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A Case of Severe QTc Prolongation During Targeted Temperature Management – What Can We Learn?

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 57-year-old
Final Diagnosis: Stroke
Symptoms: Aphasia • facial droop • weaknes of lower limbs
Medication: —
Clinical Procedure: Targeted temperature management
Specialty: Cardiology • Critical Care Medicine

Objective: Unusual or unexpected effect of treatment

Background: QTc prolongation during targeted temperature management (TTM) post cardiac arrest is a known effect of hypothermia, but its significance is unclear. Several studies suggest that temporary prolongation during TTM is not prognostic and does not potentiate fatal arrhythmias; however, there are limited cases of patients presenting with QTc intervals >700 milliseconds.

Case Report: We describe a case in which a 57-year-old woman with diabetes, hypertension, and atrial fibrillation presented with concern for stroke. The hospital course was complicated by cardiac arrest requiring TTM, which was stopped early due to significant QTc prolongation of 746 milliseconds.

Conclusions: TTM is beneficial post resuscitation for good neurological outcomes, but it also has known adverse cardiac effects such as QTc prolongation. The significance of QTc prolongation during TTM is unclear as several studies have shown no increased incidence of malignant arrhythmias. One case report in the literature describes the incidence of torsades de pointes due to QTc prolongation during TTM. Further study and guidelines regarding electrocardiogram monitoring are needed to determine the importance of QTc prolongation during TTM.

MeSH Keywords: Arrhythmias, Cardiac • Tachycardia, Ventricular • Ventricular Fibrillation

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Background

Targeted temperature management (TTM) has become standard for comatose patients after cardiac arrest. It has been shown to have neuroprotective effects through reduced brain metabolism, decreased neural apoptosis, decreased production of free radicals, and overall decreased inflammation. However, it also has several adverse cardiovascular effects due to its impact on electrolytes and the stability of the cardiac membrane, potentially leading to QTc prolongation and possible arrhythmias [1–3]. QTc prolongation is a known finding during hypothermia, and it is negatively correlated with temperature (i.e., lower temperatures are associated with prolonged QTc) [2]. In addition, several drugs (i.e., amiodarone, propofol) may be used after a cardiac arrest, which can contribute to the possibility of a prolonged QTc interval. Despite QTc prolongation being a known effect, its importance, its association with malignant arrhythmias, and whether it requires TTM termination are uncertain. We present a case involving a 57-year-old woman who experienced cardiac arrest during her hospital course but did not complete a full TTM course due to significant QTc prolongation of 746 milliseconds.

Case Report

A 57-year-old woman with diabetes, hypertension, and known history of paroxysmal atrial fibrillation presented with left-sided weakness and aphasia with unknown time of onset. Ultimately, she was found to have a large acute right posterior cerebral artery infarct and noted to have thrombosis of the left distal vertebral artery through the left basilar artery. Physical exam was significant for temperature (36.7°C), blood pressure (BP, 147/87), heart rate (HR, 76 beats/min), left-sided facial droop, upper and lower extremity weakness, and expressive aphasia. She was also noted to have clear breath sounds with increased secretions. Unfortunately, due to time of presentation, she was not a candidate for thrombolytic administration. Labs initially showed white blood cell (WBC) count of 23/nL; hemoglobin, 14.7 g/dL; hematocrit, 44%; platelets, 197/nL; sodium, 135 mmol/L; potassium, 4.2 mmol/L; chloride, 103 mmol/L; carbon dioxide, 16 mmol/L; blood urea nitrogen (BUN), 14 mg/dL; creatinine, 0.9 mg/dL; anion gap (AG), 16; lactic acid, 7.1 mmol/L; troponin, 0.020; and β-hydroxybutyrate, 26.9 mg/dL. She subsequently received empiric broad-spectrum antibiotics and 3 boluses of normal saline for possible unknown infectious source. She was noted to have a brief episode of atrial fibrillation on cardiac monitor, although electrocardiograms (EKGs) at the time of admission showed normal sinus rhythm with suspicion of mild left ventricular hypertrophy and a prolonged QTc interval of 486 milliseconds (Figure 1). Overall, patient was thought to have had an embolic stroke secondary to paroxysmal atrial fibrillation, and she was transferred to a nearby stroke center because of the large infarct. Repeat lab work was done, which showed resolution of the AG (8) and lactic acidosis (1.2 mmol/L), as well as mild improvement in leukocytosis (WBC count, 20/nL).

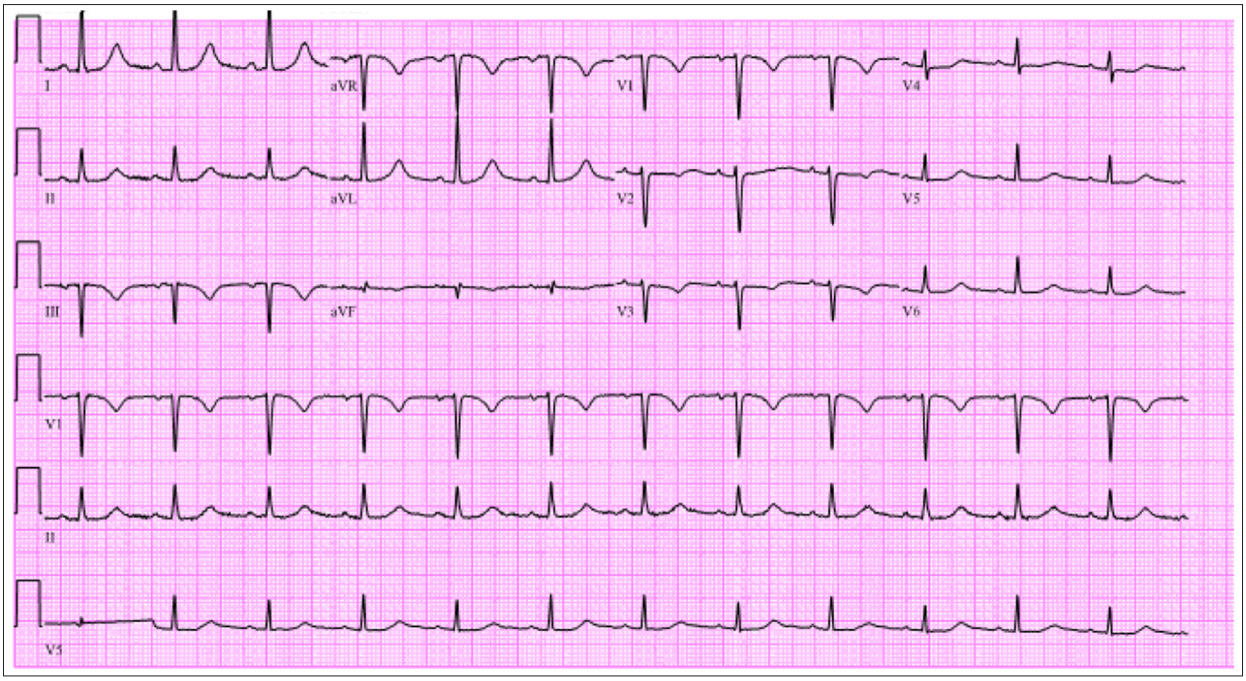

Figure 1. Electrocardiogram at time of admission showing normal sinus rhythm with left ventricular hypertrophy and prolonged QTc interval of 486 milliseconds.

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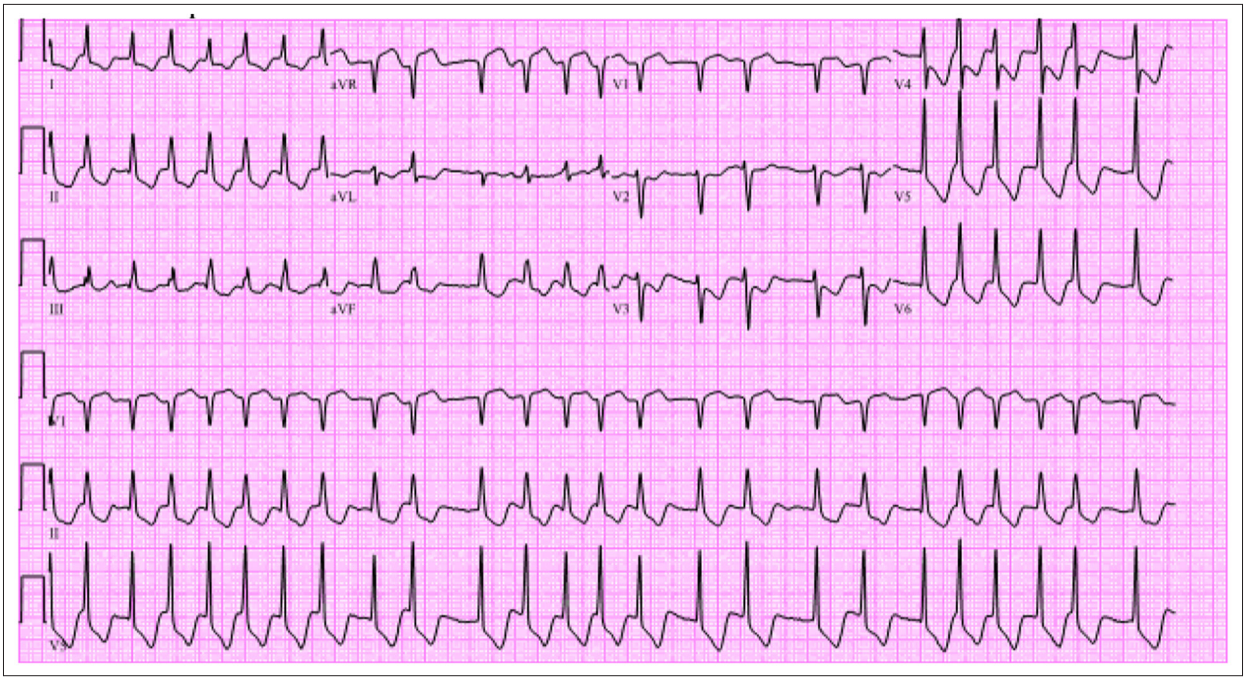

Figure 2. Electrocardiogram after return of spontaneous circulation from pulseless electrical activity/ventricular tachycardia arrest showing atrial fibrillation with rapid ventricular response.

The patient's hospital course was complicated by cardiac arrest, initially noted to be pulseless electrical activity (PEA), followed by ventricular tachycardia requiring defibrillation. During resuscitation, she received 1 mg of epinephrine and 50 mL of sodium bicarbonate and was defibrillated once at 200 J. Return of spontaneous circulation (ROSC) was obtained after 10 minutes. Her EKG after ROSC showed atrial fibrillation with rapid ventricular response (Figure 2). Computed tomography of the head was repeated and showed evolving infarct of the right corona radiata, right posterior medial temporal lobe, right occipital lobe, and bilateral cerebellar hemispheres with no bleed. Vitals were stabilized with an initial core temperature of 37.2°C, BP of 161/88, and HR of 134 beats/min. She was unresponsive to commands and determined to be a candidate for TTM to a temperature of 33°C after cardiac arrest. TTM was initiated 4 hours after ROSC using ArticSun cooling pads, cold saline infusion, propofol for sedation, and cisatracurium for neuromuscular blockade. The duration of cooling took longer than expected, possibly secondary to the patient's elevated body mass index of 35. The goal temperature of 33°C was achieved approximately 7 hours after ROSC but was terminated shortly afterward due to significant QTc prolongation of 746 milliseconds (Figure 3). At this time, she was receiving propofol, fentanyl, esmolol, insulin, and cisatracurium infusions. Her vitals were stable with HR at 68 beats/min; BP, 132/76; mean arterial pressure, 99 mmHg; and CVP, 8 cmH_2O. Labs were repeated and showed sodium at 148 mmol/L; potassium, 3.6 mmol/L; chloride, 122 mmol/L; carbon dioxide, 19 mmol/L; BUN, 16 mg/dL; creatinine, 0.68 mg/dL; and lactate, 1.0 mmol/L. Nevertheless, there was concern for development of arrhythmia with such a prolonged QTc, and subsequently, the process of rewarming began at a rate of 0.25°C/h per protocol. Overall, it was noted that the patient's temperature and QTc interval were inversely associated: With increased temperatures, her QTc decreased. However, it remained prolonged, and thus the decision was made to fully abort TTM. Within approximately 30 minutes of termination of TTM, the QTc interval decreased to 612 milliseconds (Figure 4). At a temperature of 34°C, the patient's QTc interval was measured to be 618 milliseconds, and at a temperature of 36°C, it was 562 milliseconds. After 16 hours, QTc interval continued to decrease to 503 milliseconds (Figure 5).

Overall, the cause of her cardiac arrest was unclear. Echocardiogram showed a left ventricular ejection fraction of 40% with focal severe mid septal hypokinesis, mild diffuse inferolateral hypokinesis, and stage I diastolic dysfunction. It was considered that she likely had underlying cardiac disease that was not known prior to admission due to noncompliance with physician visits. In the setting of decreased left ventricular function noted on echocardiogram, underlying coronary artery disease was a concern, but the patient was deemed a poor candidate for invasive interventions due to her neurological involvement. Her underlying central nervous system condition may have played a role in her cardiac arrest. Throughout her hospital course, she continued to have progressively worsening neurological signs, with fixed nonreactive pupils, the presence of doll's eyes, and negative caloric stimulation. Ultimately, there was concern for impending brain

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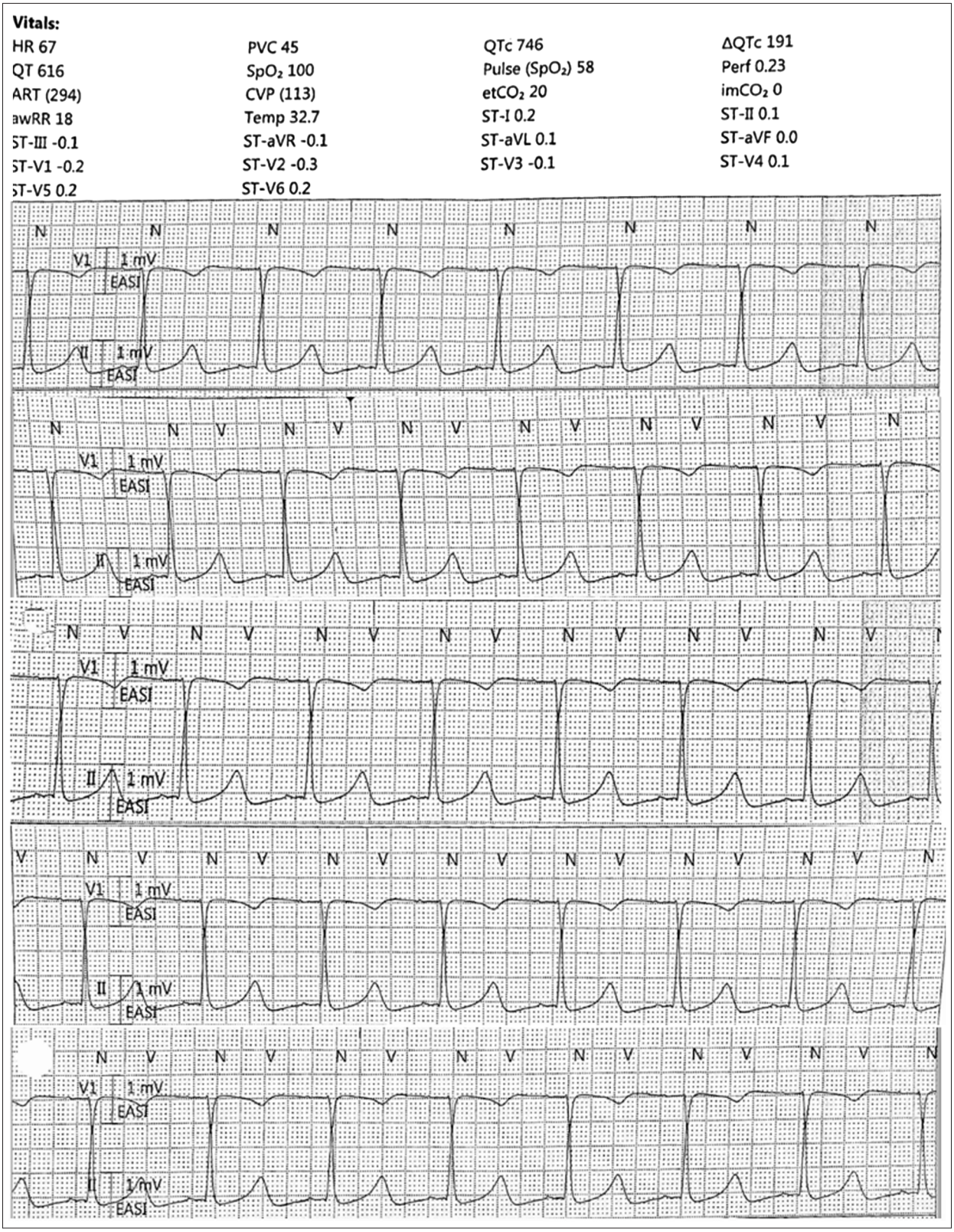

Figure 3. Telemetry strip showing QTc prolongation of 746 milliseconds, noted at 32.9°C, resulting in termination after 8 hours of therapeutic targeted temperature management.

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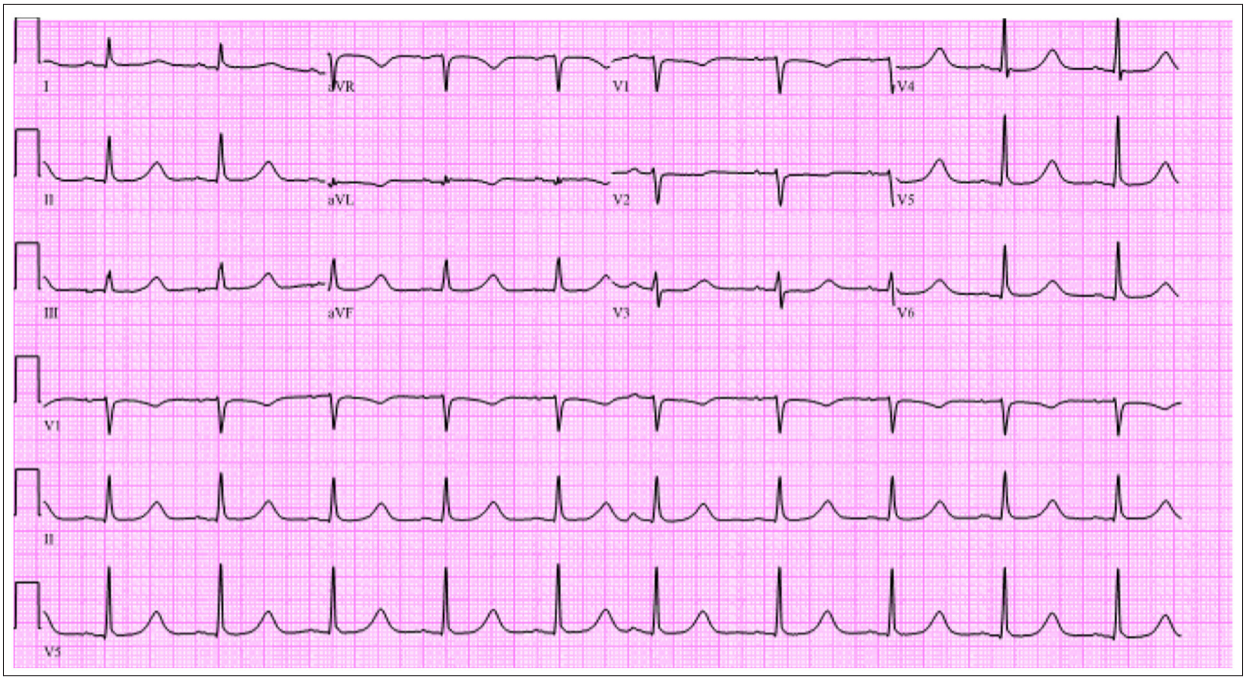

Figure 4. Electrocardiogram done 30 minutes after targeted temperature management termination showing QTc prolongation of 612 milliseconds.

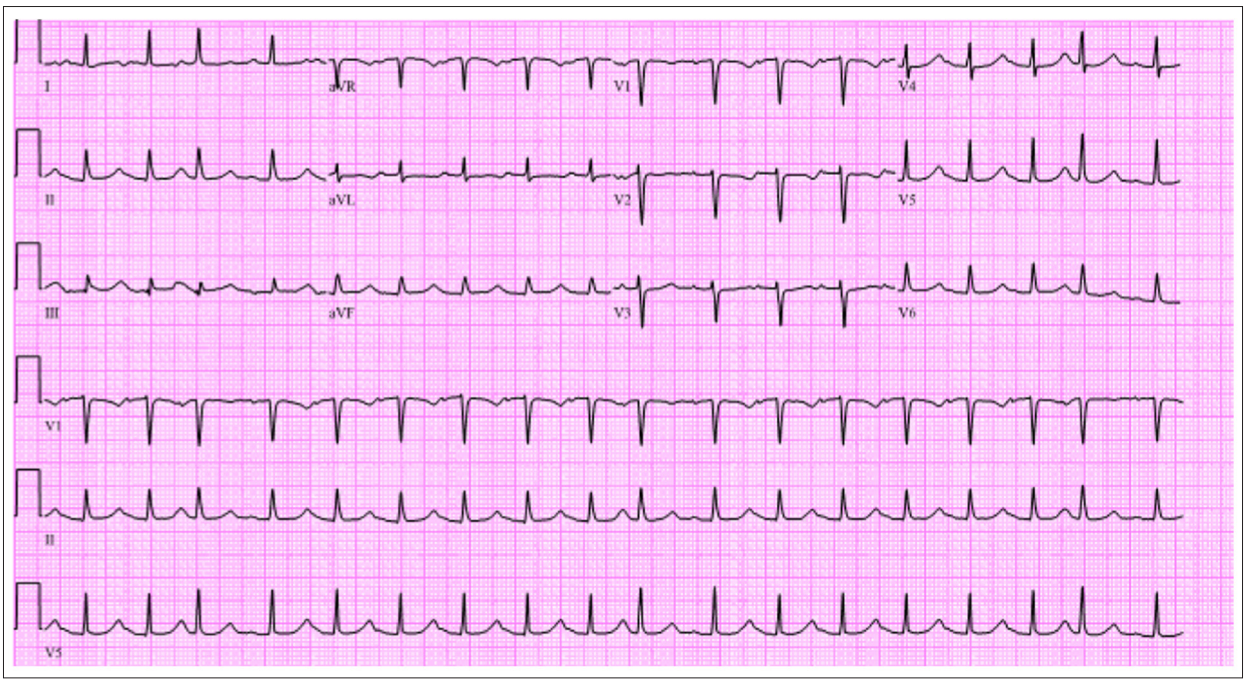

Figure 5. Electrocardiogram done after 16 hours of targeted temperature management cessation and at 36.3°C showing improved QTc prolongation to 503 milliseconds.

herniation. Repeat imaging of her head showed progression of her stroke, with developing dilation of lateral and third ventricles with mass effect on the fourth ventricle, thought to be secondary to hydrocephalus. The patient eventually met criteria for brain death via clinical examination findings and apnea testing, and she was pronounced brain dead.

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Discussion

QTc prolongation is common during therapeutic hypothermia, which is conducted for neuroprotection after ventricular fibrillation and ventricular tachycardia cardiac arrests. Hypothermia affects the cardiac cell membrane via electrolyte disturbances in potassium, magnesium, calcium, and sodium, which in turn cause prolongation of ventricular repolarization and the possibility of ventricular arrhythmias [1,3]. The physiologic effects of TTM along with the use of class III antiarrhythmic drugs (i.e., amiodarone) for ventricular tachycardia/ventricular fibrillation cardiac arrests can lead to QTc prolongation, which can in turn potentiate fibrillation and malignant arrhythmias. However, most patients are able to complete full duration of induced hypothermia [3].

The cause of our patient's cardiac arrest remained unclear. She was unable to provide medical history on admission due to aphasia, and per her family she remained secretive about her health. Her initial EKG showed a prolonged baseline QTc, with uncertain cause. Her cardiac arrest initially was thought to be from unknown underlying coronary artery disease, due to reduced left ventricular function with ejection fraction 40% noted on echocardiogram, but was considered atypical due to mild troponin elevations and no clear ischemic changes noted on any EKG even after her arrest. Cardiac catherization to further clarify whether she had preexisting silent coronary artery disease would have been ideal, but it could not be done due to her stroke. Furthermore, she was a poor candidate for anticoagulation. Her cardiac arrest was eventually attributed to her underlying stroke. With regard to management post cardiac arrest, she was unable to complete a full duration of TTM. With a significant increase in her QTc from 486 milliseconds on admission to 746 milliseconds at 33°C, there was concern for development of a fatal arrhythmia. Her striking prolongation was attributed to TTM. At the time of this prolongation, she was receiving propofol infusion for sedation. However, propofol was continued after abortion of TTM and the QTc interval continued to decrease with only changes in temperature. Therefore, we do not think the propofol infusion contributed considerably to the QTc prolongation. Attempts were made to maintain her in a hypothermic range, but her QTc level remained long. At a temperature of 34°C, her QTc was 618 milliseconds, while at 36°C, it was 562 milliseconds. Consequently, the decision was made to completely terminate TTM. The situation raised the questions about the level at which QTc prolongation remains benign and the point at which risks of this effect outweigh the benefits of neuroprotection.

Several studies have investigated the correlation between QTc prolongation and the possibility of developing malignant arrhythmias during TTM. In a small study of 34 patients, Storm et al. [4] demonstrated that even in patients with significant QTc prolongation (>670 milliseconds), no malignant arrhythmias occurred. Similar conclusions were drawn in a larger retrospective study of 193 patients by Rosol et al. [5], who concluded that there was no differential increase in QTc in patients who experienced malignant arrhythmias and those who did not. In addition, case reports have been published showing that patients with congenital long QT syndrome with QTc intervals as long as 667 and 540 milliseconds were able to tolerate TTM without the potentiation of torsades de pointes [6,7]. Previous research also suggests that a risk of clinically significant arrhythmias occurs only if the core body temperature decreases below 30°C [8]. Despite these studies, however, one case report describes a patient with significant prolongation of QTc from 390 to 720 milliseconds complicated by torsades de pointes after reaching therapeutic hypothermia range [6,7]. Therefore, it remains unclear whether the change in the QTc is more important than the QTc prolongation itself. Most studies did not include QTc intervals greater than 700 milliseconds, thus is it unknown whether a QTc interval as high as 746 milliseconds, as seen in our patient, would have adverse effects.

Neurologic injury after cardiac arrest is common, and TTM post resuscitation has been shown to improve survival with good neurologic outcomes in appropriate candidates. Although TTM has become a common practice and QTc prolongation is a known adverse effect, there are currently no guidelines regarding EKG monitoring during TTM. In addition, despite the findings of the TTM Trial, which showed no significant difference in mortality and neurological outcome between TTM at 33°C versus 36°C, patients continued to be cooled to 33°C, placing them at greater risk for prolonged QTc [9]. However, Lascarrou et al. [10] have described that patients who experienced nonshockable rhythms had favorable neurological outcomes at 90 days when cooled to 33°C compared with normothermia at 37°C [10]. Furthermore, there is no clear recommendations on when TTM should be terminated based on the QTc.

Many patients need anti-arrhythmic agents as part of their management post cardiac arrest. Hence, the situation becomes even more complicated because these agents can cause QTc prolongation. Overall, further studies are needed to determine when the potential benefits of neuroprotection outweigh the potential for malignant arrhythmias. There is also a dire need for guidelines regarding cardiac rhythm monitoring as part of TTM protocols.

Conclusions

A prolonged QTc interval of 746 milliseconds has not been described in the literature, and thus the significance of its presence during TTM is uncertain. Although one case study

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showed initiation of torsades de pointes during TTM due to a QTc of 726 milliseconds, several studies have shown that QTc prolongation during TTM has no effect on the potentiation of fatal arrhythmias; however, they do not describe QTc intervals greater than 700 milliseconds. TTM has become the standard of care per all current major critical care guidelines including those from the International Liaison Committee on Resuscitation [11] and the European Resuscitation Council [12]. However, no guidelines exist regarding EKG monitoring during TTM, nor are there recommendations describing when TTM should be stopped in association with QTc prolongation. Despite our familiarity with the current literature, we were uncertain about the risks in continuing TTM in our patient because of such a high QTc interval. Further studies and updated guidelines are required for clarification of the dilemma so that we may offer the best care to our patients. We need an adequate understanding of the importance of QTc prolongation and whether or not it is benign, so that we do not withhold life-altering therapies such as TTM.

Conflict of interest

None.

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