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Takotsubo cardiomyopathy and arrhythmic risk: the dark side of the moon

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Abstract. – BACKGROUND: "*Takotsubo*" cardiomyopathy (TTC) is a clinical disorder usually triggered by intense emotional and/or physical stress, characterized by reversible severe localized left ventricular wall dyskinesia, transient changes of ST segment, without significant coronary artery stenoses, that can mimic acute myocardial infarction.

STATE OF THE ART: Although TTC is well known to have a good mid- and long-term prognosis, arrhythmic risk is increasingly recognized and we could provide, in view of the available literature, a mean for a prognostic stratification and some practical suggestions for management of these "*vulnerable*" patients.

PERSPECTIVES: Further studies with randomized trials will be needed to prove the optimal treatment of TTC

CONCLUSIONS: TTC, generally considered a benign syndrome, should be reconsidered as a clinical condition at high risk for lethal arrhythmias in a subpopulation with QTc > 500 msec in acute phase. The studies about arrhythmias and TTC are based on case reports. TTC may present with sudden cardiac death: this results in a probable underestimate of the real arrhythmic risk. TTC is one of the causes of acquired long QT syndrome and could be a trigger able to unmask latent silent or inapparent congenital long QT syndrome. All factors that can exacerbate QT prolongation should be promptly removed. In the case of marked bradycardia and/or TdP should be implant a temporary pacemaker. In most cases, due to the transient nature of the syndrome, it is reasonable to recommend only beta-blocker therapy at discharge, despite the absence of randomized trials. If there are high-risk factor for long QT syndrome (QTc post-TCM > 500 ms, prior syncope, previous cardiac arrests) thought should be given an indication to ICD implant.

Key Words:
Takotsubo cardiomyopathy, Torsade de pointes, Long QT syndrome, Apical ballooning syndrome.

Introduction

"*Takotsubo*" cardiomyopathy (TTC), also called *"tako-tsubo" syndrome, "apical ballooning" syndrome, ampulla cardiomyopathy, broken heart syndrome, stress cardiomyopathy,* is a clinical disorder, much more common in postmenopausal women, usually triggered by intense emotional and/or physical stress, characterized by reversible severe localized left ventricular wall dyskinesia, transient changes of ST segment, mild myocardial enzymatic release, without significant epicardial coronary artery stenoses, that can mimic acute myocardial infarction[1-4].

This syndrome, first described in 1990 by Sato et al[5], is called "*takotsubo"* because the typical apical dyskinesia of the left ventricle resemble a Japanese octopus trap (Figure 1).

TTC accounts for 1% to 2% of all cases of suspected acute myocardial infarction[2]. However, during the most recent years, since the knowledge of this disease has improved and the diagnostic criteria have become more specific, the number of identified cases increased enormously: in 2009 in an italian population, Facciorusso et al[6] referred a prevalence of 4.78%. But, if we consider only the female patients with suspected acute myocardial infarction, this prevalence rises to 6%[7].

Although several pathophysiological mechanisms have been proposed, available evidence suggests that catecholamine-induced spasm of coronary arteries may play a major role[8,9].

The TTC has generally a good prognosis but the prolongation of the QT interval is typical of this disease[3]. Thus, the combination of TTC with another condition associated with the prolongation of QT, makes the acute and subacute prognosis of this disease much more severe than usually[10]. Finally, some Authors believe that the published in-hospital mortality data are underestimated[3]. Bonello et al reported an high in-hospital mortality rate of 21%[11] because of malignant ventricular arrhythmias were very frequent. Sharkey et al[2] showed that survival of the patients with TTC after initial event was significantly reduced compared with that expected in an age- and sex-matched general population.

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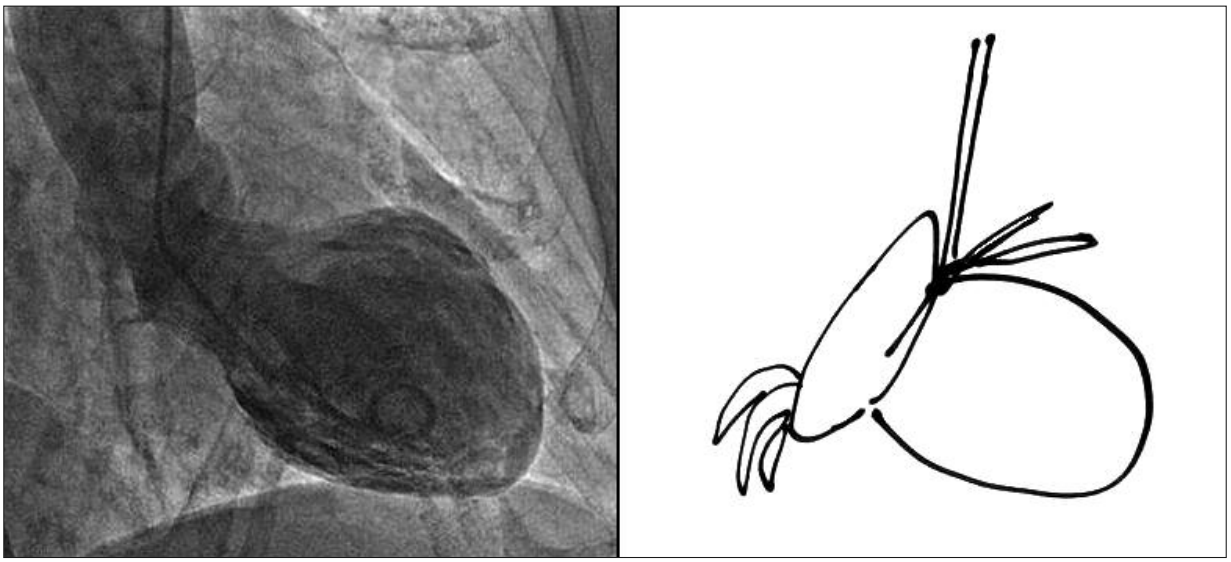

Figure 1. Left ventriculogram showing apical and midventricular left ventricular dysfunction. At right: a design of a takotsubo, a Japanese octopus trap.

Takotsubo and Prevalence of Cardiac Arrhythmias

TTC may be complicated by dangerous hypokinetic and/or hyperkinetic cardiac arrhythmias and may present with sudden cardiac death (SCD)[3].

The problem of the appearance of cardiac arrhythmias has been neglected in most earlier studies on the TTC: in first important reviews we never see the word "*arrhythmias*". The fact that the papers on the association between TTC and ventricular arrhythmias are based mainly on case reports and that this syndrome may present as SCD, may underestimate the real arrhythmic risk: Bonello et al[11], in a paper published in 2008, showed that in TTC the lethal ventricular arrhythmias were observed in 15% of patients. These Authors believe that the discrepancy between his data and the results of previous reports may be related to an underestimation of lethal arrhythmias because TTC may be revealed by SCD and thus be unrecognized. Syed et al[12] examined the current international medical literature on TTC and arrhythmias and found a prevalence of 2.2% of ventricular fibrillation, of 1.2% of sustained ventricular tachycardia, of 1% of non-sustained ventricular tachycardia, of 0.5% of asystole, of 2.9% of atrio-ventricular block, of 1.3% of sinus node dysfunction, of 4.7% of atrial fibrillation and of 1.1% of sudden cardiac death. This suggests that the risk of arrhythmias in the TTC is certainly relevant

Takotsubo and QT

It is known that the prolongation of the QT and corrected QT (QTc) is a common feature of TTC[2] (Figure 2). Some Authors have also noted an increase of dispersion of QT (QTd)[10,13] (Figure 3). The QTd is the difference between the maximum and the minimum QT intervals in a 12-lead ECG and has been linked, such as QT and QTc prolongation, as independent risk factors for sudden death due to cardiac arrest[14,15].

In first three published series[16-18], QTc intervals reported were significantly prolonged. Seth et al[16] reported that the average QTc interval, during the acute phase of the syndrome, was 578 ms, with 42% having a QTc > 600 ms. Abe et al[17] displayed a prolonged QTc interval in all patients (median 500 ms, with a range of 436 to 581 ms). Desmet et al[18], reported that, in the acute phase, 12 of the 13 TTC patients had a QTc interval of at least 400 ms (range 310-674 ms, mean 450 ms, median 436 ms). However, in none of these series were reported episodes of torsades de pointes (TdP), life-threatening ventricular arrhythmias caused by QT prolongation.

In the TTC, a significant prolongation of QT and QTc intervals, with an increased QTd, has been confirmed by Matsuoka et al[13]. However, this paper showed the rarity of ventricular arrhythmias in the TTC. According to these Authors the fact that in this syndrome, the myocardial damage is transient could ensure an electrical stability and, therefore, a protection against

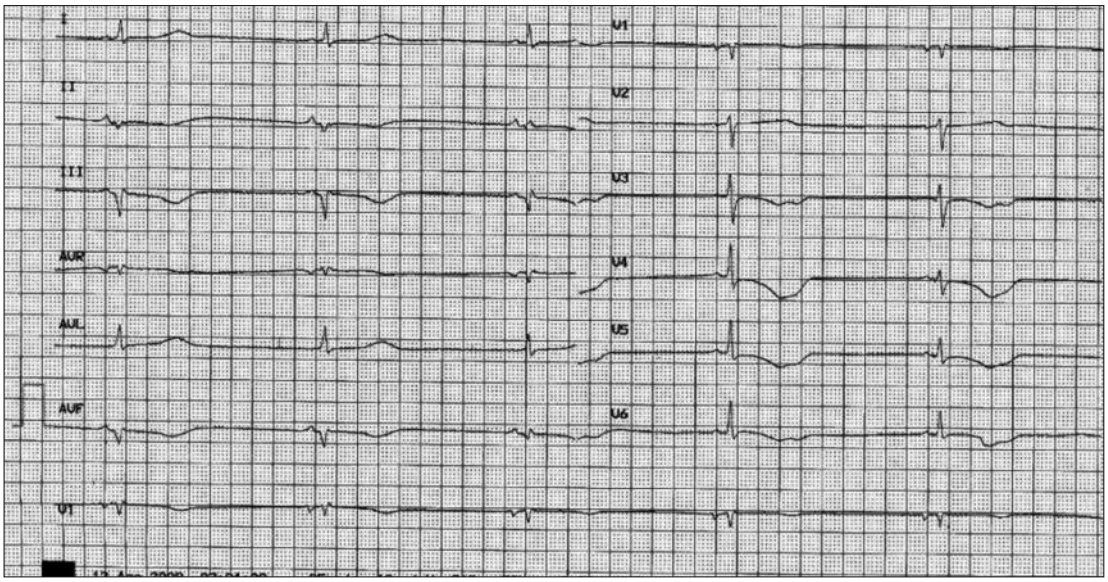

Figure 2. An ECG showing sinus rhythm at HR = 33 bpm; QT = 0.7200, QTcF (Fridericia's formula) = 0.5900, T waves inversion in V3 to V6 and in II, III, aVF.

arrhythmias. Subsequently two other series[19,20] have reported prolongation of the QTc but without reporting cardiac arrhythmias in examined patients (Table I).

Recently, however, the case reports of TTC complicated by TpP and/or other life-threatening ventricular arrhythmias have exponentially increased[10,21-35] (Figure 4). For this reason, we tried to identify some features capable of identifying those patients with higher risk of arrhythmias. Behr and Mahida[36], in an editorial published in Europace, showed that, in the acute phase of TTC, a cut-off of QTc > 500 msec has a sensibility of 82% and a specificity of 85%. These data are consistent with those of other studies: Dib et al[37] compared patients with TTC and documented arrhythmias with patients with TTC but without arrhythmias. There was a statistically significant difference between these 2 groups in QTc interval (490.5±80.8 vs 433.7±25.4, $p = 0.0025$). Moreover, the group with malignant arrhythmia had significantly more variation in R-R intervals (maximal R-R interval – minimum R-R interval in the first 24 hours of admission) and a significant increase in prior arrhythmia. Samuel-Kinori et al[38] have demonstrated that 80% of patients with TCC and TdP had risk factors for TdP, including suspicion of congenital long QT syndrome, bradycardia, hypokalemia, recent conversion from atrial fibrillation to sinus rhythm, and using QT prolonging drugs. In our paper[10], a 57-year-old woman with TTC complicated by recurrent TdP, was affected by anorexia nervosa with hypokalemia and hypomagnesemia, all risk factors for prolongation of QT and TdP. The patient presented, in addition to prolongation of QT and

Table I.

Authors	Subjects, n	Country	Phase	QTc range	Mean QTc	Median QTc
Seth et al	12	US	Acute	NS	478 ± 96	NS
Abe et al	17	Japan	NS	436-581	500	NS
Desmet et al	13	Belgium	Acute	310-674	450	436
Matsuokaet al	10	Japan	Subacute	NS	555.1 ± 45.7	NS
Bybee et al	16	US	Acute	400-574	501 ± 55	500
Yoshida et al	15	Japan	Acute	NS	NS	508

NS: Not specified.

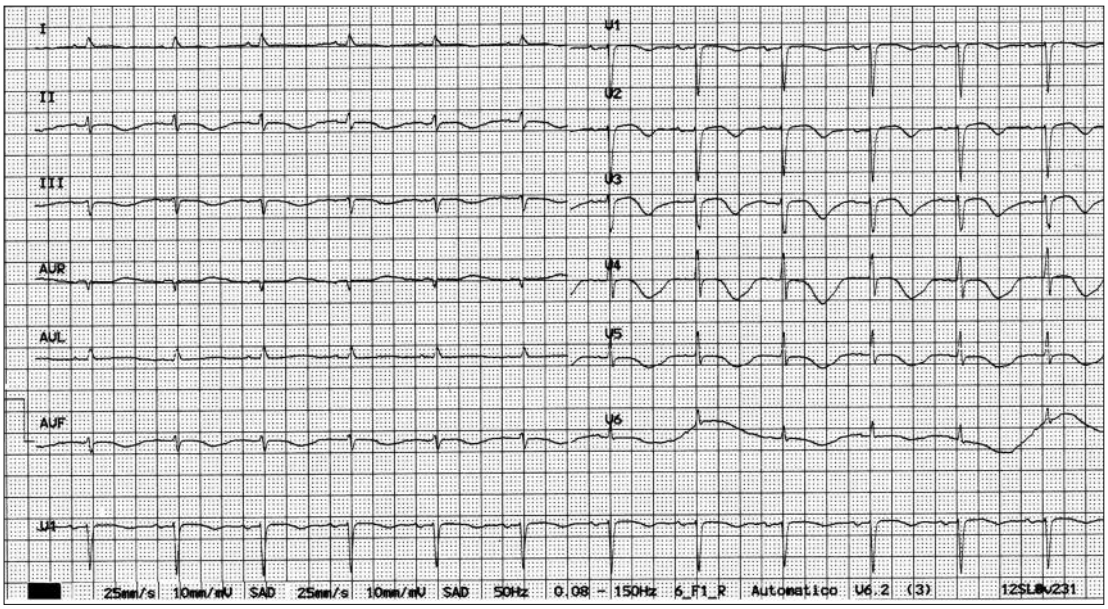

Figure 3. An ECG showing sinus rhythm at 75 bpm, T wave inversion in V1 to V6 and in II, III, aVF, QT = 0.58", QTc = 0.65", QTc dispersion = 120 msec.

QTc (QT = 0.58", QTc = 0.65"), a marked increase of corrected QTd = 120 msec.

Takotsubo e Long QT Syndrome

TTC is a cause of acquired long QT syndrome[36].

Usually, in the patients with TTC the QT intervals returned to normal between one and three months after the onset[11]. However, in about 1/3 of patients with TTC and TdP, the QT prolongation extends beyond the acute and subacute phase[36]. In this subgroup, TTC can be considered as a trigger capable of unmasking silent or inapparent long congenital QT syndrome.

Atypical Forms of TTC and Malignant Arrhythmias

Besides classic TTC, there are other forms of stress cardiomyopathy with different clinical and/or morphological patterns, sometimes with left ventricular global hypokinesia[37,40]. Some Authors have suggested that atypical forms of stress cardiomyopathies could be associated with malignant arrhythmias and cause sudden death in stressful situations in young boys[34,41].

Physiopathology

It's largely accepted that an increased concentration of catecholamines has an important

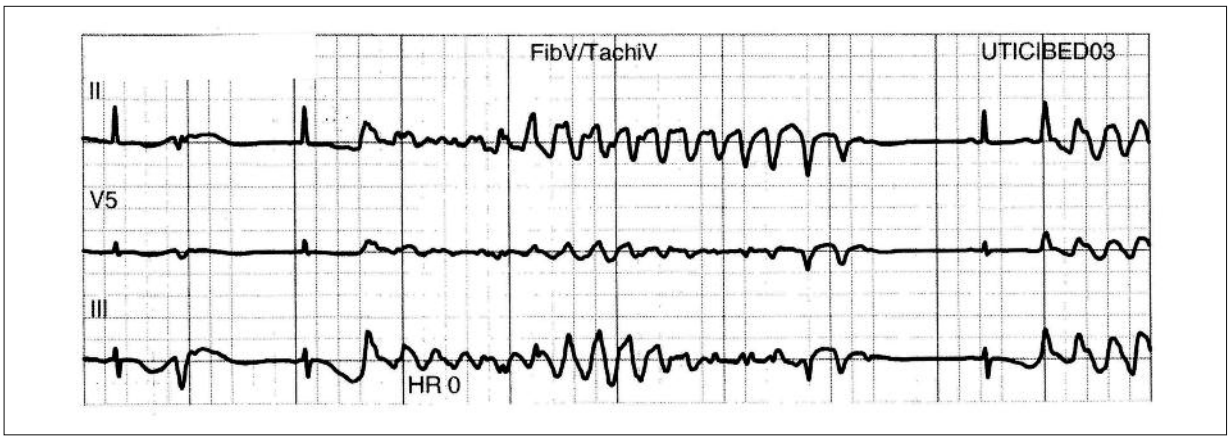

Figure 4. Episodes of torsades de pointes in a patient with takotsubo cardiomiopathy and prolonged QT.

pathogenetic role in TTC. High levels of catecholamines, which stimulate β-adrenoceptors and modify the expression of calcium-regulatory protein gene, altering the calcium regulatory system[42]. We know that intracellular calcium elevation may mediate cardiac arrhythmias[43].

Cardiac magnetic resonance in TTC is characterized by the absence of myocardial delayed enhancement and complete myocardial viability, indicative of absence of scar formation[44]: this suggests an automatic or triggered mechanism rather than re-entry.

Probably, also QT prolongation has different pathophysiology in TTC and myocardial ischemia: Bonnemeier et al[45] showed that in the TTC the "*QT dynamicity*", that is the rate adaptation of ventricular repolarization, is not significantly altered, suggesting that the autonomous nervous system acts differently in the TTC and in the myocardial infarction.

Dib et al[36] reported that patients with TTC who had malignant arrhythmia had significantly more variation in R-R intervals compared with patients with TTC but without arrhythmia. On the contrary, a reduced heart rate variability has been shown to be a predictor of mortality in patients with myocardial infarction[46]. This Author things that, when malignant arrhythmias occur in myocardial infarction, they are related to ischemia itself, whereas in TTC are linked with a prolongation of QT and then with a significant heart rate variation.

Treatment

There aren't precise guidelines regarding the treatment of TTC.

The TTC should be considered as a cause of acquired long QT syndrome and can be a trigger to be able to make overt silent or inapparent congenital long QT syndrome[36]. Therefore, the prevention and/or the treatment of arrhythmias, should be removed all the factors that exacerbate the QT prolongation: drugs (anti-arrhythmics such as sotalol, quinidine, amiodarone, ibutilide, dofetilide, disopyramide; antibiotics such as erythromycin, sparfloxacin; anti-psychotics such as haloperidol, thioridazine, pimozide, chlorpromazine; anti-malarials such as chloroquine, halofantrine; opiate agonists such as methadone, levomethadyl; gastrointestinal motility agents such as droperidol, domperidone, cisapride; anti-anginals such as bepridil; anti-cancer such as arsenic trioxide; antihistamines such as astemizole, terfenadine; antilipemics such as probucol; anti-infectives such as pentamidine etc.) and electrolyte imbalances (hypokalemia, hypomagnesemia, hypocalcemia)[47-49].

A temporary pacemaker should be implanted if there is marked bradycardia and, if programmed at heart rate, might terminate incessant TdP, by decreasing QT intervals[36].

Magnesium sulfate can be administered in case of long QT to prevent and/or treat TdP[3].

There is no clear guidance on the use of beta blockers. However, the finding of high concentrations of catecholamines and excessive sympathetic stimulation in the majority of these patients, makes hypothetically reasonable the use of beta-blockers, despite the absence of large randomized trials. It is more questionable the usefulness of chronic treatment with beta-blockers. Sharkey et al[2] indicate that beta-blockers, in standard dosages, did not prevent either the first or recurrent TTC episodes and that 20% of these events occurred while these drugs were administrated. However, in this paper was not analyzed the relationship between beta-blockers and arrhythmias. Recently, also Fazio et al[50] reported the limited useful of a long-term treatment with beta-blockers in TTC. Conversely, in the study of Dib el al[37] the TTC patients without arrhythmia were more likely to be on beta-blocker therapy than the study population (33% vs 80.6% $p = 0.02$), although these data should be interpreted with caution given the relatively small study group.

If there are elements of high-risk for Long QT syndrome (QTc post-TCM >500 ms, prior syncope, previous cardiac arrest) may be useful to the implantation of an ICD. However, at present, there aren't indications in the guidelines about ICD implantation in this patients[36].

Conclusions

TTC, generally considered a benign syndrome, should be reconsidered as a clinical condition at high risk for lethal arrhythmias in a subpopulation with QTc > 500 msec in acute phase.

The studies about arrhythmias and TTC are based on case reports. TTC may present with sudden cardiac death: this results in a probable underestimate of the real arrhythmic risk.

TTC is one of the causes of acquired long QT syndrome and could be a trigger able to unmask latent silent or inapparent congenital long QT syndrome.

All factors that can exacerbate QT prolongation (drugs, electrolyte imbalance) should be promptly removed.

In the case of marked bradycardia and/or TdP should be implant a temporary pacemaker.

In most cases, due to the transient nature of the syndrome, it is reasonable to recommend only beta-blocker therapy at discharge, despite the absence of randomized trials.

If there are high-risk factor for long QT syndrome (QTc post-TCM >500 ms, prior syncope, previous cardiac arrests) thought should be given an indication to ICD implant.

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