-defibrillators.

REFERENCES

1. Moss AJ. QTc prolongation and sudden cardiac death: the association is in the detail. *J Am Coll Cardiol.* 2006;47(2):368-9.
2. Castro Hevia J, Antzelevitch C, Tornés Bázquez F, Dorantes Sánchez M, Dorticós Balea F, Zayas Molina R, *et al.* Tpeak-Tend and Tpeak-Tend dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. *J Am Coll Cardiol.* 2006;47(9):1828-34.
3. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958; 53(282):457-81.
4. Dorantes M, Castro J, Tornés F, Quiñones MA, Zayas R, Dorticós F. Muerte súbita por causa eléctrica en sujetos sin enfermedad cardíaca estructural demostrable. Experiencia cubana. *Arch Cardiol Méx.* 2004;74(4):283-9.
5. Tornés FJ, Cisneros P, Dorantes M, Castro J, Zayas R, Quiñones MA, *et al.* Tormenta eléctrica en pacientes con cardioversor-desfibrilador automático implantable. *Arch Cardiol Méx.* 2008;78(1):68-78.

6. Jordaens LJ, Mekel JM. Electrical storm in the ICD era. *Europace*. 2005;7(2):181-3.
7. Credner SC, Klingenheben T, Mauss O, Sticherling C, Hohnloser SH. Electrical storm in patients with transvenous implantable cardioverter-defibrillators: incidence, management and prognostic implications. *J Am Coll Cardiol*. 1998;32(7):1909-15.
8. Freedberg NA, Hill JN, Fogel RI, Prystowsky EN. Recurrence of symptomatic ventricular arrhythmias in patients with implantable cardioverter defibrillator after the first device therapy: implications for antiarrhythmic therapy and driving restrictions. *J Am Coll Cardiol*. 2001;37(7):1910-5.
9. Sánchez JM, Katsiyannis WT, Gage BF, Chen J, Faddis MN, Gleva MJ, *et al*. Implantable cardioverter-defibrillator therapy improves long-term survival in patients with unexplained syncope, cardiomyopathy, and a negative electrophysiologic study. *Heart Rhythm*. 2005;2(4):367-73.
10. Healy E, Goyal S, Browning C, Robotis D, Ramaswamy K, Rofino-Nadoworny K, *et al*. Inappropriate ICD therapy due to proarrhythmic ICD shocks and hyperpolarization. *Pacing Clin Electrophysiol*. 2004;27(3):415-6.
11. Morita H, Kusano KF, Miura D, Nagase S, Nakamura K, Morita ST, *et al*. Fragmented QRS as a marker of conduction abnormality and a predictor of prognosis of Brugada syndrome. *Circulation*. 2008;118(17):1697-704.
12. Das MK, Zipes DP. Fragmented QRS: a predictor of mortality and sudden cardiac death. *Heart Rhythm*. 2009;6(3 Suppl):S8-14.
13. Viitasalo M, Oikarinen L, Swan H, Väänänen H, Glatzer K, Laitinen PJ, *et al*. Ambulatory electrocardiographic evidence of transmural dispersion of repolarization in patients with long-QT syndrome type 1 and 2. *Circulation*. 2002;106(19):2473-8.
14. Yan GX, Antzelevitch C. Cellular basis for the electrocardiographic J wave. *Circulation*. 1996;93(2):372-9.
15. Wellens HJ. Early repolarization revisited. *N Engl J Med*. 2008;358(19):2063-5.
16. Rosso R, Kogan E, Belhassen B, Rozovski U, Scheinman MM, Zeltser D, *et al*. J-point elevation in survivors of primary ventricular fibrillation and matched control subjects. Incidence and clinical significance. *J Am Coll Cardiol*. 2008;52(15):1231-8.
17. Buja G, Miorelli M, Turrini P, Melacini P, Nava A. Comparison of QT dispersion in hypertrophic cardiomyopathy between patients with and without ventricular arrhythmias and sudden death. *Am J Cardiol*. 1993;72(12):973-6.
18. Shah RR. Drug-induced QT dispersion: does it predict the risk of torsade de pointes? *J Electrocardiol*. 2005;38(1):10-8.
19. Gadaleta FL, Llois SC, Sinisi VA, Quiles J, Avanzas P, Kaski JC. Prolongación del intervalo QT corregido: nuevo predictor de riesgo cardiovascular en el síndrome coronario agudo sin elevación del ST. *Rev Esp Cardiol*. 2008;61(6):572-8.
20. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, *et al*. Improve survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *N Engl J Med*. 1996;335(26):1933-40.
21. Aiba T, Shimizu W, Inagaki M, Satomi K, Taguchi A, Kurita T, *et al*. Excessive increase in QT interval and dispersion of repolarization predict recurrent ventricular tachyarrhythmia after amiodarone. *Pacing Clin Electrophysiol*. 2004;27(7):901-9.
22. Malik M, Batchvarov VN. Measurement, interpretation and clinical potential of QT dispersion. *J Am Coll Cardiol*. 2000;36(6):1749-66.
23. Perkiömäki JS, Koistinen MJ, Yli-Mäyry S, Huikuri HV. Dispersion of QT interval in patients with and without susceptibility to ventricular tachyarrhythmias after previous myocardial infarction. *J Am Coll Cardiol*. 1995;26(1):174-9.
24. Mirvis DM. Spatial variation of QT intervals in normal persons and patients with acute myocardial infarction. *J Am Coll Cardiol*. 1985;5(3):625-31.
25. Kelly RF, Parillo JE, Hollenberg SM. Effect of coronary angioplasty on QT dispersion. *Am Heart J*. 1997;134(3):399-405.
26. Yamaguchi M, Shimizu M, Ino H, Terai H, Uchiyama K, Oe K, *et al*. T wave peak-to-end interval and QT dispersion in acquired long QT syndrome: a new index for arrhythmogenicity. *Clin Sci (Lond)*. 2003;105(6):671-6.
27. Antzelevitch C. T peak-Tend interval as an index of transmural dispersion of repolarization. *Eur J Clin Invest*. 2001;31(7):555-7.
28. Kors JA, Ritsema van Eck HJ, van Herpen G. The meaning of the Tp-Te interval and its diagnostic value. *J Electrocardiol*. 2008;41(6):575-80.
29. Desai AD, Yaw TS, Yamazaki T, Kaykha A, Chun S, Froelicher VF. Prognostic significance of quantitative QRS duration. *Am J Med*. 2006;119(7):600-

- 6.
30. Shamim W, Yousufuddin M, Cicoria M, Gibson DG, Coats AJ, Henein MY. Incremental changes in QRS duration in serial ECGs over time identify high risk elderly patients with heart failure. *Heart*. 2002; 88(1):47-51.
31. Kardys I, Kors JA, van der Meer IM, Hofman A, van der Kuip DA, Witteman JC. Spatial QRS-T angle predicts cardiac death in a general population. *Eur Heart J*. 2003;24(14):1357-64.