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ORIGINAL SCIENTIFIC PAPER

Typical dynamic electrocardiographic changes in Takotsubo syndrome

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ABSTRACT

Aims: Negative T waves and QTc prolongation often occur in patients with Takotsubo syndrome. Description of typical electrocardiographic changes could be a diagnosis element of this syndrome. This study aimed to clarify on the one hand the more preciously possible the typical electrocardiographic changes, and on the other hand, the timing of occurrence of these abnormalities compared to the trigger occurrence, the symptoms onset and the hospital admission.

Methods and results: We studied ECGs at admission of 59 patients with Takotsubo syndrome, a 'reference' ECG and each one available during the first five days after admission.

Methods and results: We observed significant changes on the pathological ECG compared to reference ECG: the mean number of leads with negative T waves (7.4 ± 1.9 mm vs 2.1 ± 1.4 mm, $p < 0.0001$), the highest value of negative T wave deflection among all the leads (-6.2 ± 4mm vs -1.4 ± 0.9 mm, $p < 0.0001$), the sum of all negative T waves (-27 ± 1.7 mm vs -2.8 ± 3.6 mm, $p < 0.0001$ and a QTc max and QTc mean prolongation (539 ± 63ms vs 457 ± 42ms, $p < 0.0001$ and 491 ± 52ms vs 421 ± 33ms, $p < 0.0001$ respectively). We also demonstrated that T waves were significantly more positive in pathological ECG in aVR and V1 compared to the reference one (mean value of T waves respectively of 1.8 ± 1.8 vs -1 ± 1.3, $p < 0.0001$ and 0.7 ± 1.6 vs 0.004 ± 1.2, $p = 0.008$).

Conclusion: The QTc prolongation, the profound negative T waves except in aVR and V1 occurring the first two days after admission are electrocardiographic changes typically of Takotsubo syndrome.

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Electrocardiogram; Takotsubo syndrome; QT duration; negative T wave

Introduction

In Takotsubo syndrome, the electrocardiogram (ECG) usually shows ST segment elevation at the acute phase, followed by deep T wave inversion and QTc interval prolongation at the subacute phase. Several studies showed that T wave inversion was deeper and QTc interval was longer at day 3 or 4 or later after admission in comparison with anterior myocardial infarction [1–3]. However, these findings are limited to some leads and the timing from the onset of symptoms or from the emotional or physical trigger is not described.

Another interesting ECG parameter susceptible to differentiate Takotsubo syndrome from acute coronary syndrome (ACS) or from pulmonary embolism with a high predictive accuracy is the combination of positive T wave in lead aVR and no negative T wave in lead V1 [4].

Other parameters like the maximal negative T wave voltage or the number of the negative T waves seem to be useful to distinguish Takotsubo syndrome from ACS but without timing accuracy [4].

An accurate and quickest diagnosis is important to select appropriate management strategies especially for patients in whom the stress of an emergency management could be deleterious.

The aim of this study was to describe the ECG changes in an all-comers caucasian population and to identify the timing of these changes compared with the onset of trigger and symptoms.

Methods

Study population

Between January 2005 and December 2016, we gathered the data from 123 patients presenting with a suspected Takotsubo cardiomyopathy for future

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*This author take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

retrospectively analysis. Among those, 59 consecutive Caucasian patients fulfilled the Mayo Clinic criteria for Takotsubo syndrome: (1) Transient akinesis, hypokinesis or dyskinesis of the left ventricular (LV) mid segments with or without apical involvement, these regional abnormalities extending beyond a single epicardial vascular distribution. (2) Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.(3) New electrocardiographic abnormalities (either elevation and/or Twave inversion) or modest elevation in cardiac troponin. (4) Absence of pheochromocytoma or myocarditis [5].

For analysis, only patients with troponin elevation were considered because electrocardiographic changes are not always present at the admission.

We excluded patients who did not undergo coronary angiography, patients with atypical LV dysfunction, with ventricular pacing, without documented LV function recovery, with insufficient information about timing or those who underwent percutaneous coronary intervention. Troponin reference values (troponin I, troponin T, high sensitivity troponin) were different through laboratories and years. For these reason, we analysed troponin levels compared with the upper normal limit.

We also collected timing from emotional and/or physical trigger, symptoms onset and admission. All patients underwent coronary angiography and LV function analysis either by LV angiography or by echocardiography.

The study was approved by Ethics Committee of our institution.

Electrocardiographic evaluation

We analysed twelve-lead ECGs at admission and each one available during the first five days after admission.

Twelve-leads ECGs were recorded with standard protocol (at setting of 10 mm/mv and 25 mm/s). All measurements were analysed using standard criteria in each lead.

We considered as 'reference ECG' either the first normal ECG at follow-up visit after Takotsubo syndrome or admission ECG or, more rarely, another normal ECG recorded before Takotsubo syndrome without relationship with an acute cardiac event.

We chose as 'pathological ECG' the one with the deepest negative T waves as described in literature [4].

All measurements were performed by the same investigator blinded from clinical data. Standard measurements included heart rate, PR interval and QRS axis. The QTc interval was calculated with Bazett's formula. Biphasic of isoelectric T waves were not analysed.

The following repolarization measurements were performed in each of the 12 leads when possible: QTc max defined as the longest QTc max among the 12 leads, QTc mean defined as the mean of the QTc interval of the 12 leads, QT dispersion defined as the difference between the longest and the shortest QTc in the 12 leads, maximal voltage amplitude of negative T waves in all leads (NTWm), the sum of the amplitudes of negative T waves in all leads (NTWs).

Statistical analysis

Differences between the reference and the pathological ECG

Statistical analysis for comparison between reference and pathological ECG results are expressed as mean ± standard deviation. Comparisons between variables were performed using Wilcoxon test (for paired samples), and Chi-squared tests, as appropriate. A p-value < 0.05 was considered statistically significant.

Timing of ECG modifications compared to trigger and symptoms occurrence

Between admission and follow-up, a median of four analysable ECG (from 2 to 6 ECG) were available per patient. There is, for instance, 53 available ECG at admission and 38 at D1, the evolution between the mean value at admission and at D1 could then change simply because the numbers of patients differ. In the longitudinal analysis, we used linear mixed models that take into account the patient effect (with a random intercept) and that is able to cope with random missing values. Such models give corrected estimate of how the mean of a parameter change over time.

These estimates were used in the graphical representation of Figure 3.

An uncorrected analysis has also been done and produced similar results (data not shown).

These analyses were performed using R 3.3 (The R Foundation for Statistical Computing, Austria, Vienna, 2017).

Results

Study population

We screened 123 patients in which the term 'Takotsubo syndrome' was mentioned. From this group, we excluded 64 patients for lack of a recovery proof [15], the absence of sufficient information about timing (7), the absence of coronary angiogram (3), the absence of troponin dosage (2), ACS with important cardiac enzyme elevation (2), coronary angioplasty (3), non-typical LV dysfunction (9), non-interpretable or missing ECG (19) or

ventricular pacing (4). Some of them had more than one exclusion criteria. We kept 59 patients with typical Takotsubo syndrome for analysis.

The mean age was 71 ± 11 years (97% of women). An emotional trigger was identified in 13 patients (22%), a physical stress in 22 patients (37%) and no trigger was found in 15 patients (26%). In 9 patients (16%), the trigger was considered together as emotional and physical trigger.

The symptoms were mainly chest pain (69%) but also dyspnoea (34%), dizziness (8%), syncope (7%), palpitations (2%) and vomiting (2%).

Troponin value peaked at 115 ± 359 times the upper limit of normal. No patient had potassium level abnormalities.

A minority of patients took medications that could prolong the QTc: 11 patients (18%) had class III and three patients (5%) had class Ic antiarrhythmic medication.

Most patients (55/59) were in sinus rhythm at admission. Four patients (7%) were in atrial fibrillation or flutter.

Coronary angiogram showed normal arteries in 22 (37%), non-significant atherosclerosis with <50% stenosis in 21 (36%), moderate (<70%) stenosis without plaque rupture in 12(20%) patients. One patient had a known chronic total occlusion of the intermediate branch and three patients had a milking of left anterior descending artery.

The mean LVEF by ventriculography was 46% (±12,4%)

Differences between the reference and the pathological ECG

One patient was excluded from this analysis for lack of reference ECG.

The main morphological modifications are summarised in Table 1.

We observed significant changes on the pathological ECG compared to reference ECG: the mean number of leads with negative T waves (7.4 ± 1.9 mm vs 2.1 ± 1.4 mm, $p < 0.0001$), the highest value of negative T wave deflection among all the leads (-6.2 ± 4mm vs −1.4 ± 0.9 mm, $p < 0.0001$) and the sum of all negative T waves (−27 ± 1.7 mm vs −2.8 ± 3.6 mm, $p < 0.0001$). We also found clearly a QTc prolongation with significant increase of QTc max (539 ± 63ms vs 457 ± 42ms, $p < 0.0001$) and QTc mean (491 ± 52ms vs 421 ± 33ms, $p < 0.0001$) on pathological vs reference ECG.

The Figure 1 shows an example of typical ECG change in one of the studied patient who presented a Takotsubo syndrome after a transthoracic biopsy.

As already described previously (4), we observed significantly more often the association of positive T waves in aVR and no negative T waves in V1 in pathological ECG compared to the reference one with a mean value of T waves respectively of 1.8 ± 1.8 vs −1 ± 1.3 ($p < 0.0001$) and 0.7 ± 1.6 vs 0.004 ± 1.2 ($p = 0.008$). In all other leads, T waves were significantly more negative in pathological compared to reference ECG as describe on Figure 2.

Timing of ECG modifications compared to trigger and symptoms occurrence

We did not find any information about the timing of the trigger in 27 (46%) and of the symptoms in 15 (25%) patients. In eight (14%) patients, we did not find either the time of the trigger or of the symptoms. These eight patients without precise time reference

Table 1. Morphological changes between the reference ECG and the pathological one.

	Reference ECG	Pathological ECG	Ref vs Path ECG[a]
Number of derivations with:	mean ± SD	mean ± SD	
Biphasic T waves	0.4 ± 0.8	0.5 ± 0.9	0.62
Isoelectric T waves	1.4 ± 1.7	0.8 ± 1.3	0.09
T wave inversion[b]	2.1 ± 1.4	7.4 ± 1.9	<0.0001
Positive T waves[c]	7.9 ± 2.3	2.8 ± 1.7	<0.0001
Value of T wave (mm)			
The highest value of positive T wave	3.6 ± 3.3	2.4 ± 1.4	0.002
The highest value of negative T wave	−1.4 ± 0.9	−6.2 ± 4	<0.0001
The sum of all positive T waves	15.4 ± 10.1	5.4 ± 4.8	<0.0001
The sum of all negative T waves	−2.8 ± 3.6	−27 ± 2.19	<0.0001
QT interval (ms)			
QT dispersion	68 ± 31	99 ± 46	<0.0001
QTc Max	457 ± 42	539 ± 63	<0.0001
QTc Mean	421 ± 33	491 ± 52	<0.0001
QRS Axis (°)	25 ± 47 ($N = 56$)	14 ± 56 ($N = 56$)	NS
Atrial fibrillation or flutter, no./no. total	3/58	6/58	NS

[a]Wilcoxon test or Chi Square test, respectively, for comparing the values/patient between the 2 ECG.
[b]T wave inversion (negative T wave) was defined as a depth of <0.5 mm (0.0.5 mV) in any lead.
[c]Positive T waves were defined as amplitude of ≥ 0.5 mm (0.05 mV).

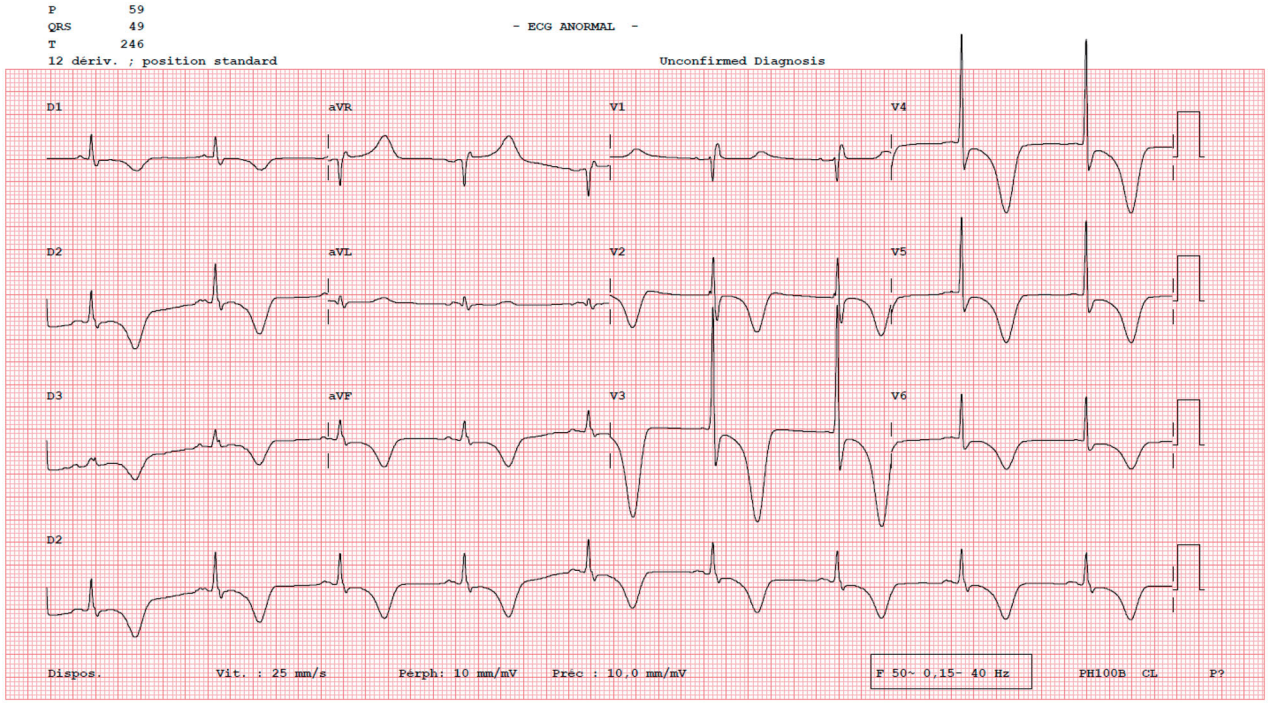

Figure 1. Example of typical ECG change in one of the studied patients who presented a Takotsubo.

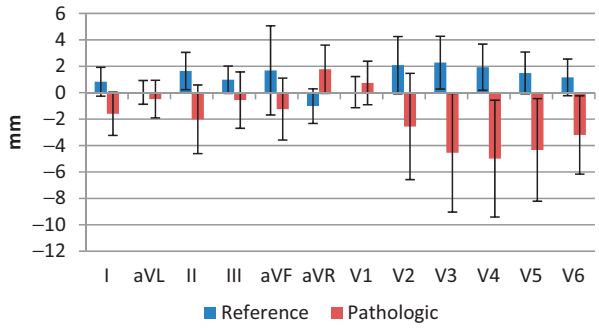

Figure 2. Mean value (+ SD) of T wave amplitude on each derivation on reference and pathological ECG.

were excluded from this part of analysis, leaving a study population of 51 patients.

The emotional and/or physical trigger or the onset of symptoms (whichever came first) was defined as time zero and occurred on average respectively 57 ± 57 h and 24 ± 32 h before the first ECG.

The repolarization abnormalities occurred progressively in the hours after the trigger, the symptoms and the admission.

During the acute phase, the QTc mean interval was the longest concordantly at the second day after the trigger moment, the onset of the symptoms and the admission (Figure 3). The QTc max and the QTc range were both the longest the first day after admission (Figure 3).

The NTWm and the NTWs were clearly the most important at the second day after admission with progressive normalisation during the next days (Figure 3).

The most precocious electrocardiographic changes are observed the first day after admission for QTc (max, mean, range) prolongation and then the second day after admission for NTWm and NTWs. We also observed that QTc (max, mean, range) maximal prolongation occurs precociously the second day after symptoms onset and that NTWm and NTWs peak the second day after symptoms onset. However, the timing of the appearance of the electrocardiographic modifications compared to the trigger does not appear clearly determined.

Discussion

Difference between the reference and the pathological ECG

This retrospective study found that the pathological ECG in Takotsubo syndrome is characterised by a great number of leads with negative T waves and deeper negative T waves. These modifications translate in a more important sum of negative T waves in 12-leads. These parameters have been reported as significantly discriminating Takotsubo syndrome from ACS and pulmonary embolism [4]. G. Mungai demonstrated a significant increase of NTWm (1.7 ± 1.8 mV to 4.6 ± 2.9 mV, difference: 2.9 ± 1.1) and of NTWs (4.7 ± 7.7mV to 17.2 ± 12.5 mV, difference 12.5 ± 4.8) while we founded a more pronounced difference both NTWm (1.4 ± 0.9 to 6.2 ± 4mV, difference 4.8 ± 3.6) and NTWs (2.8 ± 3.6 to 27 ± 2.19 mV, difference 24.2 ± 1.4) [3].

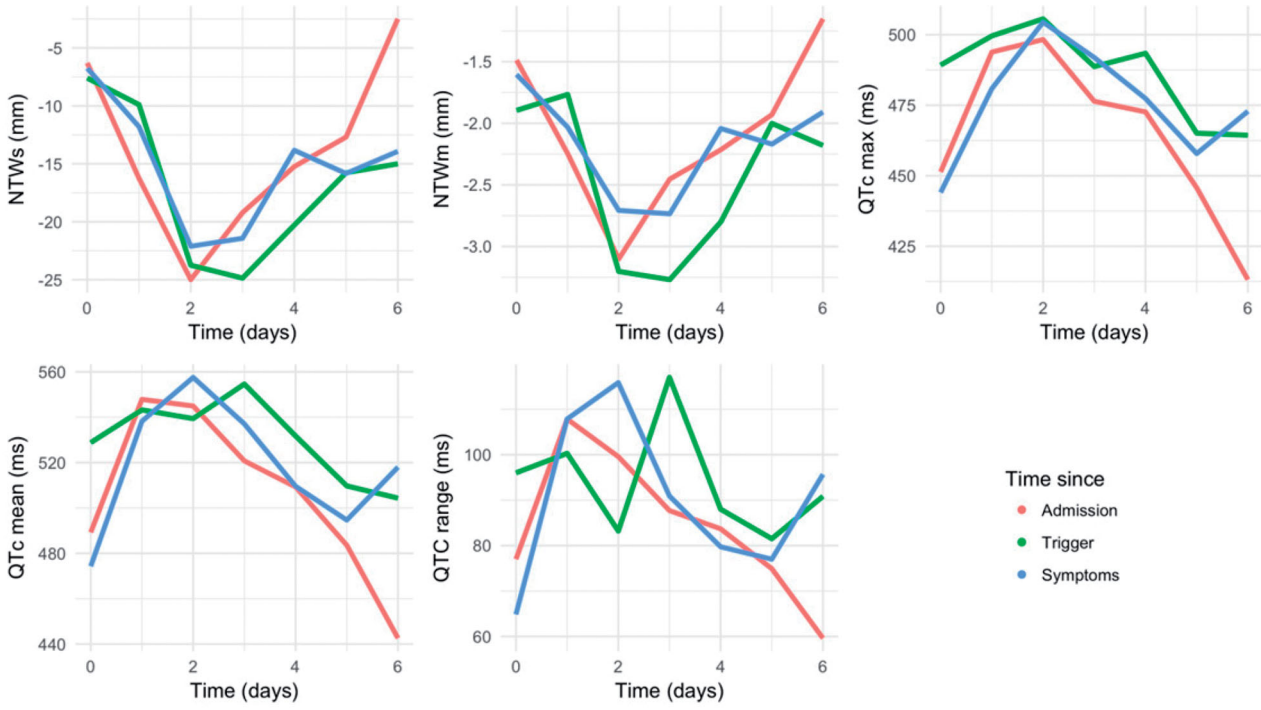

Figure 3. Temporal evolution of the mean value of each electrocardiographic parameter after trigger, symptoms and admission. Abbreviations: NTWs: the sum of the amplitudes of negative T waves in all leads; NTWm: maximal voltage amplitude of negative T waves in all leads;.

We demonstrated a significant increase of QTc max, QTc mean and QTc dispersion in concordance with different studies. Indeed, QTc pronounced prolongation (>500ms) is usually described [3,6–8]. This increase is more marked than in ACS [1,11].

We also confirm the association of positive T waves in aVR and no negative T wave in V1 as typical changes of Takotsubo syndrome. Kosuge and al. described positive T wave in lead aVR and no negative T wave in lead V1 in 95% of patients with Takotsubo syndrome in contrast to only 3% of patients with ACS or acute pulmonary embolism ($p < 0.001$) [4].

The association of pronounced negative T waves in a great number of leads, pronounced QTc prolongation and positive T waves in lead aVR and V1 are thus typical of Takotsubo syndrome and are important element to distinguish this pathology from other acute injuries.

Two of these parameters (inverted/biphasic T waves in V2-V5) and prolonged QTc are also included in a recent scoring tool for prediction of Takotsubo syndrome [9].

It is interesting to compare ECG with a previous control ECG to appreciate these changes.

Timing of the ECG modifications

We demonstrated that the most relevant electrocardiographic timing evolutions are first the QTc prolongation the first day after admission and then T waves inversion the second day after admission.

We observed also that the NTWm and NTWs are the most important the second and third days after symptoms. These findings are consistent with previous studies that show that the number of leads with negative T waves is the highest the first 24 h after symptoms [10] and more precisely at the third day [11]. It is an element of discrimination from ACS and from pulmonary embolism [4,11].

The electrocardiographic changes after trigger are not so clear and seam to occur mainly after the second and third day. We did not have precise information about the trigger in more than half of the patients. It is probably not a determinant parameter to consider for electrocardiographic analysis.

General discussion

We confirm, in a median size Caucasian population, ECG characteristics previously described in smaller series or in series in which few parameters were analysed simultaneously.

The originality of this study is the number of studied parameters on the whole 12-leads of each ECG and their evolution over time. Another important point is that we analysed a Caucasian population while a lot of previous studies are carried on Japanese

population [1,4,7,8,10,12,13] and we know that results are not always transferable to other populations. Indeed, Franco et al. demonstrated some differences concerning ECG changes in Takotsubo syndrome in an African American population [14].

We also intended to analyse the timing between the ECG modifications occurrence and the trigger that is the earlier element when it is known. However, this element does not appear useful for Takotsubo syndrome diagnosis because too infrequently identified and with a too variable delay between its occurrence and the completion of the first ECG on admission.

However, for patients admitted more than 24 h after the symptoms onset, typical ECG changes as pronounced QTc interval prolongation, giant negative T waves in a great number of leads and positive T waves in aVR and no negative T wave in V1 could be important parameters for Takotsubo syndrome diagnosis. It could eventually be an argument to postpone coronary angiography especially in patients with Takotsubo syndrome due to medical stress as a recent surgery or in patients with multiples comorbidities as severe anaemia, hyperthyroidism, chronic renal disease, … Indeed, coronary angiography can be perceived as an additional stress that may be harmful in such fragile patients.

It is speculated that T-waves inversion and QTc interval prolongation are due to interstitial oedema that create intramural repolarization inhomogeneity either transmural (between endocardial and epicardial layers) or regional (from LV apex to base). Perazzolo and al. demonstrated a correlation between the apicobasal intensity signal in T2 (representing myocardial oedema) and NTWm ($p = 0.02$), NTWs ($p = 0.03$) and QTc max ($p = 0.02$) [15].

This study has limitations. It is a retrospective study without control group and some data about the timing were not found. We considered only patients with LV regional wall motion abnormality with apical and circumferential mid-ventricular hypokinesis and basal hypercontractility. Electrical abnormalities could be different in atypical form of Takotsubo syndrome.

Conclusion

The most important changes on the ECG in patients with Takotsubo syndrome in acute phase compared with reference ECG in the same patient are the higher number of leads with T negative waves, deeper negative T waves, a more important sum of negative T waves and also a QTc max and mean interval prolongation. Another very frequent change is also the positivization of T waves in aVR and in V1 during the acute phase. The timing of the ECG modifications is difficult to establish in relation to the trigger of the syndrome but we can observe that the QTc max, mean, range interval prolongation appear mostly at the first day after the symptoms onset and after admission and that inversion of the T waves appear mostly at the second day after admission and at the second and third days after symptoms onset.

We demonstrated that the most relevant electrocardiographics timing evolution are QTc prolongation the first day after admission and negative T waves occurrence the second day after admission. Similarly, we found a QTc prolongation the second day and negative T waves occurence the second and the third day after symptoms onset.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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