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Determinants of cardiac repolarization and risk for ventricular arrhythmias during mild therapeutic hypothermia☆

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ABSTRACT

Purpose: We aimed to investigate the factors that modulate the extent of QTc prolongation and potential arrhythmogenic consequences during mild therapeutic hypothermia (MTH).
Methods: We studied 205 patients after out-of-hospital cardiac arrest (131 underwent MTH). QTc was measured at baseline, 3 h, 6 h, 12 h, 24 h (end of hypothermia), 48 h and 72 h, and ventricular arrhythmias quantified.
Results: During MTH, the QTc interval increased progressively peaking at 12 h (mean increase 42 ms, 95% CI 30–55). There was a strong gender effect ($P < 0.001$) and a significant gender-by-MTH interaction ($P = 0.004$). At 12 h, the QTc interval was markedly longer in women as compared with men (mean difference 50 ms [95% CI 27–73]. Anoxic brain injury ($P = 0.002$) was also positively associated with QTc prolongation. The risk for ventricular arrhythmic events was not higher with MTH compared with no hypothermia (incidence rate ratio 0.57, 95% CI 0.32–1.02, $P = 0.06$). However, typical cases of Torsade de pointes occurred in association with AV block and LQT2.
Conclusion: QTc prolongation during MTH is strongly affected by female gender and moderately by concomitant anoxic brain injury. Although the overall risk for ventricular arrhythmias is not greater with MTH, Torsade de pointes may develop when other contributing factors coexist.

1. Introduction

Mild therapeutic hypothermia (MTH) has become a routine procedure in survivors after cardiac arrest to improve neurological outcome [1]. Hypothermia is known to cause potentially arrhythmogenic effects, including prolonging action potential duration, prolongation of the QT interval [2], and may enhance heterogeneities of repolarization [3]. QTc prolongation leading to the development of Torsade de pointes (TdP) has been described during MTH [4,5]. Whether an increased susceptibility to arrhythmias is present in post resuscitation patients who are treated with MTH remains controversial [4,6-12].

A high ventricular arrhythmic event rate may be expected in the post-resuscitation population. However, previous studies assessing the arrhythmic risks associated with MTH did not include a control group of patients who were not exposed to MTH [5,10,11]. Thus, it is difficult to distinguish MTH-related ventricular arrhythmias from those arising from multiple additional risk factors other than exposure to hypothermia. In the present study, we compared the incidence of ventricular arrhythmic events in out-of-hospital cardiac arrest (OHCA) patients with or without MTH therapy. In addition, we investigated potential factors that might predispose patients to excessive QTc prolongation during MTH.

2. Methods

We performed an observational single-center study of OHCA patients. The study population included all consecutive patients admitted to intensive cardiac care unit after resuscitation for OHCA between 1.1.2004 and 31.12.2015 treated with or without MTH. From the beginning of 2009 all eligible patients underwent MTH at 33–34 °C for 24 h in the intensive care unit following return of spontaneous circulation. The investigational review committee on human research of the Rambam Health Care Campus approved the study protocol (0562-14-RMB) and the need for a written informed consent was specifically waived. The datasets used and analyzed in the current study are available from the corresponding author on reasonable request. The authors declare that they have no competing interests.

Candidates for hypothermia included comatose survivors of OHCA with ventricular fibrillation as the presenting rhythm, patients who sustained a witnessed pulseless electrical activity or asystolic arrest

☆ Conflicts of interest: none.

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but who responded to therapy with return of sustained spontaneous circulation.

Therapeutic hypothermia was initiated immediately after admission with an external cooling system (Criti Cool Pro system, Medical ThermoRegulation Expertise, MTRE, Yavne, Israel), and a heat exchange garment (CureWrap) [13]. Core temperature was monitored by an esophageal probe with thermoregulation system to achieve and maintain a core temperature of 33–34 °C for 24 h. Rewarming proceeded using the same system at a rate not exceeding 0.5 °C h^{-1} until the patient returns to normothermia.

Patients who underwent immediate percutaneous coronary angiography were cooled by ice-packs and cold infusions during the intervention and were afterwards treated as described above. Arterial catheters were placed in all patients and the target mean arterial pressure was 80 to 100 mm Hg with the use of inotropic support if needed [1].

2.1. Electrocardiography

Digitally stored ECG data on the MUSE system (Marquette Medical Systems, Milwaukee, Wis) was used for analysis. All QTc measurements were performed by trained physicians using the actual 12 leads ECGs that were printed or stored in the MUSE system. We used a standardized method for the QT measurements where the end of the T wave was defined as the intersection of a tangent. The method was originally described by Lepeschkin and Surawicz [14] and more recently recommended by Postema et al. [15]. The QTc was measured in lead II or V5 according to Postema et al. [15]. The QT interval was measured from the beginning of the QRS to the end of T-wave, defined as the intersection of the tangent to the downslope of the T-wave and the isoelectric line [15]. Bazett's formula was used to correct for heart rate. When U waves were present the QT was measured to the nadir of the curve between the T and U waves. QTc measurements were performed at baseline, 3 h, 6 h, 12 h and 24 h of hypothermia, and at 48 h and 72 h.

QT dispersion (QTd) was defined as difference between the longest and shortest QT interval measured in each of the 12 ECG leads [16]. Results were analyzed as QTd and rate corrected QTd (QTc/√RR). The interval from the peak to the end of the T wave (Tp-e) and QT interval were measured with electronic calipers from the V4 and V6 leads on each patient [8], as an additional measure of transmural dispersion of repolarization [17]. Tp-e was expressed as the absolute value (TpTe), and the corrected value for the heart rate (TpTe/√RR).

2.2. Neurological outcome

Neurological data was collected only in the context of its potential effect on the QTc interval. Thus, we collected data on global anoxic-ischemic cerebral insult, defined as a binary variable, based on clinical outcomes (comatose, in persistent vegetative state, or brain death) and characteristic CT findings (marked reduction of the gray-white ratio on brain computed tomography).

2.3. Ventricular arrhythmic events

Prolongation of QT interval is associated not only with TdP but also with other ventricular arrhythmias. For example, arrhythmias induced by drugs known to be potent torsadogens include polymorphic ventricular tachycardia (not meeting the morphologic criteria of TdP), ventricular tachycardia and ventricular fibrillation without a preceding TdP [18-20]. Therefore, to capture all potential proarrhythmic effects of MTH, we analyzed all ventricular arrhythmias (TdP/VT/VF) during first 72 h from initiation of MTH. The definition of VT included nonsustained VT, defined as 3 or more consecutive ventricular beats >100 beats/min.

2.4. Statistical analysis

Descriptive statistics included mean ± SD for continuous variables and percentages for categorical variables. To analyze the QTc changes over time, a repeated-measures mixed effect model with an unstructured covariance matrix were was applied. The model included fixed factors for MTH, time (0, 3 h, 6 h, 12 h, 24 h, 48 h and 72 h), MTH-by-time interaction, gender, gender-by-MTH interaction, and a random effect for the patient.

The model adjusted for age, concomitant amiodarone therapy, serum levels of potassium and magnesium, acute myocardial infarction, initial rhythm and neurological status. Electrolytes were modeled as time-varying covariates using the most recent measurement relative to the QTc measurement. All pairwise comparisons between the MTH groups and control were conducted at each timepoint with Bonferroni correction. In addition, QTc interval in each group at each time point was compared with baseline value. Additional models were used for the onset and offset of the MTH effect.

Ventricular arrhythmic events is a count variable with skewed distribution. The distribution of the events had greater variability than

Table 1
Baseline characteristics of patients with and without MTH.

Characteristics	No hypothermia ($n = 74$)	MTH ($n = 131$)	*P* value
Age (years)	64 ± 13	61 ± 14	0.007
Female gender	19 (26)	33 (25)	0.94
Hypertension	42 (57)	83 (63)	0.35
Diabetes	21 (28)	46 (35)	0.32
Coronary artery disease	31 (42)	52 (40)	0.10
Peripheral vascular disease	6 (8)	8 (6)	0.60
Cardiomyopathy	9 (12)	21 (16)	0.45
Initial documented rhythm			
Ventricular fibrillation/pulseless ventricular tachycardia	52 (70)	109 (83)	0.03
Asystole	22 (30)	20 (15)	0.01
Acute myocardial infarction	43 (58)	57 (43)	0.045
STEMI	29 (39)	42 (32)	0.30
Severely reduced LVEF	21 (28)	42 (32)	0.58
Serum K on admission (mmol l/l)	4.0 ± 0.7	4.1 ± 0.8	0.61
Lowest serum K (mmol/l)	3.6 ± 0.5	3.3 ± 0.4	0.0001
Anoxic brain injury	21 (26)	28 (22)	0.50
Medical therapy			
Antiplatelet agents	62 (84)	97 (78)	0.11
Beta blockers	45 (61)	91 (69)	0.21
ACE inhibitors/ARBs	47 (64)	66 (50)	0.07
Statins	34 (46)	70 (53)	0.30
Amiodarone	19 (26)	24 (18)	0.21
Pressors	17 (23)	43 (33)	0.14