<PE-AT>Electrocardiographic Changes in Patients Undergoing Targeted Temperature Management

Electrocardiographic Changes in Patients Undergoing Targeted Temperature Management

Running Title: Electrocardiographic Changes During TTM

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Author Contribution:

Dr. Sawyer and Dr. Swor conceived, designed and supervised the conduct of the trial. Dr. Sawyer recruited participants for the study. Dr. Sefa, Jandu, and Swor participated in data collection. Dr. Sefa, and Dr. Swor provided statistical advice on study design and analyzed data. Dr. Jandu drafted the manuscript, and all authors contributed substantially to its revision. All authors takes responsibility for the paper as a whole.

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Author Disclosure Statement

The authors have no conflicts of interest.

Abstract

Objectives

Targeted temperature management (TTM) is the recommended therapy for comatose patients after an out-of-hospital cardiac arrest resuscitation due to the reduction in neurological damage and improved outcomes. However, there may result in electrocardiographic instability depending on the degree of TTM, including minor or life threatening dysrhythmias or conduction delays. Thus, this project aims to describe the frequency of ECG interval changes and clinically relevant dysrhythmias in TTM patients.

Methods

This is a retrospective observational study from January 2009 to December 2015. Patients who qualified for the study had a non-traumatic cardiac arrest with a return of spontaneous circulation (ROSC), received TTM at 33.5^{o}C for 24 hours followed by 16 hours of rewarming. ECG interval changes and dysrhythmias were recorded immediately after ROSC, and at 24 and 48 hours post ROSC.

Results

A total of 322 patients (age 61.0 ± 16.9 years) had TTM initiated during the study period, of which 169 had complete data and 13 died prior to completing 24 hours of hypothermia. There were statistically significant changes during TTM in heart rate (96.7 ± 26.0/min before TTM; 69.5 ± 19.1/min during, p<0.001); QRS duration (115.1 ± 32.6 ms before TTM; 107.8 ± 27.9 ms during TTM, p<0.001); and QTc (486.3 ± 52.8 ms before TTM; 526.9 ± 61.7 ms during TTM, p<0.001). There were cardiac dysrhythmias that received treatment during cooling and rewarming.

Conclusion

During the period of TTM and rewarming, we observed few self-limiting ECG interval changes and no clinically significant dysrhythmias in this population during the period of TTM.

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Introduction

Background

It is estimated that there are approximately 395,000 cases of out-of-hospital cardiac arrest (OHCA) per year in the U.S. with survival to discharge ranging from 3.0% to 39.9% based on geographical region.[1,2] Patients resuscitated post cardiac arrest are at increased risk of developing further myocardial abnormalities e.g. post-cardiac arrest syndrome, along with systemic and brain injuries. Targeted temperature management (TTM) has shown to improve neurological function and outcomes thought to be due to a reduction in the body's oxygen demand and reperfusion injury associated damage.[3,4] Thus, TTM is recommended by the American Heart Association Guidelines for Cardiopulmonary Resuscitation and is standard care in adults who remain comatose after an OHCA with ROSC around the world.[5,6]

Accidental hypothermia studies have shown that hypothermia itself can cause adverse cardiac events, such as bradycardia, Osborn waves, atrial fibrillation, and QTc prolongation, predisposing patients to life-threatening ventricular arrhythmias.[7] These arrhythmias are hypothesized to be due to serum electrolyte changes, including an increase intracellular calcium, combined myocardial repolarization variability that occurs with hypothermia.[8] Multiple case reports and studies demonstrate that hypothermia is associated with a significant prolongation in QT and QTc interval.[9,10]

Importance

With the conduction delays and cardiac arrhythmias noted with hypothermia, concern is raised about the effect of TTM on the cardiac electrophysiology, specifically when there are no current guidelines for monitoring or assessing risk of arrhythmias, possibly deterring physicians from inducing TTM.

Although TTM is standard in treating comatose, post-cardiac arrest patients after ROSC, there are few large studies that have studied the incidence of arrhythmias and conduction delays during treatment.[11-15]

Goals of This Investigation

The purpose of this study was to determine the frequency of clinically relevant ECG changes and cardiac dysrhythmias in a large population undergoing TTM.

Materials and Methods

Study Design and Setting

We conducted a retrospective observational study of ECGs from adult patients (≥ 18 years) who received TTM (33.5 ^{o}C for 24 hours) and who had return of spontaneous circulation (ROSC) after non-traumatic cardiac arrest at two large academic community hospitals from January 2009 to December 2015. Both institutions provided targeted temperature management during the study period for comatose post arrest patients. Patients are cooled using either external or endovascular cooling devices, with the vast majority being surface cooling(Artic Sun, Medivance, Inc, Louisville,Co) to a target temperature of 33.5 ^{o}C, kept at that temperature for 24 hours, and then gradually rewarmed to a temperature of 37.0 C over the subsequent 16 hours. Normothermia was maintained thereafter. Metabolic, ventilation, and hemodynamic parameters were managed according to goal directed targets for the first 72 hours in

consultation with critical care unit staff. Bolus paralytics or continuous drips were dosed for patients to control shivering.

Measurements

We reviewed ECGs obtained immediately upon hospital arrival post ROSC, as well as 24 hours and 48 hours post ROSC. ECGs were abstracted for presence of dysrhythmia at these time points. ECG intervals using computerized measures including PR, QRS and QT intervals as well as ST segment changes were abstracted. Charts were also reviewed for presence of cardiac dysrhythmias that were new in onset and occurred during cooling and rewarming as well as clinically significant dysrhythmias included ventricular tachycardia and ventricular fibrillation. A single observer reviewed records for data extraction and then two independent observers reviewed a sample of the data extraction and discrepancies were resolved by consensus.

Analysis

Descriptive statistics are reported for frequency of adverse events. Continuous variables including age (years), initial temperature (degrees Celsius), and all time intervals (milliseconds, minutes or hours) are reported as means and standard deviations (SDs); categorical variables are reported as counts and percentages.

Data were analyzed using IBM SPSS (V19.0, Armonk NY) software, with a significance level of alpha = 0.05. Intervals were compared between pre-cooling, cooling and post cooling time periods and paired T-tests were calculated for associations. Beaumont Health System institutional review board approved the study.

Results

Characteristics of Study Subjects

During the study period, a total of 322 patients (age 61.0 ± 16.9 years) received TTM, of which 13 died prior to completion of treatment. Of the 13 that died, 9 died during rewarming – 1 had PEA, 1 asystole, 1 code status changed to DNR, and 6 terminally weaned. Four died during TTM - 2 terminally weaned, 1 code status changed to DNR and 1 had PEA. The deaths from PEA and asystole were primarily related to persistent hypotension and one had DIC.

ECGs were performed as directed by the clinical team and were not recovered for patients prior to cooling (N=11), during cooling (N=65), and after cooling (N=32). Seven patients had paced rhythms and were excluded from analysis. (Figure 1). Demographic characteristics of the population are summarized in Table 1. The patients were predominately male (62.5%), 76% had an out-of-hospital arrest, 16.1% had a STEMI on initial ECG, and 35.7% survived to hospital discharge. Most patients were normothermic prior to initiation of TTM, core temperature median 36.1 (IQR, 35.4, 36.7)

Main Results

Few patients developed significant dysrhythmias during and after, summarized in table 2. During cooling, there was no recorded development of ventricular tachycardia (VT) or ventricular fibrillation (VF), 3 developed atrial fibrillation, 1 developed atrial flutter, and 6 AV nodal rhythms. These dysrhythmias during cooling resolved spontaneously without treatment. Osborn waves were common occurring in 23 patients during treatment After TTM, no recorded developments of VT or VF, but 7 developed atrial fibrillation, 1 developed atrial flutter, 4 developed AV nodal rhythms, and Osborn waves were present in 5 patients.

There were statistically significant changes during TTM compared to prior with a decreased heart rate, and lengthened QRS duration and QTc (Table 3). There were also statistically significant changes after TTM compared to during TTM with an increased heart rate, and shortened QRS and QTc. (Table 4). Most intervals returned to normal after return to normothermia (Figures 2-5).

Limitations:

There are multiple limitations of this study: the first is that it is a retrospective chart review with no control group. This could allow for confounding variables, i.e. electrolyte imbalances and medications that were not reviewed by study authors but monitored and treated by clinical providers. These are known to affect ECG intervals and cause arrhythmias. The second is that 47.5% (N=153) of the patients who underwent TTM did not have complete ECG data due to missing ECGs, or died before treatment was completed, thus excluded from analysis (see Figure 1). We believe that reasons for missing data were random, as we cannot hypothesize any systemic reason for ECGs being absent. Given that our preferred cooling mechanism is a surface device with large pads, it seems likely that this was a perceived, if not real barrier to obtaining an ECG. The data was also analyzed based on single ECGs in each time period, so there may be transient arrhythmias not captured on ECG.

Discussion:

Congruent with prior studies, we showed a statistically significant decrease in heart rate with a statistically significant increase in QT and QTc interval during TTM primarily using surface cooling, that spontaneously resolved when rewarmed. The bradycardia and prolonged QT interval is thought to be due to the slowing rate of diastolic depolarization in both the sinoatrial nodal and myocardial cells as temperature decreases. This prolongs the electrical

conduction between myocardial cells, increasing the action potential duration causing prolongation of electrocardiographic intervals, including QT, as seen in our population.[15,16]

Prolonged QT/QTc interval has been associated with clinically significant cardiac dysrhythmias, i.e. Torsades de Pointes, VT and VF, as observed in congenital diseases, hypokalemia, medications, severe accidental hypothermic individuals, etc.[13] Although not analyzed in our study, prior literature has shown that electrolyte disturbances and medications are known to prolong ECG intervals in non-hypothermic states. Rosol, et al. mentioned that there was no difference in QTc intervals in patients with electrolyte imbalances and/or QT-prolonging medications compared to those without in their study. There was also not a significant difference in those who developed arrhythmias.[9] Thus, QT and QTc prolongation observed in our study and the lack of clinically significant dysrhythmias with hypothermia, is likely similar to other studies in that they are not affected by electrolyte imbalances and QT prolonging medications.

To our knowledge, the current study is the one of the largest studies examining the relationship between QT, QTc and arrhythmias during TTM. Literature on TTM has shown that the QTc prolongation during treatment is not associated with significant cardiac dysrhythmias. Gachoka, et al. reported none of 55 patients undergoing TTM developed Torsades de pointes or ventricular tachycardia.[15] Ulmenstein, et al. reported 13.7% of 95 patients had VT and VF, and Rosol, et al., the largest reported study to date, reported 11.3% of 193 patients developed a VT, VF or Torsades de pointes. Both latter studies showed no statistical difference in QT or QTc interval between those with and without ventricular arrhythmias.[8,9]

In comparison to our study, of the few patients who developed dysrhythmias, none were clinically significant (Table 2). Potentially as incongruent with other studies, we did not use continuous telemetry monitoring to determine if a clinically significant, albeit transient, dysrhythmias were present.[9,12,15] It is presumed though if a patient had even a transient arrhythmia that it would be documented on the chart. Regardless, our study found no clinically

significant dysrhythmias despite significant QTc prolongation during hypothermia, unlike other large studies.

It is thought that unlike temperatures less than 30°C, at mild hypothermic ranges (32-35°C) there is a cardioprotective effect from membrane stabilization, and decrease in metabolic waste and reactive oxygen species that protects against prolonged QTc interval arrhythmias.[15] This is important as TTM has become standard care in post-cardiac arrest patients who are already at an increased risk of arrhythmias and data is needed to identify if more stringent monitoring guidelines are needed.

It is also worth noting that we noted the QRS to significantly shorten from prior to TTM to during TTM to normothermia. This was similarly first described in Lebeidz, et al. who noted that the QRS interval decreased throughout the treatment, similar to our data.[11] In other studies, the QRS interval is noted to significantly decrease from hypothermia to after cessation of treatment. However it is not noted to be associated with arrhythmias, and likely to be a benign finding.[8,12]

Future studies should include prospective evaluations with recording of electrolytes and medications to control for other sources of QTc prolongation. Optimally continuous telemetry recordings before, during and after TTM should be used to capture transient arrhythmias that self-resolve.

In this study, TTM is associated with a number of statistically significant ECG interval changes, i.e. decrease in heart rate and QRS, and increase in QTc interval that spontaneously resolved during rewarming, congruent with other studies. Despite the transient ECG interval changes, we observed no clinically significant arrhythmias defined as VT and VF, indicating that TTM is a low risk treatment in post-cardiac arrest patients irrespective of their pre-TTM QTc.

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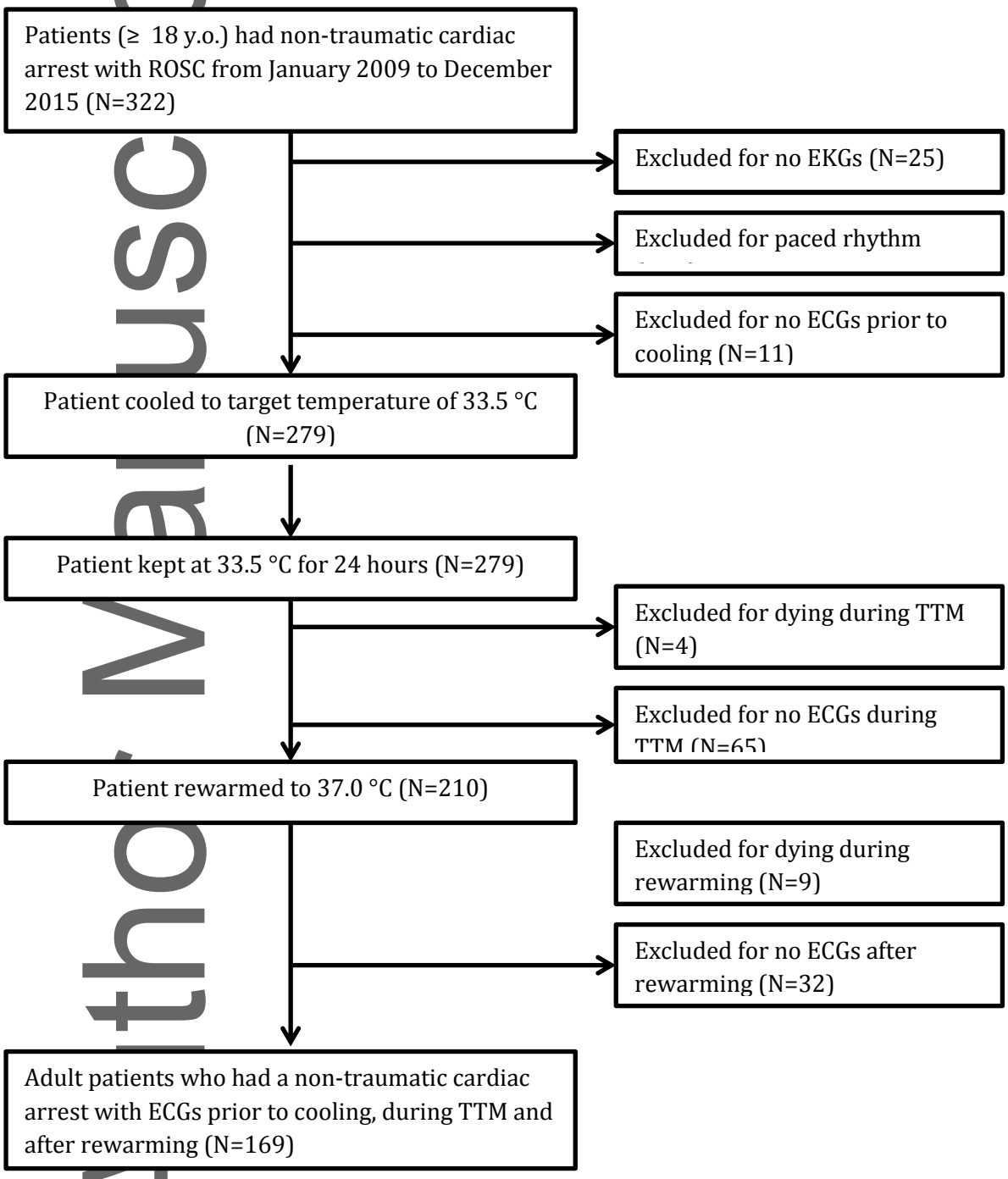
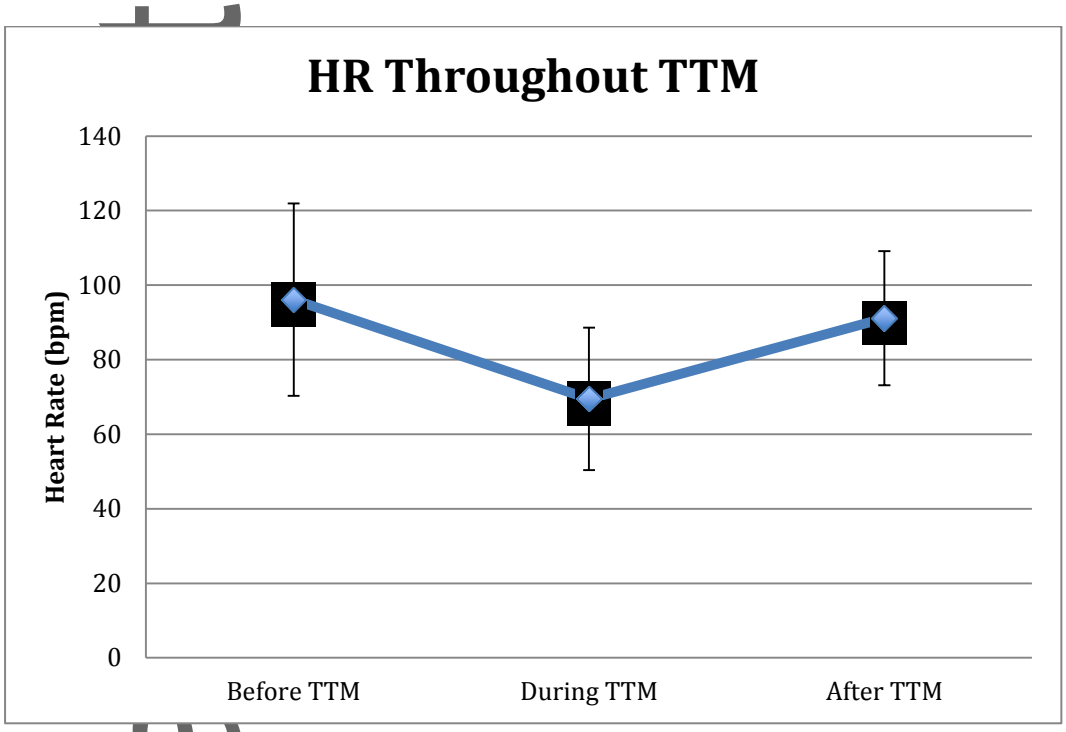
Figure 1: Flow Diagram for Included Subjects



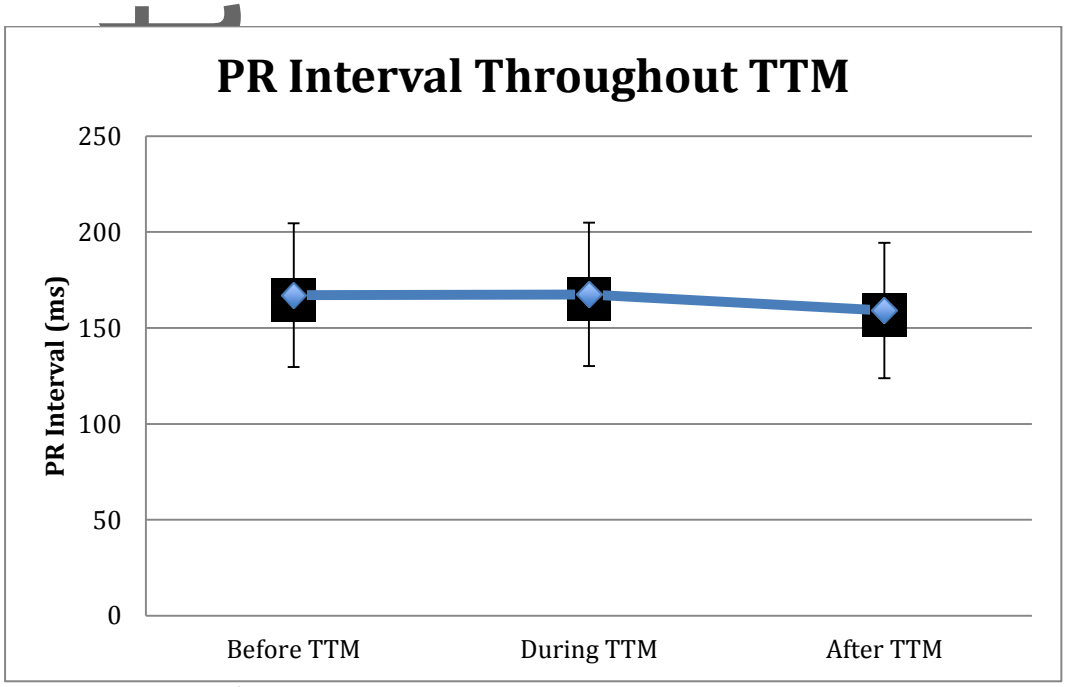
Description of how patients were excluded from the total number of populations who underwent targeted temperature management to the population in which data was analyzed. Targeted temperature management = TTM, Return of spontaneous circulation = ROSC

Figure 2: Change in Heart Rate Before, During and After TTM



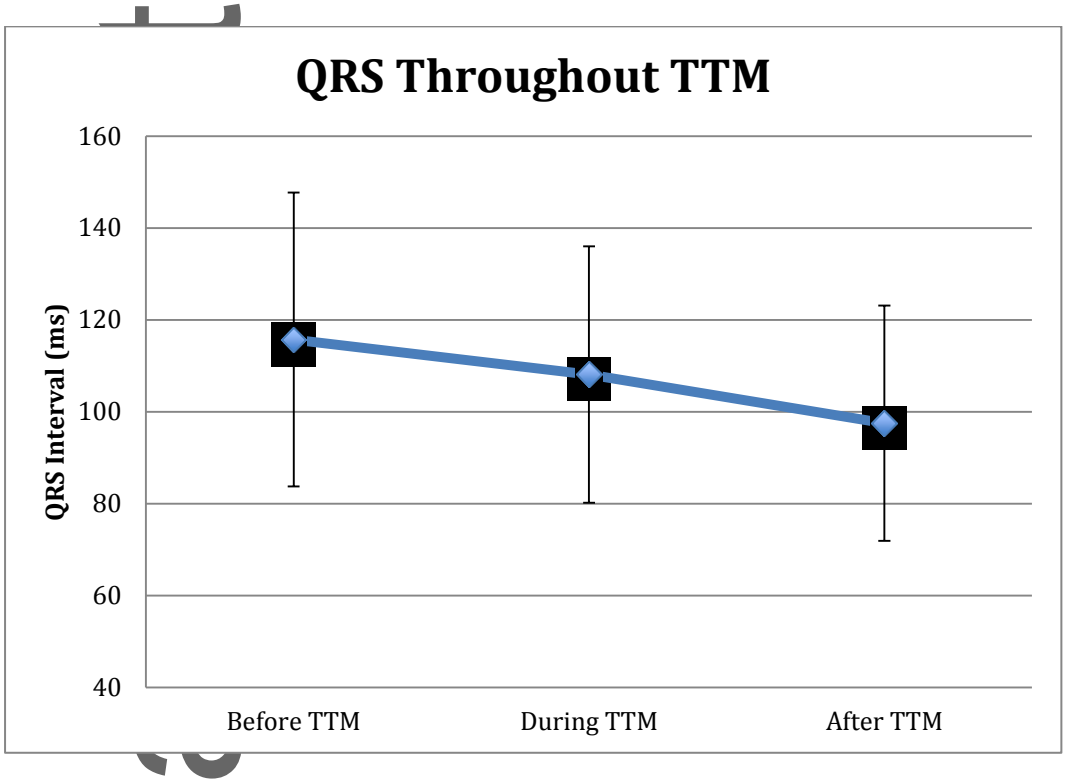
Histogram results of heart rate changes from before, during and after targeted temperature management (TTM). bpm = beats per minute.

Figure 3: Change in PR Interval Before, During and After TTM



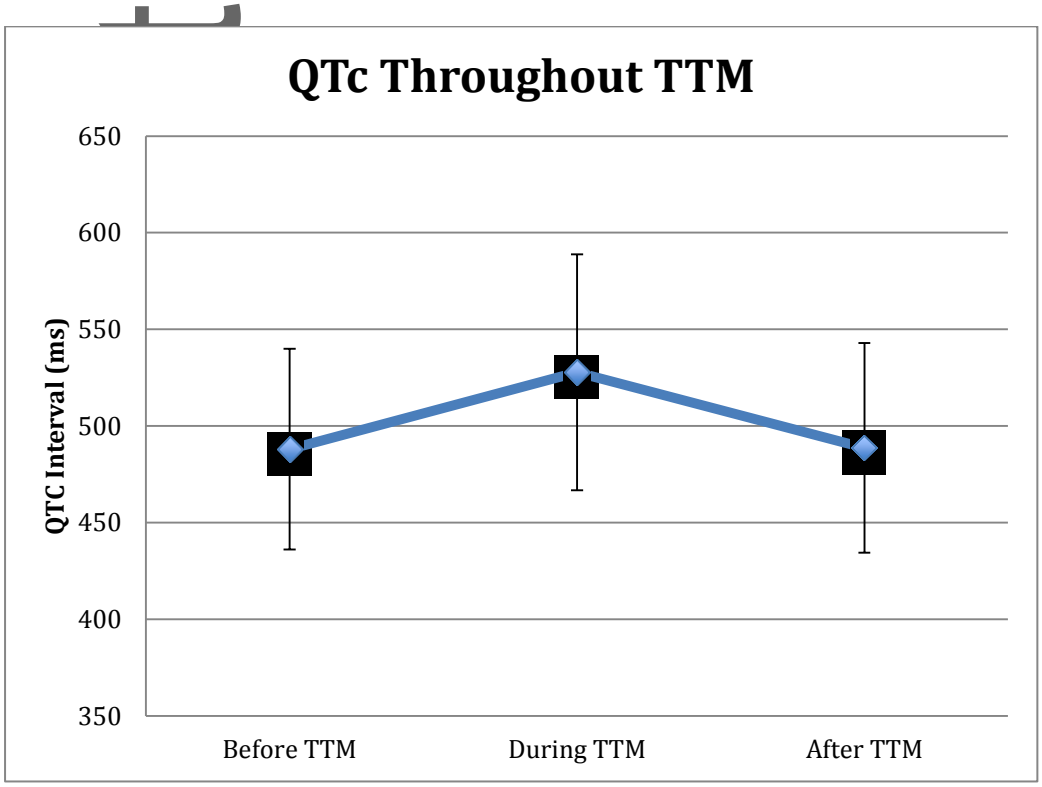
Histogram results of PR interval changes from before, during and after targeted temperature management (TTM). msec = milliseconds.

Figure 4: Change in QRS Interval Before, During and After TTM



Histogram results of QRS interval decreases when during targeted temperature management (TTM) when compared to before TTM, and decrease after TTM compared to before. msec = milliseconds.

Figure 5: Change in QTc Before, During and After TTM



Histogram results of QTc interval changes from before, during and after targeted temperature management (TTM). msec = milliseconds.

Table 1: Demographic Characteristics of Study Population

Patient characteristics	***(n = 199)***
Age (years)	61.0 ± 16.9
Male (%)	125 (62.5%)
Out-of-hospital Cardiac Arrest (%)	151 (75.9%)
Body Mass Index (Median, IQR)	29.6 (25, 35.8)
Witnessed Arrest (%)	73 (66.4%)
VT/VF (%)	33(30.0%)
Bradyasystolic (%)	67 (52.8%)
STEMI (%)	32(16.1%)
Survived to Discharge (%)	35.7
Alive at 3 month Follow-up (%)	21.1

VT, Ventricular tachycardia; VF, ventricular fibrillation

Table 2: Frequency of Cardiac Rhythms and Conduction Disturbances Before, During and After Treatment

	History Before Cooling	New Finding 24 Hours Post ROSC	48 Hours Post ROSC
Atrial Fibrillation	24	3	7
Atrial Flutter	3	1	1
Osborn Waves	1	23	4
AV Nodal Rhythm	7	6	2
Right Bundle Branch Block	29	2	5
Left Bundle Branch Block	21	0	0

AV, atrioventricular; ROSC, return of spontaneous circulation

Table 3: ECG Interval Changes in Patients Before, During Targeted Temperature Management

	Before TTM	During TTM	p-value
Heart Rate (bpm)	96.1 ± 25.8	69.5 ± 19.1	<0.05
PR interval (msec)	167.1 ± 34.5	167.5 ± 37.4	0.9
QRS Duration (msec)	115.7 ± 32.0	108.1 ± 27.9	<0.05
QTc Interval (msec)	488.0 ± 51.9	527.8 ± 61.0	<0.05

TTM, targeted temperature management; bpm, beats per minute

Table 4: ECG Interval Changes in Patients During and After Targeted Temperature Management

	During TTM	After TTM	p-value
Heart Rate (bpm)	69.5 ± 19.1	91.1 ± 18.0	<0.05
PR interval (msec)	167.5 ± 37.4	159.1 ± 35.3	< 0.05
QRS Duration (msec)	108.1 ± 27.9	97.5 ± 25.6	<0.05
QTc Interval (msec)	527.8 ± 61.0	488.7 ± 54.2	<0.05