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Clinical paper

Hypokalemia during the cooling phase of therapeutic hypothermia and its impact on arrhythmogenesis☆

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ABSTRACT

Background: Mild to moderate therapeutic hypothermia (TH) has been shown to improve survival and neurological outcome in patients resuscitated from out-of-hospital cardiac arrest (OHCA) with ventricular fibrillation (VF) as the presenting rhythm. This approach entails the management of physiological variables which fall outside the realm of conventional critical cardiac care. Management of serum potassium fluxes remains pivotal in the avoidance of lethal ventricular arrhythmia.
Methods: We retrospectively analyzed potassium variability with TH and performed correlative analysis of QT intervals and the incidence of ventricular arrhythmia.
Results: We enrolled 94 sequential patients with OHCA, and serum potassium was followed intensively. The average initial potassium value was 3.9 ± 0.7 mmol l^{-1} and decreased to a nadir of 3.2 ± 0.7 mmol l^{-1} at 10 h after initiation of cooling ($p < 0.001$). Eleven patients developed sustained polymorphic ventricular tachycardia (PVT) with eight of these occurring during the cooling phase. The corrected QT interval prolonged in relation to the development of hypothermia ($p < 0.001$). Hypokalemia was significantly associated with the development of PVT ($p = 0.002$), with this arrhythmia being most likely to develop in patients with serum potassium values of less than 2.5 mmol l^{-1} ($p = 0.002$). Rebound hyperkalemia did not reach concerning levels (maximum 4.26 ± 0.8 mmol l^{-1} at 40 h) and was not associated with the occurrence of ventricular arrhythmia. Furthermore, repletion of serum potassium did not correlate with the development of ventricular arrhythmia.
Conclusions: Therapeutic hypothermia is associated with a significant decline in serum potassium during cooling. Hypothermic core temperatures do not appear to protect against ventricular arrhythmia in the context of severe hypokalemia and cautious supplementation to maintain potassium at 3.0 mmol l^{-1} appears to be both safe and effective.

1. Introduction

Improvements in resuscitation practices have increased survival following out-of-hospital cardiac arrest, yet the majority of patients still do not survive.[1–3] To further improve the survival rates, ongoing review and alteration of current protocols are necessary. The neurological benefit of mild therapeutic hypothermia (TH) on outcomes after OHCA[4,5] has led to this practice being recommended by the American Heart Association as Class IIa therapy in patients with ventricular fibrillation (VF) as the cause of arrest.[6] Anecdotal reports and reported experience[7,8] have described declines in serum potassium during TH. However our current understanding of the effects of hypothermia on human physiology and electrophysiology remains incomplete. Malignant ventricular arrhythmias continue to be a major cause of in-hospital death after OHCA and although these in part may be driven by myocardial ischemia and reperfusion, hypokalemia and hyperkalemia are frequently implicated.[9,10] This study was undertaken to review our experience with the arrhythmogenic milieu during TH and to propose optimal management strategies.

2. Methods

This is an observational study from the Division of Cardiovascular Diseases, Department of Internal Medicine at The Mayo Clinic, Rochester, and was approved by the Institutional Review Board. Patients who sustained an OHCA between December 2005 and August 2009 in our public service area (PSA) and 17 surround-

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ing communities outside our PSA were included. Patients within our PSA were transported by ground ambulance, and those who presented to regional hospitals outside our PSA were airlifted by helicopter to our hospital. Data regarding the cardiac arrest and subsequent outcomes were collected in a prospective manner. Emergency Medical Services (EMS) personnel provided initial interventions, including both basic and advanced life support as needed. Ventricular fibrillation was the presenting rhythm in 87 patients (93%), in accord with the 2005 guidelines which recommended TH for patients presenting in VF.[6] In addition, later in our experience seven patients who sustained a witnessed pulseless electrical activity (PEA) or asystolic arrest but who responded to therapy with return of sustained spontaneous circulation yet remained comatose or unable to follow verbal commands were included. When automated external defibrillators (AEDs) were utilized the presenting rhythm and pre- and post-shock rhythm data were obtained from the devices in all instances. Patients were included if cooling could be commenced within 4 h of arrest and the arrest was of documented or presumed cardiac origin. Two patients who sustained VF arrests in our hospital (Emergency Department in one and Cardiac Catheterization Laboratory in another) were also included. Both underwent TH after prolonged and difficult resuscitations resulted in improved hemodynamics but unresponsive mental state.

Therapeutic hypothermia was terminated in seven cases before completion if mandated by advanced directives, severe hemodynamic or respiratory failure or family request for withdrawal of care. Hypothermia was initiated en route in 32 patients by helicopter flight personnel with infusion of up to 2 l of iced saline in combination with ice packs on the groin, in the axillae, and around the neck. Upon admission to the CCU patients were started on continuous infusions of midazolam and fentanyl prior to initiation of muscle relaxation with atracurium. Atracurium was terminated as soon as possible once the target temperature was achieved. Core temperature was monitored by a bladder probe and the Arctic Sun® (Medivance, Inc, Louisville, CO, USA) thermoregulation system was employed to achieve and maintain a core temperature of 33 °C for 24 h. Rewarming proceeded using the same system at a rate not exceeding 0.5 °C h^{-1}. Sedation was terminated after normothermia was achieved. Patients who did not regain consciousness received full supportive care for at least 72 h after restoration of normothermia. An overall performance category (OPC) score was used to assess clinical outcome and was assessed at discharge using categories of 1 (good recovery) or 2 (moderate disability) on a five-category scale as neurologic recovery; the other categories were 3 (severe disability), 4 (a vegetative state), and 5 (death).[11] Blood glucose was monitored every 2 h throughout cooling and rewarming, and insulin infusion therapy was initiated in all patients to maintain blood glucose of 120–140 mg dl^{-1}. Anti-arrhythmic agents (amiodarone in all instances) were prescribed for hemodynamically unstable atrial or ventricular arrhythmias.

The majority of patients with ST-elevation myocardial infarction underwent initiation of TH immediately prior to proceeding to angiography or at the time of angiography. Serum potassium was measured every 2 h during cooling and rewarming and for 24 h after restoration of normothermia. Other electrolytes were also measured though not with the same frequency. Electrocardiograms were obtained at baseline and on a daily basis unless rhythm disturbances required more frequent recording. Measurements of QRS and QTc intervals were obtained manually on each patient and were blinded to patient details. Bazett's formula was used to correct for heart rate. In addition, continuous telemetry recordings were analyzed electronically for mean changes in QTc during cooling and rewarming and utilized for QTc measurements during the hour in which PVT occurred. Arterial catheters were placed in all patients and the mean arterial pressure was maintained at 70–80 mm Hg with inotropic support as needed. Serum potassium concentrations below 3.0 mmol l^{-1} were replaced intravenously to maintain levels at or just above that level with 10 mequiv. increments every hour. Serum magnesium was replaced with magnesium sulfate if less than 1.8 mg dl^{-1}, measured every 2–4 h until hypomagnesemia was corrected. Magnesium repletion was needed in 16 patients. Polymorphic ventricular tachycardia (PVT) was defined as ventricular tachycardia with a variable morphology and a progressive change in cardiac axis, sustained for sufficient duration to cause hemodynamic deterioration.

Table 1
Patient baseline characteristics, and further grouped by the development of polymorphic ventricular tachycardia (PVT).

Baseline characteristics		PVT	No PVT
	$n = 94$ (%)	$n = 11$	$n = 83$
Age, years	63.2 ± 13	64.5 ± 113	63.0 ± 12
Male sex	73 (78)	7 (64)	66 (80)
BMI, kg/m^2	29 ± 7	27 ± 5	29 ± 7
Diabetes	32 (34)	2 (18)	30 (36)
Hypertension	60 (63)	7 (64)	53 (64)
Coronary artery disease	31 (33)	3 (27)	28 (34)
Arrest witnessed	79 (84)	9 (82)	70 (84)
Response times (min)	5.8 ± 3	5.8 ± 2	5.8 ± 3
Ventricular fibrillation	87 (93)	10 (91)	77 (93)
ST-elevation Ml	43 (46)	6 (55)	37 (45)
Angiography	77 (82)	10 (91)	67 (81)
Primary PCI	43 (46)	6 (55)	37 (45)
Amiodarone use	58 (62)	7 (64)	51 (61)
Pressor use	46 (49)	8 (72)	38 (46)
Left ventricular ejection fraction	38.9 ± 17	32 ± 15	41 ± 17
Survival to discharge	58 (62)	6 (50)	52 (63)
Median OPC score at discharge	1	1	1

Values are n (%), or ±standard deviation. TdP refers to Torsades de pointes. There was no significant difference between groups with any of these variables.

2.1. Statistical analysis

All results are expressed as mean ± standard deviation. To establish differences between groups, analysis of variance was performed. To compare values time, repeated measures analysis of variance was employed and followed by paired t-tests. Contingency analysis was performed to assess relationships between continuous variables and compared using Pearson's chi-square test. $p < 0.05$ was considered to indicate statistical significance.

3. Results

The average age was 63.2 ± 13 years, and 73 (78%) were male. The average body mass index was 29 ± 7 kg m^{-2}, with 33% and 34% of patients having a history of coronary disease or diabetes mellitus, respectively. A history of hypertension was present in 63% (Table 1). Seventy-nine (84%) of the patients sustained a witnessed arrest, with an average response time (from collapse until emergency personnel arrival) of 5.8 ± 3 min. Ventricular fibrillation was the presenting rhythm in 87 patients (93%). Forty-three patients (46%) had ST-elevation myocardial infarction, and all of these patients underwent primary percutaneous intervention of the culprit vessel. The mean left ventricular ejection fraction measured with either transthoracic echocardiography or magnetic resonance imaging was 38.9 ± 17%. These measurements were obtained within 72 h of admission (mean of 29.2 ± 18 h).

Among all patients, 58 (62%) survived to discharge with a median overall performance category (OPC) score of 1. Of the 87 patients presenting with ventricular fibrillation, 59 (68%) survived to discharge with a median OPC score of 1 at discharge. During TH 58 patients (62%) received intravenous amiodarone, while one patient received lidocaine and 3 patients received magnesium sulfate. One patient's diagnosis was made posthumously after genetic

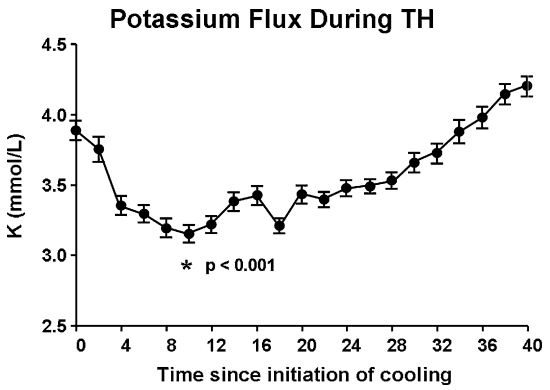

Fig. 1. Serum potassium values at 33 °C compared with baseline were significantly lower, (*$p < 0.001$). Peak serum potassium was not found to be significantly greater than control measurements.

Table 2
Serum potassium values during therapeutic hypothermia, including supplementation for hypokalemia.

Potassium levels (mmol l^{-1}) and administration (mmol)	
Serum K on admission	3.88 ± 0.7
Lowest serum K	3.17 ± 0.6* (10 h)
Peak serum K	4.19 ± 0.7 (40 h)
Patients receiving K supplementation	60 (64%)
Mean K administered	56.7 ± 97

* $p > 0.001$.

studies identified Long QT syndrome Type III. This patient did not develop PVT.

3.1. Changes in serum potassium during hypothermia

Serum potassium concentrations declined significantly during hypothermia, reaching a nadir at 10 h after initiation of cooling. The lowest average serum potassium at this time was 3.17 ± 0.7 mmol l^{-1}, decreasing from an admission average of 3.88 mmol l^{-1} ($p < 0.001$) (Fig. 1). Serum potassium peaked at 40 h after initiation of cooling with a mean of 4.19 ± 0.8 mmol l^{-1}, reaching a plateau at this time. Potassium was administered to 60 patients (64%), with a mean dose of 56.7 ± 97 mmol (Table 2).

3.2. Electrocardiographic and rhythm changes with hypothermia

Baseline QTc duration was 470 ± 60 ms on admission and prolonged to 560 ± 80 ms, ($p < 0.001$) during cooling (Fig. 2). There was no significant change in QRS duration (Table 3). Polymorphic ventricular tachycardia developed in 11 patients (11.7%), and occurred in 8 patients during the cooling phase at an average temperature of 34.7 ± 1.0 °C at onset of PVT. PVT developed in one patient during the rewarming phase, in one patient while normothermic and in one patient while at the target temperature of 33 °C. Defibrillation was necessary in 7 of the 11 patients (64%). Three patients were treated with magnesium sulfate and nine patients (82%) had recurrent episodes of PVT. Two patients were treated with isoproterenol to prevent recurrent PVT. The average serum potassium in the 11 patients with PVT was 2.4 ± 0.5 mmol l^{-1} versus 3.0 ± 0.6 mmol l^{-1} in the patients who did not have PVT ($p = 0.006$). The patients who developed PVT had an average QTc interval at target hypothermia of 563 ± 74 ms versus 527 ± 79 ms in those who did not ($p = 0.13$) (Fig. 2). QTc as analyzed with telemetry recordings within the hour of PVT was 580 ± 120 ms (Table 4). The amount of potassium replacement given to the patients who developed PVT was 75 ± 83 mmol l^{-1}, compared with 57 ± 97 mmol l^{-1} in those who did not develop this arrhythmia, ($p = 0.5$). Assessment of clinical outcomes in the 11 patients who developed PVT using OPC scoring revealed a median OPC score of 3 (versus 1 of the entire group) and 5 patients (45%) left the hospital with an OPC score of 1. Three patients died during intractable ventricular tachycardia.

Table 3
QTc prolongation with cooling, when baseline values are compared with target hypothermia, ($p = 0.01$). The QTc change with cooling was significant ($p < 0.001$). QTc values measured from continuous telemetry.

Electrocardiographic changes during therapeutic hypothermia	
Baseline QTc	470 ± 60 ms
QTc at 33 °C	560 ± 80 ms
QTc change with cooling	+90 ± 130 ms*
QRS duration at baseline	128.5 ± 47 ms
QRS duration at 33 °C	120.8 ± 30 ms

* $p > 0.001$.

Table 4
Serum potassium, QTc and QRS changes during therapeutic hypothermia. QTc values were taken from continuous telemetry strips and QRS duration from 12-lead electrocardiograms on that day.

Serum potassium and QTc variability during hypothermia			
	PVT	No PVT	*p*-Value
Serum K on admission (mmol l^{-1})	3.65 ± 0.7	3.9 ± 0.7	0.2
Core temp at onset of TdP, (°C)	34.7 ± 1.0	n/a	
Lowest serum K (mmol l^{-1})	2.44 ± 0.5	3.0 ± 0.5	0.002
Peak serum K (mmol l^{-1})	4.26 ± 0.9	4.28 ± 0.7	0.9
Baseline QTc (ms)	466 ± 73	472 ± 49	0.7
QTc at 33 °C (ms)	563 ± 74	527 ± 79	0.13
QTc change with cooling (ms)	97 ± 68	55 ± 47	0.01*
QRS duration at baseline (ms)	117 ± 44	129 ± 48	0.4
QRS duration at 33 °C (ms)	122 ± 83	120 ± 129	0.9
QTc at onset of PVT (ms)	580 ± 120	n/a	

Severe hypokalemia ($K < 3.0$ mmol l^{-1}) was a predictor of PVT ($p = 0.01$) but hyperkalemia ($K > 5.5$ mmol l^{-1}) was not. Absolute QTc duration did not predict PVT but the change in QTc with cooling was found to be strongly associated with PVT ($p = 0.01$) (Fig. 2B, Table 4). The use of anti-arrhythmics (amiodarone in all cases) was not associated with the development of PVT ($p = 0.93$). Serum magnesium levels, including those in the 16 patients who were hypomagnesemic and required repletion, were not associated with PVT. Use of vasoactive or inotropic drugs was also analyzed for an association with PVT and none was found ($p = 0.12$).

4. Discussion

Therapeutic hypothermia is of established benefit in mitigating neurological injury after OHCA secondary to VF. Optimal management during this intervention requires a comprehensive understanding of its effect on cellular physiology, especially on the potentially pro-arrhythmic effects of potassium fluxes during cooling and rewarming. We observed a significant decline in serum potassium levels after initiation of TH, which was strongly associated with prolongation of the QT interval and the development of PVT. The majority (72%) of the PVT episodes occurred during cooling; suggesting that more frequent electrolyte assay and rigorous but cautious repletion is required during this vulnerable period. Importantly, potassium replacement during this phase does not appear to be linked to adverse outcomes from rebound hyperkalemia. Moreover, the degree of change in the QT interval, possibly driven by hypokalemia or hypothermia, was also found to be a strong predictor of PVT. Once patients were at target temperature, during rewarming or at normothermia low potassium levels were unlikely to cause PVT. Hypothermia has been well-demonstrated to increase cell membrane stability,[12–15] and these findings allude to

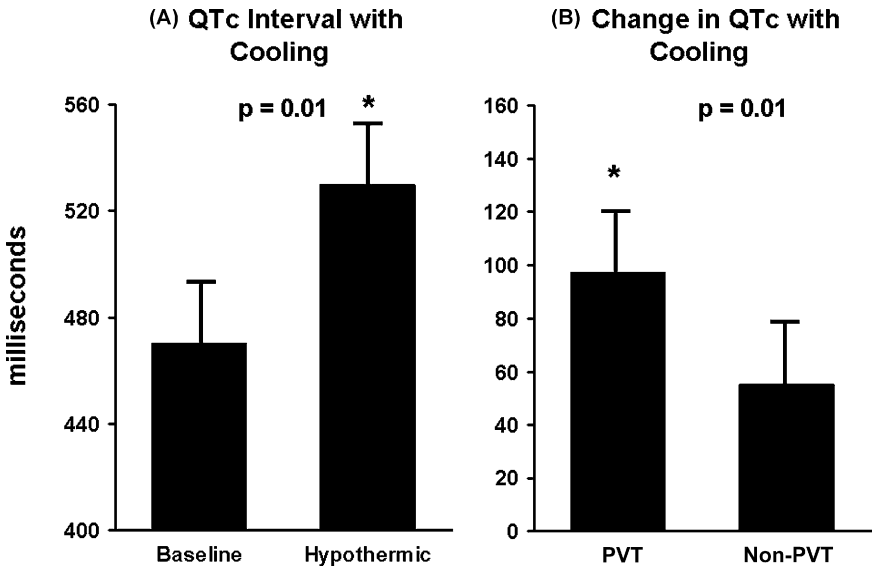

Fig. 2. (A) The QTc prolonged with TH, measured by 12-lead ECG at admission and at 33 °C. (B) Patients who developed PVT had significantly greater QTc prolongation compared with those without PVT ($p = 0.01$).

this action once a new steady-state at 33 °C has been achieved. Cooling, however, does appear to engender an arrhythmia-susceptible stage and this is potentially aggravated by coexistent ischemia or reperfusion injury to cellular membranes.

Mild hypothermia has been shown to have a salutary effect on ventricular tachyarrhythmias in animal models. Not only does hypothermia confer resistance to the initiation or maintenance of VT/VF,[16] but also appears to improve defibrillation efficacy.[17] With hypothermia in patients with atherosclerotic heart disease the vasodilator responses appear to be impaired and vasoconstriction can result with ensuing myocardial ischemia.[18] Hence, this potential response may also provoke ventricular arrhythmias during initiation of cooling. Our data suggests that clinical TH may be also be complicated by hypokalemia, with subsequent destabilizing effects on cardiac rhythm. The change in beat to beat intervals or heart rate variability is considered a measure of autonomic influence. Disruption of the variability has been shown to be associated with more frequent adverse outcomes after acute myocardial infarction, and has also been implicated in the development of ventricular tachyarrhythmias.[19,20] Therapeutic hypothermia has recently been shown to preserve heart rate variability compared with controls, potentially attenuating the pro-arrhythmic effects of neural regulation of the heart.[21]

A clear limitation of the study is the sample size. While vasoactive and inotropic drugs were used more frequently in those patients who developed PVT, no association was found with contingency analysis. A further limitation of this study is the lack of a control group – either normothermic or without potassium supplementation. Both of these scenarios are difficult to implement in current clinical practice in light of the established benefit of TH and the clinical practice of treating hypokalemia. Serum potassium measurements were also not performed concurrently with ECG recordings and up to an hour lag could have been a source of error when evaluating dynamic shifts in potassium. Concurrent serum magnesium measurements were not performed as frequently as were potassium measurements. Given the influence of this electrolyte on myocardial stability this also is a limitation. Prolongation of the QT interval cannot be directly linked to hypokalemia in a causative manner without knowledge of magnesium levels. Several other factors are known to impact the QT interval in this population, and this study was not designed to identify those determinants. Hypomagnesemia, however, was not frequently seen during this study and no association was found between serum magnesium or hypomagnesemia and PVT. Our study also did not allow us to control for size of infarct or changes in reperfusion therapy – both of which are independent risk factors for the development of PVT. Furthermore, anoxic-intracranial injury has also been shown in basic and clinical studies to affect cardiac autonomic influence with resultant repolarization abnormalities. The degree of cerebral injury was not studied in our analysis.

5. Conclusion

Therapeutic hypothermia is associated with a significant decline in serum potassium, occurring predominantly during the cooling phase. Our data suggest concomitant alterations in myocardial repolarization with a propensity for the development of PVT. Maintenance of potassium levels above 3.0 mmol l^{-1} during this potentially vulnerable period may be critical in avoiding the development of PVT.

Conflict of interest statement

No conflicts of interest declared.

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