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Special Article

Ventricular repolarization in cancer therapy

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ARTICLE INFORMATION

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Acronyms
LQT: Long QT
LQTI: Long QT interval
QTI: QT interval
TdP: Torsades de pointes
Tp-Te: T_{PEAK}-T_{END}

ABSTRACT
Ventricular depolarization and repolarization processes are discussed, including their differences and heterogeneity both in patients with a healthy/sick heart, a matter of ranges. Measurements expressing the characteristics of ventricular repolarization are analyzed: the QT interval and other even more reliable measurements such as the T_{PEAK}-T_{END} interval, its dispersion and others. We emphasize on the existence of the long QT syndrome (and sign) and the three basic processes of arrhythmogenesis: heterogeneity, alternation and dispersion, with differences in action potentials in the three zones of the ventricular myocardium. The risk factors of long QT (common in this therapy) and ventricular arrhythmias (especially torsades de pointes, extremely rare in these cases) are highlighted. The need to assess clinical and electrical features, comorbidities, aggregate conflicts, and management of these patients is also discussed.
Keywords: Ventricular repolarization, Cancer therapy, Antineoplastic agents, Cardiac arrhythmias, QT interval

Repolarización ventricular en la terapia oncológica

RESUMEN
Se discuten los procesos de despolarización y repolarización ventriculares, con su falta de uniformidad y su heterogeneidad, tanto en pacientes con corazón sano como en aquellos enfermos, cuestión de rangos. Se analizan las mediciones que expresan las características de la repolarización ventricular: el intervalo QT y otras mediciones incluso más fidedignas como el intervalo T_{PICO}-T_{FINAL}, su dispersión y otras. Se precisa la existencia del signo y del síndrome de QT largo, así como los tres procesos básicos de la arritmogenia: la heterogeneidad, la alternancia y la dispersión, con las diferencias de los potenciales de acción en las tres zonas del miocardio ventricular. Se precisan los factores de riesgo del QT largo (común con esta terapia), de las arritmias ventriculares (en especial la torsión de puntas, extremadamente rara en estos casos) y se discute la necesidad de valorar datos clínicos, eléctricos, comorbilidades, conflictos agregados y las medidas a tomar en estos pacientes.
Palabras clave: *Repolarización ventricular, Terapia oncológica, Antineoplásicos, Arritmias cardíacas, Intervalo QT*

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GENERALITIES OF THE VENTRICULAR ARRHYTHMIAS

There is a close relationship between cancer therapy and the cardiovascular processes that can take place in these patients, therefore, a harmoni-

ous relationship between oncologists and cardiologists is essential when dealing with these conflicts and making the most appropriate decisions. This work is focused in problems related to cancer therapy and alterations in the ventricular repolarization.

The second author works in the development of the first Cardio-Oncology group at the *Instituto Nacional de Oncología y Radiobiología*, with future plans to create units in other hospitals throughout the country. This would benefit the patients, by focusing on the stratification of cardiovascular risk, its early detection, prevention and treatment. All of this closely related with oncologists, who would guide and outline the strategies to follow.

A previous basic concept

In the processes of ventricular depolarization and repolarization, there is no uniformity or homogeneity, but rather the opposite, heterogeneity and lack of uniformity in the formation and conduction of the impulse at the level of all the structures of the heart's electrical system, in both, patients with structural heart disease and regular individuals. It is a matter of ranks[1].

QT interval and others

The QT interval (QTI) demonstrates the total duration of the depolarization and repolarization; the T_{PEAK}-T_{END} (Tp-Te) expresses the dispersion of the ventricular repolarization, that is, the non-uniformity of recovery. Not only the QTI is important, but also other measures, even better in order to evaluate ventricular repolarization[1-3].

Long QT interval

The acquired long QT interval (LQTI) is more frequent than the congenital one, with which it shares some similarities. It should be remembered that there may be a sign of long QT (LQT) and LQT syndrome, the first being the mere presentation of the electrical sign; in the second, syncopal episodes or sudden death events occur. Although during the clinical evolution, the sign can become a syndrome and the behavior to follow, thus, will be different[4].

Arrhythmogenesis and M cells

There are three fundamental processes in relation to arrhythmogeny: alternation, heterogeneity, and spatial and temporal dispersion. The pathophysiology of these alterations is based on the action potentials and their several characteristics in the three zones of the ventricular myocardium: the epicardium, the endocardium and the midmyocardium. Therefore, the duration of the epicardial action potential expresses the peak QT, as the midmyocardium represents the complete repolarization, until the end of the T wave[1,5-8].

The starting order of the action potential is: endocardial, epicardial and midmyocardial; while the end of the potential follow this order: epicardium, endocardium and midmyocardium. The M cells are a hybrid between the Purkinje cells and the ventricular tissue with ionic, electrophysiological and pharmacological differences among the three cell types. The electrical heterogeneity of the ventricular repolarization is present, at the transmural and transseptal level, in both sick and healthy people. The M zone has a longer area than the action potential of the endocardium and epicardium, even more if the heart rate is low or if certain antiarrhythmic drugs are used[1,5-7].

The M zone is a subpopulation of cells with unique electrophysiological properties, which improve the pump efficiency but increase electrical instability, which is compensated by the epicardial and endocardial zones[1].

Risk factors

It is important to recall some risk factors that contribute to the increase of the QTI and which can cause torsades de pointes (TdP) due to drugs [9,10]:

- Genetic: Genetic susceptibility, mutations.
- Congenital: Subclinical congenital LQTI.
- Sex and age: Females (twice risk), greater age.
- Electrolyte disorders: Hypomagnesemia, hypokalemia, hypocalcemia.
- Drugs: Employment of diuretics (regardless of electrolytic alterations) and digitalis, high concentration of some drugs (except quinidine), use of more than one antiarrhythmic drug, intravenous bolus administration of a drug.
- Associated heart disease: ventricular hypertrophy, heart failure with reduced ejection fraction, mitral failure, mitral valve prolapse, cardiomyopathies, valvulopathies.
- Comorbidities: Renal or hepatic disease.
- Cardiac arrhythmias: Ventricular arrhythmias (extrasystoles with short coupling interval, non-sustained ventricular tachycardia), atrioventricular block, bradycardia.
- Electrocardiographic signs: LQTI, early afterdepolarizations, recent reversal of an atrial fibrillation event, abnormal Tp-Te, notched T waves, changes of the QTI or postextrasystolic TU, TU mor-

phology, biphasic T, prominent U, postextrasystolic large U wave, aberrant or giant TU, beat-to-beat instability, aberrance of the T wave after a long RR interval.

There are also risk factors for the origin of the TdP, which are shown in **Box 1**.

Box 1. Risk factors for the origin of the torsade de pointes[9,10].

- Start of arrhythmia with giant TU
- Abnormal TU
- Early afterdepolarizations
- Slow rise of the QRS of the ventricular extrasystole
- Short-long-short cycle
- Pauses
- Increased duration of the QRS of the torsades de pointes' first beat
- Lower angle of the QRS
- Prominent U
- Alternation of QT-T (in duration, configuration, polarity, amplitude
- QRS fragmentation
- Long QT
- Abnormal T_{PEAK}-T_{END}

Dispersion and heterogeneity

The spatial and temporal dispersion can be presented between base and apex, *septum* and free walls, myocardial wall and between both ventricles (circumferential). In normal hearts, there can be dispersion until 55 ms and it reflects the non-uniformity of the ventricular repolarization, within certain limits. Heterogeneity occurs in terms of R, J and T waves, if their characteristics are compared in an individual resuscitated from a sudden death event with another who has not had it[5-8].

Other measurements

It should be remembered that the LQT is not a perfect marker for risk of malignant ventricular arrhythmias (fibrillation and ventricular tachycardia or death) and the T_{PEAK}-T_{END} (transmural dispersion of the repolarization, normal value 100 ms) is more valuable than the cQT and likewise, its dispersion (normal value 20 ms). Furthermore, not all LQT leads to TdP[1,3,11-13].

Factors that contribute to the lengthening of the QTI

In patients who receive cancer therapy, there are other conflicts that contribute to the lengthening of the QTI[14-16]:

1. Coexistent conditions: greater age, female sex, hypothyroidism, congenital LQT syndrome, fever, cardiac diseases as: left ventricular dysfunction, myocardial ischemia, bradycardia, high blood pressure, heart failure, pulmonary thromboembolism, stroke.
2. Concomitant drugs: antidepressants, antifungals, antihistamines, antiemetics, antibiotics, antipsychotics, antianginals, laxatives, antiarrhythmic drugs.
3. Related to the anticancer therapy: poor oral intake, dehydration, electrolyte disorders, nauseas, vomiting, diarrhea, poorly controlled diabetes, liver dysfunction, renal failure.

Where to measure the QT and some figures

The QT interval must be measured in the lead with the earliest beginning of the QRS and the latest end of the T wave, and always where it is seen more accurately. Some authors indicate as normal cQT that greater than 360 ms and less than 460 ms in the adult woman; and greater than 350 ms and less than 450 ms in the adult man. There are special conditions in which these measurements are difficult: branch block, implanted pacemaker, prolonged PR and junctional rhythm with presence of U wave[2,4,11,14,15].

How to consider ventricular repolarization

There are several possible measurements (**Figure 1**), which is the best?: QT, cQT, QT_{PEAK}, JT_{PEAK}, Tp-Te, JT_{END}, QT dispersion, Tp-Te dispersion. They are all useful but some more reliable, as the Tp-Te interval and its dispersion[2,3,11-13].

Mechanisms that induce arrhythmias in cancer therapy

The mechanisms of cancer therapy that induce arrhythmias are not well defined. There are the primary ones, that decrease the critical molecular pathways for developing arrhythmias, and the secondary (more common) due to epicardial, pericardial and endocardial damage (due to ischemia or inflammation). These mechanisms can be grouped, as shown in **Box 2**.

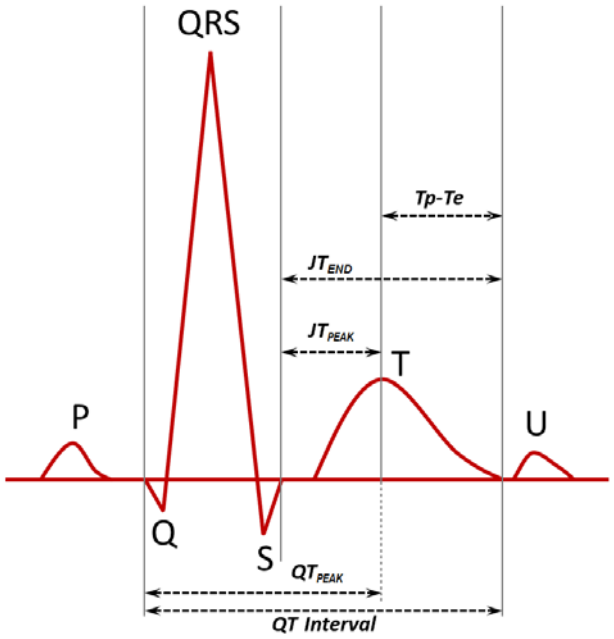

Figure 1. Several electrocardiographic measurements to evaluate ventricular repolarization. Tp-Te: T_{PEAK}-T_{END}.

Strategy to assess ventricular repolarization disorders

From the cardiological point of view, in a patient receiving anticancer therapy should be considered: a) in clinic: syncope, rapid heartbeat, fainting and vertigo; b) in the electrocardiograms: the increase of the QTI (there is referred that before the therapy, 6% present cQT prolongation), and c) other factors such as the condition of the excretion routes (kidney and liver), use of synergistic drugs with therapy that modifies the cQT and metabolism inhibitors of anticancer drugs that increase the QT[14-16].

Other mechanisms of prolonged QT

As noted above, the mechanisms for increasing the QT in this therapy are not well known, there has been considered the interaction with the average function of the proteins of the potassium channels in cardiomyopathies (hERG) and others. There is an increase in the QT and its dispersion, with biphasic T wave, late potentials in the Purkinje cells' plateau, preferential increase in the action potential duration of midmyocardium, increase in the transmural dispersion of repolarization (even more important than the increase in the QTI). These cases mimic the LQT syndrome type 2 (**Figure 2**), with biphasic T wave and possible TdP substrate[14-16]. When considering the LQT in the anticancer therapy, it is necessary to take into account the comorbidities, the risk factors and the initial increase of the QT. It has been observed that, in general, the risk of having these complications is presented later[14-16].

Risk of increased QT and arrhythmias

In 173 relevant publications, it is considered that the increase in the cQT is a more common risk in the conventional treatment (anthracyclines), because in the unconventional one it varies from 0-22%. It is considered serious if it is greater than 500 ms (0-5%). Nonetheless, arrhythmias (TdP, fibrillation and ventricular tachycardia, and sudden cardiac death) are extremely rare. If the cQT is greater than 500 ms or greater than 60 ms compared to the basal, the medication suppression should be evaluated[14-16].

Decision making

In severe cases, the next measures can be taken: intravenous magnesium sulfate, isoprenaline, external electric shock, lidocaine, temporary auricular or ventricular pacemaker if there is bradycardia (dual-chamber pacemaker), and implantable cardioverter-defibrillator, if the life expectancy is greater than 12 months and there is an event of resuscitated sudden death or severe arrhythmia without correctable cause (electrolytes). Monitoring is necessary as well

Box 2. Mechanisms that induce arrhythmias in cancer therapy[14-16].

1. Direct affectation of the heart
- Primary cancer
- Metastasis to the heart
- Cardiac amyloidosis
2. Electrolyte disorders
- Vomiting
- Diarrhea
- Drug-induced imbalance
3. Independent factors from the anticancer therapy
- Previous basic substrate for arrhythmias
- Arrhythmias after cancer surgery
- Radiation that can induce pericarditis, atherosclerosis
- Adjuvant medications, antiemetic and others
4. Effect on cardiac myocytes
- hERG block (human Ether-a-go-go-Related Gene 2)
- Abnormal calcium homeostasis
- Mitochondrial damage
- Cardiac apoptosis

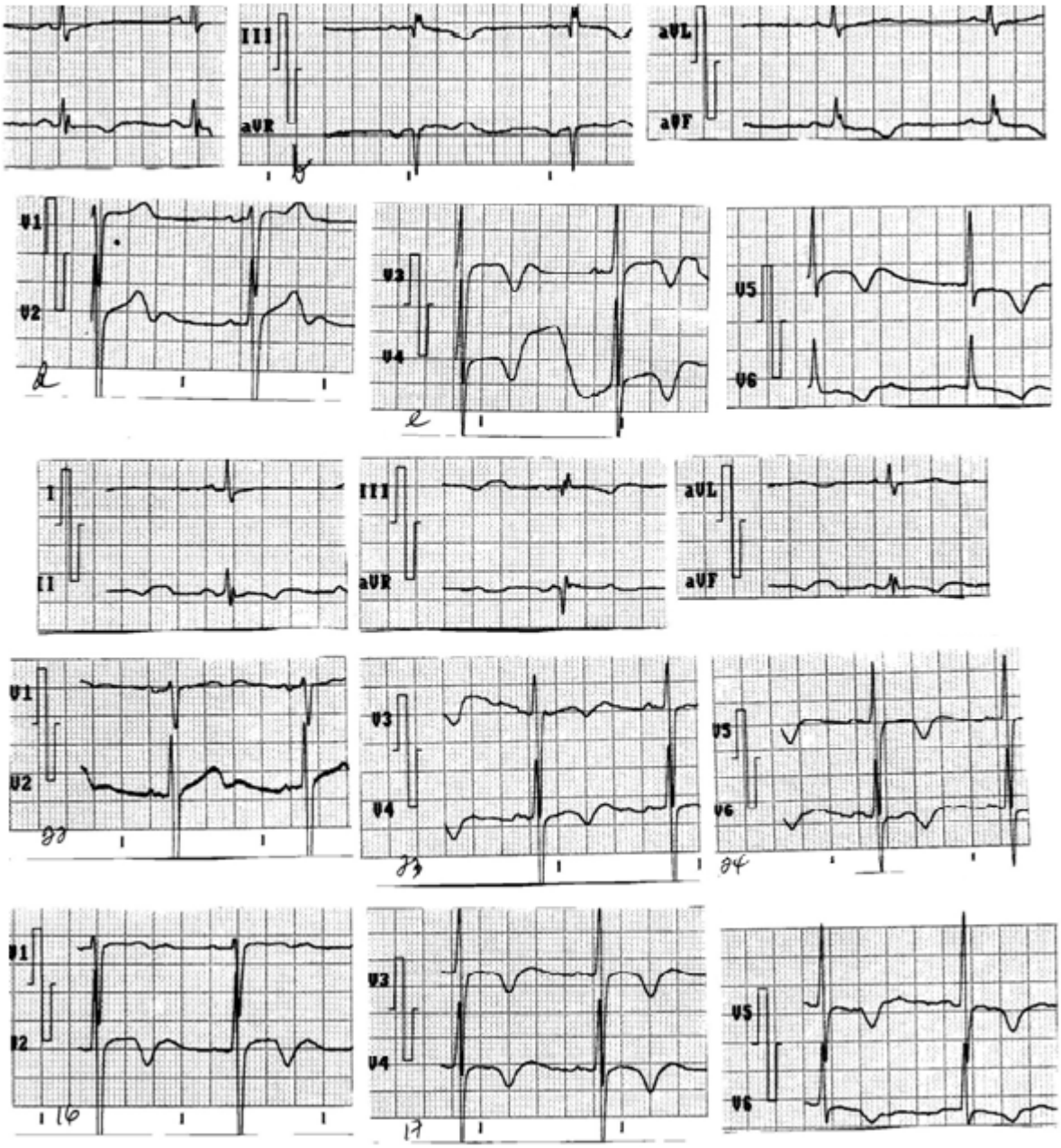

Figure 2. Electrocardiograms of the same patient at different times in his evolution: long QT interval due to drugs, alterations of the T wave (in magnitude, duration, bimodalism, T1T2 wave). These characteristics are observed in some patients with cancer therapy, resembling long QT syndrome type 2.

as deciding whether to discontinue the treatment[14-16].

Cardiovascular toxicity

There is a classification of the potential QT prolongation by anticancer drugs. According to Coppola[15], Vejpongsa and Yeh (*J Am Coll Cardiol* 2014;64:938-45) report that in 1807, among the survivors of cancer with follow-up for seven years, 51% of patients died by cancer itself and 33% due to cardiovascular disease. In these patients, not only their survival must be considered, but also their quality of life. The adverse effects in terms of cardiomyopathy are known since 1966, but the treatment of cancer inducing arrhythmias has been studied since 2009. The cardiovascular toxicity is one of the most dangerous conflicts in these patients. As a final thought, the

LQT is a common finding in them, against the TdP, that is rare but dangerous[14-16].

Risk groups

Several groups have been considered according to the QTI measurements: 1) cQT of 450-480 ms, 2) of 481-500 ms, 3) greater than 500 ms in two electrocardiograms, and 4) greater than 501 ms or more than 60 ms with respect to the basal, TdP, ventricular polymorphic tachycardia or symptoms related to these arrhythmias. Some accepted values of the QTI are referred in several articles[2,14-16].

The future of cardiovascular adverse effects in the cancer therapy, specifically in relation to arrhythmias, is aimed at researching on how these drugs alter the electrophysiological features of the heart[14-16].

Adjuvant factors

In these patients, several conflicts may arise: cancer itself can predispose arrhythmias (generally the series take into account an inadequate number of patients), a preexisting condition would provide greater vulnerability to anticancer therapy inducing arrhythmias; in addition, the synergy, a previous treatment against cancer, the use of polypharmacy, the preexisting arrhythmia with poor previous monitoring and common risk factors[14-16].

Strategies to reduce risks of prolonged QTI and severe arrhythmias

Some recommended strategies to minimize the risks of prolonged QTI and TdP in patients with anticancer therapy are[14-16]:

1. To avoid the use of drugs that prolong the cQT in patients with an interval greater than 450 ms before starting treatment.
2. To stop the use of these drugs if the cQT is prolonged more than 500 ms or greater than 550 ms, if there is a widening of the QRS base (greater than 120 ms, secondary to pacemaker or right bundle branch block).
3. To reduce dosage or discontinuing the treatment if the cQT lasts more than 60 ms compared to the previous value at the start of treatment.
4. To maintain the concentration of serum electrolytes (K, Mg, Ca), within the standard range.
5. To avoid drug interactions.
6. To adjust the doses of these drugs that are excreted by the kidneys in patients with acute dysfunction or established renal disease.
7. To avoid intravenous bolus administration of these drugs.
8. To avoid the administration of a drug with potential danger of QT prolongation.
9. To avoid the employment of these preparations in patients with a history of TdP due to drugs or previously resuscitated from events of sudden death.
10. To avoid its use in diagnosed patients with congenital LQT syndrome.
11. To carry out an electrocardiographic monitoring, concentration of the drug and dose changes in the therapy.

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