Electrocardiographic changes in therapeutic hypothermia

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Abstract

Introduction: During therapeutic hypothermia (TH), electrocardiographic (ECG) abnormalities such as Osborn waves and/or ST-segment elevation have been described. However, the incidence and prognostic value of these ECG changes are uncertain given the small-scale studies that have been carried out to date. The aim of this study is to further evaluate the electrocardiographic changes during TH.

Methods: During a period of 3 years, 81 patients (age 63 ± 14 years) were included retrospectively. All patients underwent TH after being resuscitated. ECG registrations before, during and after TH were collected and analyzed. Patients were divided into two groups based on the presence or absence of transmural ischemia ST elevation on the first representative ECG upon arrival at the hospital (ST-segment elevation myocardial infarction (STEMI) and non-STEMI).

Results: A total of 243 ECGs were analyzed. During TH 24 patients (30%) had Osborn waves, which disappeared in 22 patients (92%) after regaining normal body temperature. The presence of Osborn waves was not associated with age, gender, average pH, electrolytes, or lactate levels and was not associated with excess in-hospital mortality. In 10 patients (12%, six non-STEMI patients) new STEMI was observed during TH, which disappeared after TH discontinuation. The STEMI group (44 patients) had significantly more Osborn waves during TH than the non-STEMI group (38.6% vs. 15.2%, odds ratio = 3.508; 95% confidence interval = 1.281 to 9.610).

Conclusions: Hypothermia-induced Osborn waves are relatively common and are not associated with an unfavorable short-term outcome. TH is associated with ECG changes that may mimic STEMI.

Introduction

Post-anoxic encephalopathy is a common complication after an out-of-hospital cardiac arrest (OHCA). The risk of neurological damage remains high even after being successfully resuscitated [1-5]. Hours and days after successful resuscitation, further damage can be caused by multiple deployed cascades - such as excitotoxicity by the release of certain amino acids and free oxygen radicals that trigger a chemical reaction leading to further DNA damage and apoptosis of brain cells [6,7].

The current guidelines recommend mild therapeutic hypothermia (TH) to prevent neurological damage after a cardiac arrest. Hypothermia is defined as a body temperature <35°C [8]. Using mild temperatures of 32 to 33°C, relatively few side effects have been reported. A number of studies have conclusively shown that mild hypothermia significantly reduced the risk of hypoxic brain damage and has a beneficial effect on short-term survival [9-11]. Although the pathophysiology underlying these results has insufficiently been clarified, applying mild hypothermia after resuscitation has become a standard of care worldwide.

Hypothermia also has an influence on the conduction of the heart. Some small studies have shown that hypothermia leads to electrocardiographic (ECG) changes including Osborn waves [12,13]. Several case reports describe abnormalities during TH that may be indicative of cardiac ischemia, particularly ST-segment elevation myocardial infarction (STEMI) [14-17]. However, these studies were too small to make clear conclusions on the incidence and prognostic value of these changes. The aim of the present study is to further evaluate the electrocardiographic changes during TH after
Materials and methods
The study was approved by the VU University Medical Center institutional review board (number R 2011/161, IRB 00002991. In the period of January 2007 to October 2009 TH was applied to 109 consecutive patients. By protocol, midazolam and propofol were used for sedation. A 12-lead ECG was collected from all patients in addition to clinical and laboratory parameters.

Patients were included if one or more ECGs with the patient’s corresponding body temperature before, during and after TH were present. Patients with a complete left bundle branch block (11 patients) and patients with a pacemaker rhythm (2 patients) were excluded. ECG registration was incomplete in 15 patients and these patients were also excluded. Eighty-one patients were thus included and 243 ECGs were analyzed.

All ECGs were assessed by two experienced cardiologists (CDC, EJL). During TH a temperature averaging 32°C (minimum 29°C, maximum 34°C) was maintained for 12 to 24 hours. The presenting arrhythmia was defined as that initially recorded by the emergency medical services report. Ventricular fibrillation (VF) was defined as a pulseless condition with specific features on the cardiac recording, while pulseless electrical activity was defined as the absence of a pulse with the appearance of an organized electrical rhythm [18].

Patients were divided into two groups, based on the presence or absence of signs of acute transmural ischemia on the 12-lead ECG on admission: STEMI group and non-STEMI group. Patients with ST segment elevation ≥1 mm in ≥2 contiguous leads were considered to have STEMI, and these patients underwent emergency coronary angiography and primary percutaneous coronary intervention [19]. In the non-STEMI patient group, a different cause than coronary artery disease was assumed based on the clinical and electrocardiographic data upon arrival at the hospital. In these patients, no emergency coronary angiography was performed. We did not use the cardiac enzymes as markers for ischemia, considering there are conflicting data on the sensitivity and specificity of these markers in these patients to assess myocardial infarction [20].

The following parameters were analyzed before, during and after TH: heart rate, basic heart rhythm, PQ conduction time, QRS conduction time, QTc time, left anterior fascicular block, Osborn waves, pathological Q waves and ST-T segment abnormalities. Q and QS patterns were scored according to the Minnesota Code Classification System [20]. QTc intervals were calculated as described by Bossaert and colleagues [21]. The following arrhythmias were scored; atrial fibrillation, atrioventricular nodal rhythm, atrioventricular block, ventricular tachycardia, ventricular.

Statistical analysis
All statistical analyses were carried out using SPSS (SPSS Inc, Chicago, Illinois, USA). Results with \( P < 0.05 \) were regarded as statistically significant. When comparing two discrete variables, the chi-square test or the odds ratio (OR) was used. We used a paired \( t \) test when comparing two groups of patients. For assessment of a linear relationship between a continuous variable and a dichotomous variable, the chi-square test for trend was used.

Results
Table 1 presents the demographics of the 81 patients included. The mean age of the patients was 63 ± 11 years and 74% were male. In all patients the onset of the cardiac arrest was outside the hospital. In 56 patients (69%) the initial rhythm was VF. In the remaining group, 19 patients (24%) presented with asystole and five patients (6%) had pulseless electrical activity. VF was more commonly present in the STEMI group \((\text{OR} = 3.333; 95\% \text{ confidence interval (CI)} = 1.239 \text{ to } 9.429)\). Acute STEMI was considered the cause of OHCA in 54 patients (56%). The in-hospital mortality in the total group was 50%. From the group of patients that survived, 38 patients (47%) were diagnosed to have moderate to severe post-anoxic encephalopathy. Survival to discharge was substantially more likely after documented VF than after documented non-VF \((68\% \text{ vs. } 12\%, \text{ OR} = 15; 95\% \text{ CI} = 4.093 \text{ to } 58.552)\).

All 243 ECG tracings were assessed for the presence of TH-induced electrocardiographic changes (Table 2). The heart rate showed a consistent reduction from 95 ± 15 to 58 ± 13 beats/minute \((39\% \text{ reduction}, \text{ \( P < 0.0001 \)})\), and QTc showed a significant 7% increase \((466 ± 54 milliseconds \text{ before TH to } 498 ± 65 milliseconds \text{ during TH, \( P < 0.0001 \)})\). The ECG before initiating TH showed no Osborn waves in any patient. Osborn waves occurred in 24 patients (30%) during TH. In 22 of these patients, the Osborn waves disappeared after regaining normal body temperature. A direct correlation between the temperature during TH and the emergence of Osborn waves was not observed \((P = 0.382)\). Osborn waves were significantly more prevalent during cooling in the STEMI group than in the non-STEMI group \((38.6\% \text{ vs. } 15.2\%, \text{ OR} = 3.508, 95\% \text{ CI} = 1.281 \text{ to } 9.610). The presence of Osborn waves was not associated with an increase in in-hospital mortality \((50.9\% \text{ vs. } 45.8\%, \text{ OR} = 0.817, 95\% \text{ CI} = 0.314 \text{ to } 2.12)\). TH-induced Osborn
waves also showed no relation to age or gender, and potassium and calcium levels did not correlate with any ECG changes. The two patients with persistent Osborn waves both survived until hospital discharge.

The average pH level at admission was 7.09 ± 0.18, ranging from 6.67 ± 0.12 to 7.39 ± 0.20. The average lactate concentration at admission was 6.93 ± 2.1 mmol/l, ranging from 0.50 ± 0.12 to 51.4 ± 16.0 mmol/l. A correlation between pH and lactate levels at admission and Osborn waves during cooling was not observed (P = 0.651 and P = 0.187, respectively). Of the 37 patients in the non-STEMI group, six patients developed new ST elevation during TH (Table 2). Two of the six patients were younger than 35 years old without a cardiac history (see Figure 1). As a result of the ST-segment changes during TH, two patients underwent emergency coronary angiography showing normal epicardial coronary arteries. In five of the six patients, the ST segment elevation disappeared after TH.

In addition, four patients in the STEMI group developed new ST elevation during TH (Table 2). Two of the four patients had a proven acute anterior wall infarction and developed new ST-segment elevation in the inferior leads during TH. The remaining two patients had a proven inferior wall infarction and developed new ST-segment elevation in the anterior leads. Of interest, there was no reciprocal depression corresponding with the new ST elevations during TH. In two of the four patients, the ECG tracing after TH showed ST-segment elevation in the leads that represented the myocardial infarction. In the six patients classified as nonischemic, all had echocardiography to assess the need for coronary intervention. Global and/or regional wall motion abnormalities were observed in two patients, who subsequently underwent emergency coronary angiography showing no abnormalities. In none of the patients was a percutaneous coronary intervention performed. The new ST elevation that developed during TH disappeared in all patients after TH. Eight patients developed a pathological Q wave during cooling, while there were no pathological Q waves before TH. All eight of these patients, however, were classified as the STEMI group before TH initiation.

**Discussion**

The Advanced Life Support Task Force of the International Liaison Committee on Resuscitation published guidelines on OHCA patients, recommending cooling to 32 to 34°C for 12 to 24 hours in 2003 [22]. TH has been rapidly implemented since then, with the number of ICUs using this therapy reported to be up to 95% [23]. Although ECG abnormalities associated with hypothermia were described in 1938, remarkably few studies including a limited number of patients have focused on the prevalence and possible predictive value of these abnormalities [12-17].

Rankin and Rae studied 22 patients with accidental hypothermia and observed Osborn waves in one-half of the study cohort [12]. The mean temperature was low (29.8 ± 3.3°C) as compared with TH, however, and in

**Table 1 Demographic factors in the total study cohort**

| Age (years)          | 63 ± 14 |
|----------------------|---------|
| Male/female          | 60 (74%)/21 (26%) |
| Index arrhythmia     |         |
| Ventricular fibrillation | 56 (69%) |
| Nonventricular fibrillation (pulseless electrical activity/asystole) | 25 (31%) |
| Heart rhythm at hospital arrival |         |
| Sinus rhythm         | 56 (69%) |
| Atrial fibrillation  | 18 (22%) |
| Atrial flutter       | 1 (1%)  |
| Atroventricular nodal rhythm | 6 (8%) |
| Underlying condition |         |
| Myocardial infarction| 45 (56%) |
| Asphyxia/aspiration  | 5 (6%)  |
| Pulmonary embolism   | 5 (6%)  |
| Chronic obstructive pulmonary disease | 2 (3%) |
| Brugada syndrome     | 1 (1%)  |
| Myocarditis          | 1 (1%)  |
| Severe aortic valve stenosis | 3 (4%) |
| Advanced heart failure | 2 (3%) |
| Unknown              | 17 (21%) |

Data presented as mean ± standard deviation or n (%).

**Table 2 Electrocardiographic changes and arrhythmia before, during and after therapeutic hypothermia**

|                   | Before TH | During TH | After TH |
|-------------------|-----------|-----------|----------|
| Heart rate (beats/minute) | 95 ± 26   | 58 ± 15   | 87 ± 17  |
| PQ duration (milliseconds) | 172 ± 45  | 175 ± 44  | 155 ± 34 |
| QRS duration (milliseconds) | 103 ± 28  | 99 ± 21   | 89 ± 18  |
| QTc (milliseconds) | 466 ± 54  | 498 ± 65  | 460 ± 55 |
| LAFB               | 14        | 7         | 6        |
| Osborn waves       | 0         | 24        | 2        |
| ST elevation       | 38        | 22        | 12       |
| ST depression      | 79        | 74        | 68       |
| Right bundle branch block | 7        | 9         | 8        |
| Left bundle branch block | 0        | 1         | 0        |
| Q wave             | 15        | 23        | 21       |
| Atrial fibrillation| 16        | 4         | 4        |
| Atroventricular nodal rhythm | 6        | 3         | 3        |
| Ventricular tachycardia/ventricular fibrillation | 6        | 1         | 0        |

Data presented as mean ± standard deviation or n (%). TH, therapeutic hypothermia.
50% of patients the temperature on admission was <30°C. Atrial fibrillation was seen in 27% and QTc prolongation in 90% of patients. Mortality was high (64%) and a relation with outcome of ECG abnormalities or arrhythmias was not reported [12].

Vassallo and colleagues studied 100 ECGs in 43 consecutive patients with accidental hypothermia [14]. Presenting temperatures were low, with 63% of patients ranging from 31.7 to 26.1°C. Osborn waves were present in all ECGs where the temperature was ≤30.5°C. Changes in QTc were not reported, and atrial fibrillation was seen in 19% of patients. Okada and colleagues studied 50 patients with accidental hypothermia and reported Osborn waves in 80% of patients [13]. The presence and size of the Osborn wave were inversely related to body temperature, and in three patients persistent Osborn waves were seen after prolonged hypothermia. The same group studied the incidence of arrhythmias during accidental hypothermia and observed atrial fibrillation in 23 patients (38%). A substantial number (70%) had a presenting body temperature <32°C. No significant difference in mortality was observed between patients with or without atrial fibrillation during hypothermia [13].

No studies on ECG abnormalities and arrhythmias during TH have been published. The main finding of the present study is that Osborn waves are a relatively common finding in OHCA patients receiving TH, being observed in 30% of all patients. The prevalence of TH-associated Osborn waves is substantially lower as

Figure 1 Electrocardiogram changes before and during therapeutic hypothermia. Example of electrocardiogram changes (A) before and (B) during therapeutic hypothermia in an 18-year old out-of-hospital cardiac arrest patient.
compared with studies on patients with accidental hypothermia and is in concordance with earlier observations that these ECG abnormalities are inversely correlated with temperature [14]. In our study, the temperature maintained during TH was on average 32°C and 86.4% of the study cohort had a body temperature between 32 and 34°C during TH. The presence of Osborn waves was not associated with a higher in-hospital mortality. TH-induced Osborn waves were not correlated with age, gender, average pH, electrolytes or lactate levels on admission. Osborn waves were significantly more present in the ischemic group than in the nonischemic group (38.6% vs. 15.2%, OR = 3.508, 95% CI = 1.281 to 9.610). In 22 of the 24 patients, the Osborn waves disappeared spontaneously after TH. This suggests that Osborn waves are not an expression of cardiac structural changes occurring during hypothermia. Persistence of Osborn waves was also reported by Vassallo and coworkers and might reflect underlying structural heart disease [14].

A significant increase in QTc during TH was observed, which is in concordance with earlier studies. QRS duration was not influenced by TH. The most common arrhythmia during TH is atrial fibrillation, which has been reported to range from 19 to 38%. In our study, atrial fibrillation was seen in 18 patients (22%) and no association with the presence of atrial fibrillation and in-hospital mortality was found. ST-segment abnormalities are almost always present in up to 98% in our series. TH-associated ST-segment elevation has occasionally been reported in earlier studies and can mimic acute myocardial infarction [17]. Misdiagnosis in these cases can lead to inappropriate administration of thrombolytic therapy or unnecessary transport of these critically ill patients to a catheterization room. In addition, these patients can be subjected to nephrotoxic agents during coronary angiography.

Characteristics of the 10 patients in the present study who developed ST-segment elevation (12%) are shown in Table 3. Reciprocal ST-segment depression was not observed in any of these cases. Six out of the 10 patients with new ST elevation developing during TH belonged to the non-STEMI group. However, three of the six patients had a history of myocardial infarction. In the ischemic group, two patients with angiographically proven inferior infarction developed new ST-segment elevation during TH in the anterior leads, whereas two patients with an angiographically proven anterior STEMI had new ST elevations in the inferior leads. TH-induced ST-segment elevation disappeared in all patients after regaining normal body temperature. Reciprocal ST-segment depression in STEMI is often considered to be mirror-image changes or remote ischemia in a distant territory in patients with multivessel coronary artery disease [24,25]. The observed ST-segment elevation during TH probably reflects a different mechanism where heterogeneity in repolarization leads to a current flowing from the normal myocardium towards an area with the short action potential [26]. This mechanism may potentially lead to re-entrant tachycardia, but this was not observed in the present cohort.

Limitations
Some important limitations have to be discussed. Although this is to date the largest study evaluating ECG findings in hypothermic patients, absolute numbers in this retrospective analysis are relatively small. In addition, comparison with studies on accidental hypothermia is ambiguous since body temperature in accidental hypothermia is substantially lower as compared with

| Patient | Before TH | New during TH | After TH | Diagnosis at admission | Cardiac history | Age (years) | Gender |
|---------|-----------|---------------|----------|-------------------------|-----------------|-------------|--------|
| Nonischemic | 1 | 0 | AW = 4, IW = 2 | 0 | Unknown | Hypertension | 72 | Female |
| | 2 | 0 | AW = 4 | 0 | Asphyxia | COPD | 25 | Male |
| | 3 | 0 | AW = 2 | 0 | Unknown | CABG | 67 | Male |
| | 4 | 0 | AW = 2 | 0 | Aspiration | - | 34 | Male |
| | 5 | 0 | IW = 2 | 0 | Unknown | Old MI | 52 | Male |
| | 6 | 0 | AW = 2 | AW = 2 | Aspiration | CAD | 59 | Female |
| Ischemic | 1 | IW = 0, AW = 4 | IW = 3, AW = 3 | IW = 0, AW = 3 | Acute AW infarction | Hypertension | 65 | Female |
| | 2 | IW = 0, AW = 5 | IW = 3, AW = 5 | 0 | Acute AW infarction | - | 50 | Female |
| | 3 | IW = 3, AW = 0 | IW = 2, AW = 4 | 0 | Acute IW infarction | - | 58 | Male |
| | 4 | IW = 3, AW = 0 | IW = 3, AW = 2 | IW = 2, AW = 0 | Acute IW infarction | Old MI | 47 | Male |

AW, anterior wall; CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; IW, inferior wall; MI, myocardial infarction; TH, therapeutic hypothermia; VF, ventricular fibrillation.

Table 3 Characteristics of patients that developed ST-segment elevation during therapeutic hypothermia
TH. Finally, patients were divided into STEMI and non-STEMI etiology of OHCA based on the first 12-lead ECG, which may not always reflect the true underlying pathophysiological substrate.

Conclusion
TH is not uncommonly associated with abnormal ECG findings such as Osborn waves, prolongation of the QTc interval and atrial fibrillation, which have no impact on in-hospital outcome. TH-induced ST-segment elevation mimicking STEMI was seen in 12% of all patients. Absence of reciprocal ST-segment depression may be indicative of pseudo-infarction, which may prevent inappropriate or hazardous therapy.

Key messages
- Osborn waves are the most common ECG changes during TH, observed in almost one-third of patients.
- The presence of Osborn waves is not associated with adverse in-hospital outcome.
- ST-segment elevation during hypothermia was seen in 12% of patients and may mimic acute myocardial infarction; however, unlike acute infarction, an absence of reciprocal ST depression was found in all patients.

Abbreviations
CI: confidence interval; ECG: electrocardiogram; OHCA: out-of-hospital cardiac arrest; OR: odds ratio; STEMI: ST-segment elevation myocardial infarction; TH: therapeutic hypothermia; VF: ventricular fibrillation.

Authors’ contributions
CLR carried out the study, collected all data including ECG tracings and blood analysis, performed the statistical analysis and drafted the manuscript. EJL and CCdC supervised the conduct of the study and writing of the paper and performed ECG tracing analysis. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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