High Resolution ECG Differences between Hospital Survivors and Non-survivors of Out-of-Hospital Cardiac Arrest during Mild Therapeutic Hypothermia

Martin Rauber[1], Dušan Štajer[1,2], Marko Noč[1,2], Todd T Schlegel[3], Vito Starc[1]

[1]University of Ljubljana, Faculty of Medicine, Ljubljana, Slovenia
[2]Centre for Intensive Internal Medicine, University Medical Centre, Ljubljana, Slovenia
[3]Nicollier-Schlegel Sàrl, Trélex, Switzerland

Abstract

Our aim was to evaluate electrocardiographic (ECG) differences between survivors and non-survivors of out of hospital cardiac arrest (OHCA).

The study included 76 patients that suffered from OHCA. In all patients, serum arterial lactate was obtained on admission to the intensive care unit was obtained as an index of ischemia during cardiac arrest and resuscitation. A 5-minute 12-lead high fidelity ECG recording was recorded during mild therapeutic hypothermia (MTH) (defined as core body temperature of 32-34°C). Custom software programs were used to calculate conventional and advanced spatial, repolarisation and interval variability ECG parameters. Survival versus non survival to hospital discharge was considered as the outcome variable.

There were 38 survivors of OHCA among our patients. Survivors displayed significantly lower serum arterial lactate levels and lower values of beat-to-beat QT interval variability parameters.

We conclude that a relatively greater degree of anoxic injury in patients that fail to survive OHCA results in altered electrophysiological properties of the heart muscle leading to increased ventricular repolarisation variability.

1. Introduction

Out of hospital cardiac arrest (OHCA) 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 OHCA.

The introduction of mild therapeutic hypothermia (MTH), defined as core body temperature of 32-34°C, has revolutionized treatment of comatose survivals after OHCA, increasing survival and improving neurological outcome. Despite novel therapeutic strategies, management of patients resuscitated from OHCA remains challenging for clinicians, and the mortality rate of those who achieve return of spontaneous circulation (ROSC) and hospital admission remains high. Prognostication of outcome in OHCA is of importance because it could help physicians simplify therapeutic efforts in patients with good prognosis, intensify therapeutic efforts in patients with less favourable prognosis and withdraw futile intensive treatment in patients with no possibility for survival. A number of factors and markers have been proposed for prediction of outcome after OHCA with greater or lesser reliability, but none of them has been derived from electrocardiogram [1]. Due to the low cost, accessibility and non-invasiveness of ECG, it would be clinically helpful to identify any parameters from ECG that might help predict outcome in OHCA patients.

While the definitive identification of any such parameters would require a large outcomes-based trial, the aim of this present pilot trial was to first evaluate general differences between the ECGs of survivors versus non-survivors of OHCA.

2. Methods

2.1. Patients

The 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. All the patients with indications for percutaneous coronary intervention had already undergone the procedure before admission. Patients were deeply sedated with propofol, and whenever needed, with addition of fentanyl, sufentanil, remifentanil, or sevoflurane during their treatment with MTH. In all patients, core body temperature was measured by thermistor intravesically. Serum arterial lactate on admission to the intensive care unit was acquired from patients' clinical registry. Every patient

was followed until hospital discharge. Survival versus non survival to hospital discharge was considered the outcome variable. Five-minute ECG recording was recorded in the first 24 hours after admission during MTH.

Patients with rhythm other than stable sinus rhythm, and those with intraventricular conduction disturbances, were excluded from the study since regular rhythm without conduction disturbances is a prerequisite for reliable calculation of RR and QT interval variability. Additionally, patients that displayed a nearly flat T wave (<0.1 mV) were also excluded, it having been shown that accuracy of determining QT variability parameters is inversely proportional with T wave amplitude [2]. Also, all the included patients had their QRS axis in the frontal plane between -20° and 60°.

2.2. Data collection

High fidelity (1000 samples/sec/channel) ECG system from Cardiax/Cardiosoft (Budapest, Hungary / Houston, Texas) [3] was utilized to acquire 5-minute ECG recordings in all patients in MTH to obtain a minimum of 256 QRS-T complexes 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

A. Conventional ECG parameters.
Signals from the conventional ECG recording were analysed automatically by software, developed by Institute of Physiology, Medical Faculty Ljubljana, Slovenia in cooperation with NASA, Houston, Texas [3,4]. The parameters obtained were the RR interval, QRS deviation in the frontal plane, corrected QT (QTc) and T-wave amplitudes. To calculate corrected QT interval, we used Fridericia's formula, $QTc = QT / RR^{\alpha}$ with $\alpha = 0.31$ [5]. For T-wave amplitude we used a program that calculated average vector amplitude from all 12 leads.

B. Advanced ECG parameters derived from beat-to-beat variability analyses.
Signal averaging was performed using software developed by the authors [3,6] to generate results for parameters of:

1) Derived 3-dimensional electrocardiogram, using the Frank-lead reconstruction technique of Kors et al [7] to derive vectorcardiographic parameters including the spatial mean QRS-T angle.

2) Beat-to-beat RR and QT interval variability (RRV and QTV) were evaluated via custom software programs developed by the authors, as described in previous publications [3,4,6]. These included components of the frequency power spectra (LFP and HFP: low and high frequency powers, respectively), obtained using Lomb periodogram [8], and time domain parameters (SDNN RR, SDNN QT, uSDNN QT: standard deviation from the mean of all normal-to-normal RR and QT intervals and its unexplained component, respectively). The "QT variability index" (QTVI) was obtained using the means and variances of the RR interval [4] rather than those of the heart rate [3,4] 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 [4]. 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" QTV (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 uQTV.

2.4. Statistical methods

Data were analysed using IBM SPSS Statistics, Version 20.0 (IBM Corp., Armonk, NY). Distribution type was evaluated using the Shapiro-Wilk test. To evaluate numeric differences between the survivor and non-survivor groups, we used independent samples t-test for normally distributed variables and Mann–Whitney U test for variables that did not have normal distribution.

3. Results

After applying the above stated exclusion criteria, 76 patients out of 127 were enrolled in the study. Of these, 38 were ultimately survivors, and 38 were non-survivors. Demographic, clinical and other characteristics of patients in the two study groups are shown in Table 1.

Comparing the two study groups, there were significant differences in beat-to-beat QT interval variability (Table 2). This was reflected by higher ventricular repolarisation variability in the non-survivor group as demonstrated by differences in all QT variability parameters (QTVI, UTVI, SDNN QT, uSDNN QT). However, no statistically significant differences were found in RR interval variability parameters (SDNN RR, LoLFP, LoHFP) between the two groups. Also, we did not find any statistically significant differences in observed standard ECG parameters (RR mean, QTc, Ampl T) or in spatial QRST-T angle.

Table 1. Characteristics of patients included for further analysis of standard and advanced ECG parameters (n = 76). Values are arithmetic mean ± SD.

Variable	Value	
	Survivors (n = 38)	Non-survivors (n = 38)
Gender (male)**	33 (87 %)	24 (63 %)
Age (years)	56.8 ± 12.7	60.6 ± 14.5
Age males (years)	54.8 ± 12.0	58.3 ± 12.1
Age females (years)	69.6 ± 10.2	64.6 ± 17.5
Primary OHCA	31 (82 %)	26 (68 %)
Secondary OHCA	6 (16 %)	12 (32 %)
Undetermined OHCA	1 (2 %)	0 (0 %)
Core body temp. at ECG recording (°C)	33.0 ± 0.7	32.9 ± 0.6
Sevoflurane for sedation	8 (21%)	3 (8%)
Time after OHCA until ECG recording (hours)	20 ± 8	
Serum lactate (mmol/L)*	3.0 ± 3.3	5.7 ± 3.7

**: $p = 0.018$; *: $p = <0.0001$

Table 2. Observed standard and beat-to-beat variability parameters in survivors and non-survivors of OHCA. Values are arithmetic mean ± SD.

Parameter	Survivors	Non-survivors	P value
RR mean	1096 ± 221	1002 ± 286	0.111
QTc	563 ± 83	537 ± 112	0.246
Ampl T	223 ± 86	211 ± 108	0.363
QRS-T angle	78.2 ± 34.2	89.7 ± 45.6	0.430
SDNN RR	24.4 ± 36.3	15.3 ± 15.5	0.253
LoLFP	3.68 ± 2.22	3.32 ± 2.46	0.495
LoHFP	4.00 ± 2.27	4.03 ± 2.25	0.629
QTVI	-0.97 ± 0.82	-0.61 ± 0.82	0.035
UTVI	-0.76 ± 1.03	-0.18 ± 1.06	0.012
SDNN QT	3.45 ± 2.20	5.45 ± 4.42	0.013
uSDNN QT	1.50 ± 1.06	3.1 ± 3.13	0.013

Legend: RR mean: mean RR interval [ms]; QTc: corrected QT interval [ms]; QRS-T angle: spatial mean QRS-T angle [deg]; Ampl T: average T wave vector amplitude from all 12 leads [µV]; SDNN RR: standard deviation from the mean of all normal-to-normal RR intervals [ms]; LoLFP, LoHFP: logarithm of the LF, HF components of the RR interval power spectrum obtained using Lomb periodogram [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.

4. Discussion and conclusions

Both study groups had their electrocardiograms recorded during MTH, thus their core body temperatures were low, but without a statistically significant difference between groups.

Previously we showed that MTH itself causes several changes in both conventional and advanced ECG parameters [9]. Such changes include increased mean RR interval and narrowing of the QRS-T angle (by 27.8 ± 44.1 deg.). Thus while in MTH, the QRS-T angle values of our patients often fell into the normal or high-normal range, their values would be expected to substantially increase during normothermia into borderline or overtly abnormal ranges, consistent with the patients' underlying cardio-vascular disease [10].

The extremely high values of QTc in both groups might be explained by a synergistic effect of MTH and heart muscle pathology, both of which increase QTc. Comparing the hypothermic to the normothermic electrocardiograms of the same patients in our previous publication, we observed a mean increase in QTc of 112 ± 94 mV during MTH [9]. Among drugs used for sedation in our patients, sevoflurane has been shown to have modest, dose dependent effect on QTc (5-15% prolongation, depending on the study). 8 (20%) of the survivors and 3 (8%) of the non-survivors were sedated using sevoflurane. In high concentrations sufentanil has also been reported to prolong QTc, although far lower dosing was used in our patients [11].

We have also previously reported that MTH substantially decreases QT variability and increases RR variability. Thus parameters of QTV such as QTVI were lower (less pathological) during MTH than what one might expect for patients with recent OHCA (similar to the situation for the spatial QRS-T angle). For survivors in this study, QTVI values were even closer to those reported in other studies as "normal" for healthy individuals [12]. Moreover we also previously reported that treatment with MTH increases the amplitudes of QRS complexes. One of the mechanisms we proposed was higher tissue impedance in MTH [9]. By analogy we could speculate that MTH increases all ECG waveform amplitudes, including T wave amplitudes. If so, then a higher amplitude-driven slight improvement in the accuracy of detecting QRS and T-wave fiducial points might, purely for methodological reasons, decrease measured QTV values even further [2].

Our study groups showed no statistically significant differences in age. Statistically significant differences were however observed in sex distribution, non-survivors being comprised of a higher percentage of females. This might be attributed to the fact that women suffer from CVD later than males and that physiological compensatory mechanisms, including those that help compensate for low tissue perfusion and anoxia experienced during cardiac arrest, decline with age [13]. Studies of QTV in healthy individuals have also shown that gender-related differences in QTV exist, with healthy women having slightly but significantly higher QTVI values than healthy men [12]. Based on our groups'

ultimate gender distributions, this fact might have impacted our results, although by definition our patients were severely diseased.

Serum arterial lactate on admission has been shown to correlate well with outcome in patients with OHCA [14]. We found highly significantly higher serum arterial lactate values in group of non-survivors. Lactate being the by-product of anaerobic metabolism, we can conclude that higher admission lactate in non-survivors is a marker of more severe anoxic injury.

Myocardial injury can result in an increase in membrane instability, a steepening of the restitution relationship between the QT and diastolic interval, and an increase in the ratio of sympathetic to parasympathetic tone, all of which result in increased QT variability [9]. Also, it has been shown that QTVI negatively correlates with left ventricular ejection fraction and positively with left ventricular dimension [15]. Our results showed that non-survivors had statistically higher QTVI values, which could reflect the severity of the disease (anoxic injury, impaired cardiac function), slight gender differences as noted above and increased ratio of sympathetic to parasympathetic tone. Impaired cardiac function and diminished catecholamine response in metabolic acidosis [16], with lower pH due to higher levels of serum arterial lactate in non-survivors, would require greater sympathetic response in this group. However, our results failed to show any statistically significant differences in parameters of RR interval variability between groups. Additionally, almost the entirety of QTVI in both groups was actually represented by UTVI, a portion of QT variability that is independent of RR variability. Taking that into the account, the impact of vegetative tone on QT variability parameters increase in non-survivors in our study seems less probable.

In conclusion, we may speculate that a relatively higher degree of anoxic injury in patients who fail to survive until hospital discharge results in altered electrophysiological properties of the heart muscle leading to increased ventricular repolarisation variability. Additionally in these patients, as seen from changes in the above studied ECG parameters, inability to adequately increase sympathetic tone relative to parasympathetic tone could be an additional reason for failure to survive until hospital discharge. Post-anoxic encephalopathy with damaged autonomic nervous system centres or pathways stands out as a possible culprit.

Further work towards identifying one or multiple ECG parameters that could predict hospital outcome for patients who achieve ROSC after OHCA needs to be done.

Acknowledgements

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Address for correspondence.
Martin Rauber,
Ljubljana University, Faculty of Medicine, Vrazov trg 2, 1104 Ljubljana, Slovenia   martin.rauber88@gmail.com