

High Resolution ECG Changes in Survivors of Out-of-Hospital Cardiac Arrest during and after Mild Therapeutic Hypothermia

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Abstract

Our aims were to determine whether mild therapeutic hypothermia (MTH) is associated with ECG changes similar to those observed in accidental hypothermia, and to use advanced ECG parameters to further characterize any electrophysiological changes associated with MTH.

The study included 46 patients (35 after primary, 9 after secondary, and 2 after heart arrest of undetermined type), treated with MTH. In all patients, a 5-minute 12-lead high fidelity ECG was recorded during MTH and in normothermia, with core body temperatures 33.0 ± 0.6 and 37.2 ± 0.6 °C, respectively. Custom software programs were used to calculate several conventional and advanced ECG parameters.

During MTH, changes in standard ECG parameters included significantly increased RR, PR and QTc intervals, as already described in the literature. Utilizing advanced ECG, we also found significantly increased HRV, QRS vector amplitude and spatial ventricular gradient, but decreased QTV and narrower spatial QRS-T angle.

We conclude that hypothermia significantly affects electrophysiological characteristics of heart muscle and suggest that recovery from MTH is associated with increased sympathetic drive.

1. Introduction

Sudden cardiac arrest (SCA) is one of the leading causes of death in developed countries, with an annual incidence ranging from 36 to 81 events per 100000 inhabitants. Post-anoxic encephalopathy is a common complication after an out-of-hospital cardiac arrest. The risk of neurological damage remains high even after being successfully resuscitated. The introduction of MTH (defined as core body temperature of 32-34°C) in 2002 has revolutionized treatment of comatose survivors after cardiac arrest, increasing survival and improving neuro-

logical outcome. Recent studies suggest that MTH might also reduce myocardial damage [1].

Accidental hypothermia has been shown to cause electrocardiographic changes such as increase in RR, PR and QT intervals, appearance of Osborn waves, conduction blocks and various arrhythmias. Although a few studies of standard ECG parameters in MTH have also shown similar changes [2-4], no study to date has utilized more advanced ECG parameters to more fully characterize the electrophysiological effects of MTH versus normothermia.

2. Methods

2.1. Patients

Our study was approved by the Institutional Review Board at the University Medical Centre, Ljubljana, Slovenia, and included comatose patients, older than 16 years, after cardiac arrest treated with MTH at the University Medical Centre, Ljubljana. In all patients, core body temperature was measured by thermistor intravesically. ECG was recorded during MTH and after restoration of normal body temperature.

2.2. Data collection

High fidelity (1000 samples/sec/channel) ECG system from Cardiax/Cardiosoft (Budapest, Hungary/Houston, TX) [5] was utilized to acquire 5-minute ECG recordings in MTH and during normothermia to get a minimum of 256 beats acceptable for both signal averaging and variability analyses. Custom software programs were used to calculate standard and advanced ECG parameters in standard and derived orthogonal leads.

2.3. Analysis of ECG signals

The initial group of patients was assessed for presence of Osborn waves and type of heart rhythm. In compute-

rized analysis of standard and advanced ECG parameters, we included those patients who survived long enough to have had two ECG recordings (in MTH and in normothermia). They also had to have sinus rhythm in both ECGs, since sinus rhythm is a prerequisite to calculate repolarization parameters and parameters of RR interval variability.

A. Conventional ECG parameters. Signals from the conventional ECG were analysed automatically by software, developed by Institute of Physiology, Medical Faculty Ljubljana, Slovenia in cooperation with NASA, Houston, Texas [5,6]. The parameters obtained were the RR, PR, uncorrected and corrected QT (QTc) and JT intervals; P, QRS and T-wave amplitudes; frontal plane QRS and T-wave axes; and ST segment levels. Corrected QT interval was calculated using an exponential formula [7]. For calculating P, QRS and T-wave amplitudes we used a program that calculated average vector amplitude from all 12 leads.

B. Advanced ECG parameters derived from signal averaging and from variability analyses. Signal averaging was performed using software developed by the authors [8-10] to generate results for parameters of:

1) derived 3-dimensional ECG, using the Frank-lead reconstruction technique of Kors et al [11] to derive vectorcardiographic (VCG) parameters including the spatial mean QRS-T angle and spatial ventricular gradient (VG);

2) QRS and T-waveform complexity via singular value decomposition (SVD), to derive parameters such as the principal component analysis (PCA) ratio, intradipolar ratio (IRD) [9] the "relative residuum" [9] and the dipolar and non-dipolar voltages [8] of the QRS and T waveforms;

3) 12-lead high frequency (HF, 150-250 Hz) QRS ECG, from which principal vectors were determined by SVD, and the first three vectors used to calculate a root mean square (RMS) HF QRS amplitude defined as a square-root of the sum of the squared first three principal signals. Both the peak (HFQRS A) and mean (HFQRS M) HFQRS RMS signals were determined;

4) beat-to-beat RR and QT interval variability (RRV and QTV), evaluated via custom software programs developed by the authors as described in previous publications [5,6,8]. These included different components of the frequency power spectra (LP, HP and TP: very low, low, high and total, respectively), obtained using Lomb periodogram or autoregressive model [12], and time domain parameters (SDNN RR, RMSSD RR, SDNN QT: standard deviation from the mean of all normal-to-normal RR and QT intervals, respectively; root-mean-square of the successive RR interval difference). The "QT variability index" (QTVI) was obtained using the means and variances of the RR interval [6] rather than those of the heart rate [5,6] in the denominator of the QTVI equation. The QTV signal was further decomposed into

two parts: the "explained" part that can be accounted for by the concomitant HRV and/or by the concomitant variability of the QRS-T angle and ECG voltages, and the other part representing the "unexplained" part of QTV [6]. This was obtained by fitting the QT signals by a linear combination of the RR interval, QRS-T angle and voltage signals to obtain the calculated QT signal. Then, the cross-correlation (QTcor) between the measured QT signal and calculated QT signal was determined for all ECG leads. Finally, the "explained" eQTV was defined as $QTV * QTcor$, with the remaining "error" part representing the "unexplained" QTV, $uQTV = QTV - eQTV$. A modified "index of unexplained QTV" (UTVI) similar to QTVI was then calculated by replacing the variance of the total QTV by the variance of the unexplained uQTV. QTcor and the related parameters were finally determined as a mean QTcor value, belonging to leads with the highest T wave amplitudes.

2.4. Statistical methods

Parameters thus obtained in MTH and normothermia were tested for significant differences. We used paired samples T-test for normally distributed variables and Wilcoxon signed rank test for variables that did not have normal distribution.

3. Results

Assessment of 91 hypothermic ECGs showed presence of Osborn waves in 33 (36%). After applying the exclusion criteria, ECGs from 46 of the original 91 patients were included for standard and advanced ECG analyses. The demographic and other characteristics of the included patients are outlined in Table 1.

Table 1. Characteristics of patients (n=46) whose ECGs were included for further analysis of standard and advanced ECG. Values are arithmetic mean \pm SD.

Variable	Value
Gender (men)	34 (74%)
Age (years)	59.6 \pm 13.0
Primary heart arrest	35 (76%)
Secondary heart arrest	9 (20%)
Undetermined type of heart arrest	2 (4%)
Temperature at 1 st ECG ($^{\circ}$ C)	33.0 \pm 0.6
Temperature at 2 nd ECG ($^{\circ}$ C)	37.2 \pm 0.6
Time between ECG recordings (hours)	35.1 \pm 12.3

During MTH, we observed statistically significant increases of the following standard ECG parameters: RR interval, PR interval, QT and QTc interval. Additionally, an increase in average QRS complex amplitude, derived from average QRS vector amplitude from all 12 leads,

was observed in MTH compared to normothermia (Table 2). All other standard ECG parameters proved not to have statistically significant different values during MTH compared to normothermia.

Table 2. Statistically significant changes in standard and advanced ECG parameters in MTH and normothermia. Values are arithmetic mean \pm SD.

Parameter	MTH	Normother.	P value
RR mean	1105 \pm 268	679 \pm 123	<0.0001
PR mean	150 \pm 55	121 \pm 59	0.006
QTc	547 \pm 69	427 \pm 74	<0.0001
Amp_QRS	1123 \pm 455	947 \pm 375	<0.0001
VG	61.9 \pm 110.6	25.7 \pm 15.4	<0.0001
QRS-T angle	74.2 \pm 46.5	102.1 \pm 44.2	<0.0001
SDNN_RR	49.7 \pm 39.9	25.0 \pm 44.5	<0.0001
RMSSD_RR	52.0 \pm 62.7	31.0 \pm 76.2	0.003
ARHF	5.0 \pm 2.0	3.0 \pm 2.4	<0.0001
ARLF	4.5 \pm 2.1	2.6 \pm 2.3	<0.0001
ARTP	5.9 \pm 1.8	4.2 \pm 2.2	<0.0001
QTVI	-1.1 \pm 0.74	-0.38 \pm 0.84	<0.0001
UTVI	-0.71 \pm 0.83	-0.03 \pm 0.68	<0.0001
QTcor	0.49 \pm 0.16	0.42 \pm 0.15	0.007
SDNN_QT	2.8 \pm 1.5	4.6 \pm 3.7	<0.0001
uSDNN_QT	1.5 \pm 0.92	2.4 \pm 1.5	<0.0001

Legend: RR mean, PR mean: mean RR, PR interval [ms]; QTc: corrected QT interval [ms]; Amp_QRS: average complex QRS vector amplitude from all 12 leads [μ V]; VG: ventricular gradient [mV*ms]; QRS-T angle: spatial mean QRS-T angle [deg]; SDNN_RR: standard deviation from the mean of all normal-to-normal RR intervals [ms]; RMSSD_RR: root-mean-square of the successive RR interval difference; ARHF, ARLF, ARTP: logarithm of the HF, LF components and TP of the RR interval power spectrum calculated with autoregressive model [Ln ms²/Hz]; QTVI, UTVI, SDNN_QT, uSDNN_QT: QT variability index and index of unexplained part of QTV, standard deviation from the mean of all normal-to-normal QT intervals and its unexplained component [units], as described in the text.

Among advanced ECG parameters, we found statistically significant differences in parameters of 3-dimensional ECG (VG, QRS-T angle) and in several parameters of RR and QT variability. The parameters of RRV all significantly decreased in normothermia. Components of the frequency spectra (LP, HP, TP) calculated with Lomb periodogram and autoregressive model all significantly decreased in normothermia, with autoregressive model having higher significance (lower P values). On the other hand, parameters of QTV all increased in normothermia except for QTcor (Table 2). The explained part of QTV was not statistically different in MTH compared to normothermia. We also did not find any statistically

significant changes of high frequency QRS parameters and parameters of QRS and T-waveform complexity, except QRS dipolar voltages that followed changes of the vector QRS amplitude.

4. Discussion and conclusions

Our study was in accordance with previous findings of increased RR, PR and QTc intervals and the presence of Osborn waves in MTH [3,4]. Additionally, we discovered statistically significant increases in RR variability parameters, QRS complex amplitudes and VG, but decreases in QT variability parameters and the spatial QRS-T angle during MTH.

Analysis of beat-to-beat RR interval variability showed statistically significant increases in both time domain (SDNN_RR and RMSSD_RR) and frequency domain parameters (HF, LF, TP) during MTH. A possible physiological mechanism behind these changes in our patients might be the following: Hypothermia is known to decrease tissue metabolism; an increase in tissue metabolic demand in our patients in normothermia compared to MTH had to be matched with increased tissue perfusion. Since most of our patients had a primary cardiac cause of arrhythmic arrest and thus limited cardiac reserve, increased tissue perfusion could only be achieved by increased sympathetic and decreased parasympathetic activity. This would stimulate the heart to increase cardiac output and by doing so increase tissue perfusion. Increased sympathetic and decreased parasympathetic activity would explain relatively decreased parameters of RRV in normothermia [13].

Whereas parameters of RRV were significantly increased during MTH compared to normothermia, parameters of QTV were significantly decreased. These changes that occurred in QTV after return to normothermia go hand in hand with seemingly opposite changes in RRV, since it is known that increased QTV is associated with increased sympathetic drive [14]. Therefore, the same physiological mechanism as outlined above for RRV could also be applied for QTV. In addition, statistically significant changes in the unexplained part of QTV but not in the explained part of QTV indicate the change in QTV parameters was predominantly driven by the unexplained part. This can also be seen from observing cross-correlation parameter QTcor. Most ECG findings after return to normothermia might therefore be explained by increased sympathetic drive due to increased cardiac and other tissue metabolism in the face of on-going limitations in cardiac performance and reserve.

We discovered that our patients had higher average QRS complex amplitudes in MTH compared to normothermia. This could be attributed to protocol of inducing MTH, since all patients received 30 ml/kg – 0.9% NaCl venous infusion cooled to 0 °C during first 30 minutes

after admission. This large fluid bolus initially increased intravascular fluid volume which increased cardiac preload and size of heart chambers. Higher QRS complex amplitudes in MTH can be explained in part by the Brody effect [15], with higher tissue impedance also occurring in MTH compared to normothermia. Added infusion for the purpose of MTH induction, at first increasing intravascular volume, has later diffused into the extravascular space, and remained there because of reduced cardiac pumping capacity in our patients. Increase in extracellular fluid volume in the time between the two recordings (35.1 ± 12.3 h) would decrease tissue impedance and thus decrease QRS complex amplitudes in normothermia. Similar rise of QRS amplitudes was observed in patients with end stage renal failure just after haemodialysis [16]. During MTH compared to normothermia, the spatial QRS-T angle was significantly decreased. This change, along with the relatively decreased QTV and increased HRV during MTH, potentially provides some electrophysiological rationale for the cardioprotective effect of MTH, inasmuch as opposite changes (increased spatial QRS-T angle and QTV and decreased HRV) are known to be associated with increased risk for SCA [9, 17]. The higher VG values and lower unexplained QTV during MTH might also specifically suggest that MTH has beneficial effects on spatial and temporal dispersion of repolarization, presumably as mediated through changes in cardiac action potentials.

We speculate then, based especially on changes in the advanced ECG pattern, that MTH provides relative cardioprotection from an electrophysiological standpoint. Later, during the normothermic recovery phase after MTH, when increased tissue metabolic needs and sympathetic drive occur in the face of improved but still compromised cardiac performance and reserve, the degree of cardioprotection is relatively diminished.

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References

- [1] Erlinge D, Götberg M, Grines C, et al. A pooled analysis of the effect of endovascular cooling on infarct size in patients with ST-elevation myocardial infarction. *Euro Intervention* 2013;8:1435–40.
- [2] Chhabra L, Devadoss R, Liti B, et al. Electrocardiographic changes in hypothermia: a review. *Ther Hypothermia Temp Manag* 2013;3:54–62.
- [3] Lebiez P, Meiners J, Samol A, et al. Electrocardiographic changes during therapeutic hypothermia. *Resuscitation* 2012;83:602–6.
- [4] Rolfast CL, Lust EJ, de Cock CC. Electrocardiographic changes in therapeutic hypothermia. *Crit Care* 2012;16:R100.
- [5] Starc V, Schlegel TT. Real-time multichannel system for beat-to-beat QT interval variability. *J Electrocardiol* 2006;39:358–67.
- [6] Starc V, Schlegel TT. The effect of aging and cardiac disease on that portion of QT interval variability that is independent of the heart rate variability. *Computers Cardiology* 2008;35:315–17.
- [7] Sarma JS, Sarma RJ, Bilitch M, et al. An exponential formula for heart rate dependence of QT interval during exercise and cardiac pacing in humans: reevaluation of Bazett's formula. *Am J Cardiol* 1984;54: 103–8.
- [8] Batdorf BH, Feiveson AH, Schlegel TT. The effect of signal averaging on the reproducibility and reliability of measures of T-wave morphology. *J Electrocardiol* 2006;39:266–70.
- [9] Schlegel TT, Kulecz WB, Feiveson AH, et al. Accuracy of advanced versus strictly conventional 12-lead ECG for detection and screening of coronary artery disease, left ventricular hypertrophy and left ventricular systolic dysfunction. *BMC Cardiovascular Disorders* 2010;10:28.
- [10] Schlegel TT, Kulecz WB, DePalma JL, et al. Real-time 12-lead high frequency QRS electrocardiography for enhanced detection of myocardial ischemia and coronary artery disease. *Mayo Clin Proc* 2004;79:339–350.
- [11] Kors JA, van Herpen G, Sittig AC, van Bommel JH. Reconstruction of the Frank vectorcardiogram from standard electrocardiographic leads: diagnostic comparison of different methods. *Eur Heart J* 1990;11:1083-92.
- [12] Press WH. Numerical recipes in C : the art of scientific computing. In. 2nd ed. Cambridge ; New York: Cambridge University Press; 1992:59-70.
- [13] Camm AJ, Malik M, Bigger JT Jr, et al. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Eur Heart J* 1996;17:354–81.
- [14] Baumert M, Schlaich MP, Nalivaiko E, et al. Relation between QT interval variability and cardiac sympathetic activity in hypertension. *Am J Physiol Heart Circ Physiol* 2011;300:1412–7.
- [15] Brody DA. A theoretical analysis of intracavitary blood mass influence on the heart-lead relationship. *Circ Res* 1956;4:731–8.
- [16] Madias JE, Narayan V. Augmentation of the amplitude of electrocardiographic QRS complexes immediately after hemodialysis: a study of 26 hemodialysis sessions of a single patient, aided by measurements of resistance, reactance, and impedance. *J Electrocardiol* 2003;36:263–71.
- [17] Kardys I, Kors JA, van der Meer IM, et al. Spatial QRS-T angle predicts cardiac death in a general population. *Eur Heart J* 2003;24:1357–64.

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