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Effect of level of temperature management and risk of arrhythmia and death

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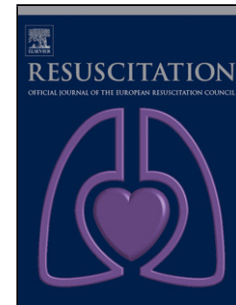
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Osborn waves following out-of-hospital cardiac arrest – Effect of level of temperature management and risk of arrhythmia and death

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ABSTRACT

Background: The Osborn or J-wave, an upright deflection of the J-point on the electrocardiogram (ECG), is often observed during severe hypothermia. A possible relation between Osborn waves (OW) and increased risk of ventricular arrhythmia has been reported. We sought to determine whether the level of targeted temperature management (TTM) following out-of-hospital cardiac arrest (OHCA) affects the prevalence of OW and to assess the associations between OW and risk of ventricular arrhythmia and death.

Methods and results: The present study is part of the TTM-trial ECG-substudy (including OHCA-patients randomized to TTM at 33°C vs. 36°C from 24 of 36 sites). Serial 12-lead ECGs from 680 (94%) patients were analysed and stratified by OW at predefined time-points (0, 4, 28, 36, 72-hours after admission).

On admission, the overall prevalence of OW was 16%, increasing to 32% at target temperature, with higher prevalence in the 33°C-group (40% vs. 23%, $p<0.0001$). No difference in prevalence was found between the 33°C- and 36°C-groups on admission (18% vs. 14%, $p=0.11$) or after rewarming (13% vs. 10%, $p=0.44$). OW were not associated with increased risk of ventricular arrhythmia (Odds ratio=0.78 (0.51-1.20), $p=0.26$), but associated with significantly lower 180-day mortality as compared to no OW (38% vs. 52%, $p_{\log\text{-rank}}=0.001$) in univariable analyses only.

Conclusion: OW are frequent during TTM, particularly in patients treated with 33°C. OW are not associated with increased risk of ventricular arrhythmia, and may be considered a benign physiological phenomenon, associated with lower mortality in univariable analyses.

Key words

Cardiac arrest; hypothermia; repolarization; ventricular arrhythmia; cardiac arrhythmia; Osborn waves; J-waves; Out-of-hospital cardiac arrest; Targeted temperature management; Therapeutic hypothermia; TTM;

INTRODUCTION

Mild hypothermia in the form of targeted temperature management (TTM) between 32° and 36°C remains a guideline supported treatment modality for attenuation of neurological injury following out-of-hospital cardiac arrest (OHCA)[1, 2]. The treatment is generally considered safe[3], however a subset of OHCA-patients is affected by potentially life-threatening arrhythmias during post-cardiac arrest care and TTM[4].

Studies on accidental hypothermia and the effects of TTM in both animals and humans have contributed with knowledge of the pathophysiological and physiological processes during cooling[5]. Lowering of the core temperature affects the body in various ways; especially cardiac electrophysiology is affected with distinct changes in the electrocardiogram (ECG)[6], e.g. lowering of the heart rate, prolongation of PR, QRS and QT intervals, and presence of Osborn waves (OW)(*Figure 1*)[7]. Case reports of severe accidental hypothermia below 30°C have reported occurrence of arrhythmia including malignant ventricular tachycardia (VT) and fibrillation (VF)[8], potentially leading to fatal outcome.

Markers of patients at risk of arrhythmia during TTM could be useful in providing basis for individualized post-cardiac arrest care. Tomaszewski was the first to report hypothermia-induced ECG changes in 1938[9]. He observed an upright deflection of the J-point (terminal part of the QRS complex) in an accidentally hypothermic patient. Osborn later confirmed this hypothermia-triggered change in dogs[10], as a distinct deflection progressively seen by lower core temperature and reversible by rewarming. Recent case reports in cardiac

arrest patients have suggested a possible relation between OW and an increased risk of ventricular arrhythmia[11], while a smaller observational study has failed to confirm this association[12].

We sought to assess the effect of two levels of TTM on the prevalence of OW following OHCA. Furthermore, we assessed the associations between OW and risk of ventricular arrhythmia and death.

METHODS

The present study is part of the multicenter-ECG and single-center Holter sub-study of the TTM-trial[13]. The main trial included adult comatose patients resuscitated after OHCA (N=939) from a presumed cardiac cause with return of spontaneous circulation (ROSC) for at least 20 minutes (regardless of initial rhythm). Patients were enrolled and randomized in a 1:1 fashion to a 36-hour TTM protocol aimed at either 33°C or 36°C. The main trial showed no difference in outcome between the two temperature groups[13]. Patients were included as fast as possible but within 240 minutes from sustained ROSC. A complete list of inclusion and exclusion criteria has been published previously[13].

Twenty-four out of 36 sites participated in the ECG sub-study, with 726 eligible patients. The present sub-study included 680 (94%) patients with at least one 12-lead ECG after admission (*Figure S1*). In addition, a subgroup of 113 patients admitted at the cardiac intensive care units (ICU) at Copenhagen University Hospital (Rigshospitalet) was continuously Holter-monitored during TTM.

TTM was controlled by automated feedback devices and intravascular or surface cooling were used with similar frequencies between the groups. The target temperature (TT) was reached as fast as possible. After 28 hours rewarming to 37°C was commenced with a maximum increase of 0.5°C/hour. Post-cardiac arrest care including mandatory seda-

tion, intubation and mechanical ventilation were carried out through the specified intervention period of 36 hours.

The serial 12-lead ECGs after OHCA were obtained at fixed time points: ECG₁ – on admission to the hospital, ECG₂ – at the allocated TT, ECG₃ – 24 hours after induction of TTM, ECG₄ – 36 hours after induction (at normothermia after rewarming) and ECG₅ – 72 hours after induction. Trained assessors, blinded for temperature group and outcome, manually analysed available ECGs. Obtained ECGs were stratified by OW vs. no OW at any given time-point, with an OW defined as an upright deflection of the J-point compared to the isoelectric baseline (*Figure 1*). We chose a pragmatic approach including all upright deflections at the J-point including QRS end-slurs, irrespective of lead location and amplitude height. Right bundle branch block (RBBB)/ R wave – S wave – R wave (RSR) configuration in lead V1-V2 was not considered an OW. In three ECGs, however, it was judged that the changes could represent both OW and RBBB. Interobserver agreement with regards to presence of OW was assessed in 30 randomly selected patients, with observers blinded to temperature group and previous assessment, with very good agreement (total of 113 ECGs assessed with a Cohen's kappa coefficient = 0.81).

Demographics and prehospital data concerning the circumstances of the OHCA were collected according to the Utstein guidelines.[14]

Ethics

The main study protocol was approved by Ethics Committees in all participating countries. Written informed consent was obtained or waived, either from included patients after regaining consciousness or as proxy consent from the patients' relatives (next of kin), the latter either alone or combined with the patients' general practitioner's consent in

accordance with national legislation. The TTM-trial complied with the Declaration of Helsinki and was registered at ClinicalTrials.gov (Identifier: NCT01020916).

Statistical analysis

Baseline characteristics were presented and stratified by OW during TTM at any given time, including sub-stratification by TT. Categorical variables were presented by proportions (%) and differences tested by χ^2 -test. Continuous normally distributed variables were presented by mean \pm standard deviation (SD) and tested by t-test. Non-normally distributed variables were presented with median and the 25-75 percentile range and compared by Wilcoxon rank sum test. To assess the interaction between presence of OW and allocated TT over time, a repeated measure model (generalized linear model) was used and the fixed type 3 effects reported (SAS Genmod).

For assessment of 6 months survival between the groups, we used Kaplan-Meier survival curves and log-rank tests. Uni- and multivariable proportional hazards Cox-regressions were used to assess the associations between OW at any time point and 6 months mortality. Logistic regression was used to assess the association between OW and unfavourable neurological outcome after 6 months. Neurological outcome, based on the Cerebral Performance Categories Scale (CPC) score, was dichotomized into favourable vs. unfavourable outcome as follows: a) favourable neurological outcome included patients with a CPC score of 1 or 2, capable of carrying out independent activities of daily life and b) unfavourable neurological outcome included patients with a CPC score of 3 to 5 incl. severe cerebral disability depending on daily support, comatose and expired patients. Further, logistic regression was used for analysis of the association between OW and risk for ventricular arrhythmia (ventricular-tachycardia (VT) and fibrillation (VF)) during the day 1-3 of post-cardiac arrest care. The multivariable models were adjusted for cardiac arrest characteristics and factors known

to influence mortality (age, sex, time to ROSC, witnessed arrest, bystander cardiopulmonary resuscitation (CPR), bystander defibrillation, shockable primary rhythm, admission lactate level, ST-elevation myocardial infarction (STEMI), TTM group and cumulated number of comorbidities). All tests were 2-sided and results presented as Hazard ratios (HR) and Odds ratios (OR) with corresponding 95% confidence intervals (CI). Further, logistical regressions for OW on admission and during TTM were assessed including randomisation, age, sex, time to ROSC, witnessed arrest, bystander CPR, bystander defibrillation, initial rhythm, admission lactate level, left ventricular ejection fraction (LVEF), STEMI and comorbidity. Statistical significance was defined as a p-value <0.05 . Statistical analyses were performed using the SAS statistical software, version 9.3.

Assessment of ventricular (VEB) and supraventricular ectopic beats (SVEB) in the Holter-monitored subpopulation was performed by hourly registrations during the maintaining phase between the TTM allocation groups and compared using repeated measures mixed models with a random intercept and an unstructured covariance structure.

RESULTS

Prevalence and baseline characteristics

Of the 680 included patients, the overall OW prevalence was 16% on admission, increasing to 32% at TT. OW were found in 274 (40%) patients at least once during TTM, and were more prevalent in the 33°C-group (46% vs. 35%, $p<0.01$) (*Table 1 and Figure S1*). Stratified analysis of the serial ECGs revealed that OW were similarly prevalent on admission ($p=0.11$) with increasing prevalence during TTM in both temperature groups. The OW prevalence was significantly higher in the 33°C-group at TT after 4 (40% vs. 23%, $p<0.0001$) and 24 hours ($p=0.02$) from randomization. After rewarming, the groups had simi-

lar prevalence (*Figure 2*). The allocated TT modified the prevalence throughout the course of TTM ($p_{\text{interaction}} < 0.01$).

Patients with OW were younger (62 ± 12 vs. 65 ± 12 years, $p=0.01$), had lower admission lactate levels and were more frequently subjected to acute coronary angiography (CAG) and percutaneous coronary intervention (PCI). Patients with OW had a lower prevalence of previous known: coronary artery disease, acute myocardial infarction (AMI), coronary artery bypass graft (CABG), cardiac arrest and a lower burden of pre-arrest comorbidities. We observed a higher OW prevalence in patients with initial shockable rhythm, bystander CPR and defibrillation. An overall difference in LVEF was found between the groups ($p=0.02$), with more preserved LVEF in patients with OW (*Table 1*). Increasing numbers of comorbidities were significantly associated with lower OW prevalence (OR 0.82 (0.69-0.99), $p=0.03$). At TT, allocation to 36°C (OR 0.46 (0.29-0.74), $p<0.01$) and lower LVEF (OR 0.60 (0.43-0.85), $p<0.01$) were associated with lower OW prevalence. Initial STEMI was associated with higher OW prevalence at TT (OR 1.81 (1.11-2.92), $p=0.2$) but not on admission (OR 1.1 (0.61-1.97) $p=0.75$). The heart rate corrected QT interval (Bazett's formula) was similar between patients with and without OW within the TTM groups (*data not shown*).

Risk of ventricular arrhythmia

The overall occurrence of VF during the first three days after OHCA was 6% (38/680), while VT (85/680) occurred in 13% of patients and combined VF and/or VT affected 16% (110/680) of patients. Presence of OW during post-cardiac arrest care was not significantly associated with increased risk of ventricular arrhythmia (VT/VF) during the first three days after OHCA (OR= 0.78 (0.51-1.20), $p=0.26$), nor did stratification by OW at TT (OR= 0.81 (0.49-1.34), $p=0.42$) or at 24 hours after induction reveal an increased risk of ventricular

arrhythmia. Each point estimate, though not statistically significant, indicated lower and not higher risk by OW.

Risk of ventricular and supraventricular ectopic beats

The detailed Holter recordings did not reveal any group difference regarding burden of ventricular ($p_{\text{group}} = 0.93$) or supraventricular ectopy ($p_{\text{group}} = 0.55$) during TTM. Significant overall interactions between the OW groups over time during the maintenance phase of TTM with regards to the burden of ventricular ($p_{\text{interaction}} = 0.02$) and supraventricular ectopy ($p_{\text{interaction}} < 0.01$) were seen (*Figure 4*). A significant decrease over time in ectopic activity was seen in both OW and non-OW patients.

Osborn waves and outcome after OHCA

The presence of an OW was associated with a significantly higher 180-day survival rate (62% vs. 48% ($p = 0.001$)), corresponding to a lower univariable HR for 180-day mortality ($\text{HR}_{\text{unadjusted}} = 0.68$ (0.54-0.86, $p = 0.001$)). The association between OW and lower mortality diminished after adjustment ($\text{HR}_{\text{adjusted}} = 0.87$ (0.68-1.11, $p = 0.27$)) (*Table 2*). The same pattern was found, when stratified by TT with higher 180-day survival rates by OW in both TTM groups (*Figure 3*). Occurrence of OW was associated with lower odds of unfavorable neurological outcome ($\text{OR}_{\text{unadjusted}} = 0.58$ (0.43-0.79, $p < 0.001$)) in the univariable analysis only. To avoid risk of time bias, sensitivity analyses in patients surviving for three days were performed, with similar results and lower mortality by OW in univariate analysis only ($p < 0.01$). Stratified analysis by OW in STEMI and non-STEMI patients, revealed that OW were only associated with lower mortality in non-STEMI patients (non-STEMI ($p < 0.01$) vs. STEMI ($p < 0.22$)).

DISCUSSION

The overall prevalence of OW in comatose OHCA patients treated with TTM at 33°C and 36°C was 40%. Patients treated at 33°C, showed a higher OW prevalence during the maintenance phase of TTM, compared to 36°C. OW were not associated with an increased risk of ventricular arrhythmia, and outcome analyses indicated that OW may be considered a benign physiological phenomenon during TTM, associated with favorable outcome in univariable analyses. As the association diminished after adjustment, this association is likely explained by more favorable cardiac arrest characteristics and lower comorbidity.

History and physiology of Osborn waves

Ever since Tomaszewski's discovery in 1938 of the hypothermia-related[9] J-waves in man and Osborn's clinical demonstration (1953) in acidotic and hypothermic dogs[10], the presence of the upright deflection in the ECG has been thought to be pathognomonic of hypothermia. Case reports have since shown that in addition to accidental and induced hypothermia, OW can be observed in other conditions, e.g diabetic ketoacidosis[15], sepsis[16], hypothyroidism[17] and brain death[18]. OW can thereby be observed in normothermic conditions[19] and have been detected in numerous case reports in different heart-related diseases, STEMI[20], acute myocardial ischemia[21] and LV hypertrophy caused by hypertension[22].

A case report has proposed a relation between faulty elimination of pCO₂ and occurrence of OW after cardiac arrest[23], similar to the initial hypothesis of Osborn between acidosis and J-waves[10], which was rejected by others later on[7, 24, 25]. Our data do not support these previous hypotheses. We found a higher occurrence of OW at a lower target temperature during TTM after OHCA, but found no relation between OW and pH, lactate and pCO₂ levels post cardiac arrest (*Figure S3 a-d*).

It has been shown that the amplitude of the J-point is inversely proportional to the core temperature and is reversible by gradual rewarming[7, 26]. This phenomenon fits with our results of higher prevalence in patients treated with 33°C. The relatively high overall OW incidence on admission (16%) may be attributable to a low admission temperature of around 35°C[13]. Recent smaller studies have shown a OW prevalence in OHCA-patients treated with TTM at 33°C ranging from 40-60%[12, 27, 28], likewise, OW were more prevalent in patients with STEMI vs. non-STEMI (38.6% vs. 15.2%)[29]. These findings correlate with our data showing that patients after OHCA presenting with OW have more invasive procedures performed (PCI 49% vs. 39%, $p=0.01$) possibly explained by higher degree of coronary ischemia.

Although OW have raised interest for decades, there is no consistent definition of the phenomenon. Across studies different definitions of OW have been used, with in- and exclusions of QRS end-slurs and notches[21, 30, 31], and with different criteria for amplitude height (≥ 0.1 mV, ≥ 0.2 mV, but also morphological criteria including < 0.1 mV)[6, 21, 27, 30, 31]. Also different criteria for inclusion of subgroups of leads have been used[6, 10, 21, 27, 30-32].

Osborn waves and arrhythmogenicity

The correlation between OW and risk of ventricular arrhythmia in patients with coronary ischemia has been reported in several studies, including in patients with vasospastic angina[21], acute coronary syndrome (ACS)[33], and STEMI after PCI[30]. These studies link together an increased incidence and augmentation of OW prior to the occurrence of malignant ventricular arrhythmias[21], higher in-hospital mortality[33] and suggest that OW could be indicative of an electrical vulnerability and susceptibility to arrhythmia[21]. This is in contrast to our findings, in which OW was associated with lower mortality and had no as-

sociation to increased risk of ventricular arrhythmia.

A causal correlation between malignant cardiac arrhythmias (VT/VF) and OW during hypothermia remains to be revealed and our data do not support such correlation. While some studies and case reports[5, 10, 11] found an association of arrhythmia and presence of OW, other studies[7, 27, 34, 35] found no association and considered the presence of OW of limited value as a predictor of malignant ventricular arrhythmias.

The incidence of ventricular arrhythmia in our study (6% VF, 13% VT) is seemingly higher than the one recently reported by Lee et al.[12] with only 1.7% of patients with VF. However, we report the occurrence of arrhythmia the first three days after OHCA in a cohort including a majority of patients resuscitated from a shockable rhythm. Lee et al. reported VF during a 12 hour TTM period and the study included a majority of patients with an initial non-shockable rhythm.

Osborn waves and association to mortality and neurological outcomes

OW may, according to our findings, be considered a normal and reversible physiological response to mild hypothermia. In a review regarding J-wave syndromes[36] presence was characterized as benign when they occurred in lateral precordial leads and are considered as the typical ECG findings in young, healthy and well-trained men.

Interestingly, we found that initial STEMI was associated with higher chance of OW at TT after PCI, which may suggest a possible relation of OW and reperfusion after coronary ischemia. This may also explain the increase in prevalence seen in the 36°C-group.

Unlike our findings, higher in-hospital mortality in patients with OW resuscitated from VF during ACS (24% vs. 0%, $p=0.02$) was found[33]. Some studies show, similar to our results, favourable survival by OW in hypothermic conditions[37].

OW may also occur in cases of brain injury and brain death due to dysfunction

of the hypothalamic temperature regulation centre[19], which may provide an explanation for cardiac complications in cerebral catastrophes[38]. However, our results point in opposite direction, as OW in both temperature groups were associated with favorable outcome. As no independent association with outcome was found, OW are unlikely to behold a protective effect but are merely more prevalent in the healthiest and stabile patients following OHCA.

LIMITATIONS

The present study has strengths due to prospectively collected data as part of a large randomized, multicentre clinical trial. Limitations should be acknowledged. Since ECGs were recorded at point measurements, all transient OW may not have been detected. The per-protocol collection of ECGs in this study was similar between the temperature groups and seems representable and sufficient to identify the vast majority of OW. We chose to include all Osborn-like changes and performed sensitivity analysis for lead specific OW. The OW amplitude was not measured in the present ECG database, although this might have provided further insights into the relationship between the association of electrophysiological changes during TTM, outcome and risk of arrhythmia. Several confounding factors with regards to OW should be recognized during post-cardiac arrest care. Coronary, global ischemia and admission temperature may influence early repolarisation, but the randomized design with two TTM-levels provides novel knowledge as to the effect of temperature on OW and risk of arrhythmia and death in this setting.

CONCLUSION

OW are frequent during TTM following OHCA and more often seen in patients managed at 33°C compared to 36°C. OW were not associated with an increased risk of ventricular arrhythmia. Moreover, OW may be considered a benign physiological phenomenon

associated with favourable outcome in univariable analyses only, likely explained by more favorable cardiac arrest characteristics as the association diminished after adjustment.

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DISCLOSURES

None

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REFERENCES

- [1] Nolan JP, Soar J, Cariou A, Cronberg T, Moulaert VR, Deakin CD, et al. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015: Section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015. *Resuscitation* 2015;95:202-22.
- [2] Callaway CW, Donnino MW, Fink EL, Geocadin RG, Golan E, Kern KB, et al. Part 8: Post-Cardiac Arrest Care: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2015;132:S465-82.
- [3] Salinas P, Lopez-de-Sa E, Pena-Conde L, Viana-Tejedor A, Rey-Blas JR, Armada E, et al. Electrocardiographic changes during induced therapeutic hypothermia in comatose survivors after cardiac arrest. *World J Cardiol* 2015;7:423-30.
- [4] Poles JC, Vadeboncoeur TF, Bobrow BJ. Persistent ventricular fibrillation during therapeutic hypothermia and prolonged high-dose vasopressor therapy: case report. *J Emerg Med* 2012;43:36-40.
- [5] Richter S, Ehrlich JR, Fassbender S, Fichtlscherer S. Malignant Osborn waves during therapeutic hypothermia. *Europace* 2009;11:668-9.
- [6] Vassallo SU, Delaney KA, Hoffman RS, Slater W, Goldfrank LR. A prospective evaluation of the electrocardiographic manifestations of hypothermia. *Acad Emerg Med* 1999;6:1121-6.
- [7] Emslie-Smith D, Sladden GE, Stirling GR. The significance of changes in the electrocardiogram in hypothermia. *Br Heart J* 1959;21:343-51.
- [8] Bigelow WG, Lindsay WK, Greenwood WF. Hypothermia; its possible role in cardiac surgery: an investigation of factors governing survival in dogs at low body temperatures. *Ann Surg* 1950;132:849-66.
- [9] W T. Changement electrocardiographiques observes chez un homme mort de froid. . *Arch Mal Coeur Vaiss* 1938;31:525-8.
- [10] Osborn JJ. Experimental hypothermia; respiratory and blood pH changes in relation to cardiac function. *Am J Physiol* 1953;175:389-98.
- [11] Kim CY, Bae MH, Kim NK, Yang YA, Kim KY, Lee JH, et al. Case of Recurrent Ventricular Fibrillations with Osborn Wave Developed during Therapeutic Hypothermia. *Korean Circ J* 2015;45:81-4.
- [12] Lee WS, Nam GB, Kim SH, Choi JH, Jo U, Kim WY, et al. ECG features and proarrhythmic potentials of therapeutic hypothermia. *Heart* 2016.
- [13] Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. *N Engl J Med* 2013;369:2197-206.
- [14] Lanchelle A, Nolan J, Herlitz J, Castren M, Wenzel V, Soreide E, et al. Recommended guidelines for reviewing, reporting, and conducting research on post-resuscitation care: the Utstein style. *Resuscitation* 2005;66:271-83.
- [15] Gale EA, Tattersall RB. Hypothermia: a complication of diabetic ketoacidosis. *Br Med J* 1978;2:1387-9.
- [16] Kopterides P, Synetos A, Theodorakopoulou M, Armaganidis A, Lerakis S. Osborn waves in sepsis-induced hypothermia. *Int J Cardiol* 2008;129:297-9.
- [17] Pace A, McGuire C, Kim J, Feierabend T, Chadha S, Shetty V. Osborn waves in a patient with hypothermia due to severe hypothyroidism. *QJM* 2013;106:1151.
- [18] Omar HR, Rashad R, Helal E. The giant waves of Osborn in brain death. *Intern Med J* 2011;41:841-2.
- [19] Omar HR. The Osborn wave: what have we learned? *Herz* 2016;41:48-56.

- [20] Omar HR. The J wave during ST-segment elevation myocardial infarction and its implications. *Herz* 2014;39:598-600.
- [21] Sato A, Tanabe Y, Chinushi M, Hayashi Y, Yoshida T, Ito E, et al. Analysis of J waves during myocardial ischaemia. *Europace* 2012;14:715-23.
- [22] Patel A, Getsos JP, Moussa G, Damato AN. The Osborn wave of hypothermia in normothermic patients. *Clin Cardiol* 1994;17:273-6.
- [23] Edelman ER, Joynt K. J waves of Osborn revisited. *J Am Coll Cardiol* 2010;55:2287.
- [24] Okada M. The cardiac rhythm in accidental hypothermia. *J Electrocardiol* 1984;17:123-8.
- [25] Thompson R, Rich J, Chmelik F, Nelson W. Evolutionary changes in the electrocardiogram of severe progressive hypothermia. *J Electrocardiol* 1977;10:67-70.
- [26] Omar HR, Camporesi EM. The correlation between the amplitude of Osborn wave and core body temperature. *Eur Heart J Acute Cardiovasc Care* 2015;4:373-7.
- [27] Harhash A, Gussak I, Cassuto J, Winters SL. Clinical Significance of J waves in Patients Undergoing Therapeutic Hypothermia for Out-of-Hospital Cardiac Arrest. *Pacing Clin Electrophysiol* 2016.
- [28] Dzieciol M, Kacprzak M, Goleniewska B, Zielinska M. Osborn wave in patients with ST-elevation myocardial infarction undergoing mild therapeutic hypothermia after cardiac arrest. *Acta Cardiol* 2014;69:532-40.
- [29] Rolfast CL, Lust EJ, de Cock CC. Electrocardiographic changes in therapeutic hypothermia. *Crit Care* 2012;16:R100.
- [30] Nakayama M, Sato M, Kitazawa H, Saito A, Ikeda Y, Fujita S, et al. J-waves in patients with an acute ST-elevation myocardial infarction who underwent successful percutaneous coronary intervention: prevalence, pathogenesis, and clinical implication. *Europace* 2013;15:109-15.
- [31] Haissaguerre M, Derval N, Sacher F, Jesel L, Deisenhofer I, de Roy L, et al. Sudden cardiac arrest associated with early repolarization. *N Engl J Med* 2008;358:2016-23.
- [32] Yan GX, Antzelevitch C. Cellular basis for the electrocardiographic J wave. *Circulation* 1996;93:372-9.
- [33] Aissou L, Hermida JS, Traulle S, Delaverhne A, Diouf M, Leborgne L, et al. Prevalence and prognostic significance of 'J waves' in patients experiencing ventricular fibrillation during acute coronary syndrome. *Arch Cardiovasc Dis* 2012;105:578-86.
- [34] Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002;346:557-63.
- [35] Tiainen M, Parikka HJ, Makijarvi MA, Takkunen OS, Sarna SJ, Roine RO. Arrhythmias and heart rate variability during and after therapeutic hypothermia for cardiac arrest. *Crit Care Med* 2009;37:403-9.
- [36] Antzelevitch C, Yan GX. J wave syndromes. *Heart Rhythm* 2010;7:549-58.
- [37] Schober A, Sterz F, Handler C, Kurkciyan I, Laggner A, Roggla M, et al. Cardiac arrest due to accidental hypothermia--a 20 year review of a rare condition in an urban area. *Resuscitation* 2014;85:749-56.
- [38] van der Bilt IA, Hasan D, Vandertop WP, Wilde AA, Algra A, Visser FC, et al. Impact of cardiac complications on outcome after aneurysmal subarachnoid hemorrhage: a meta-analysis. *Neurology* 2009;72:635-42.

TABLES

Table 1. Baseline

Demographics and cardiac arrest characteristics

	Osborn N=274 (40 %)	no Osborn N=406 (60 %)	p-value
Demography:			
Age - mean (\pm SD)	62 (\pm 12)	65 (\pm 12)	0.01
Male gender n (%)	233 (85%)	326 (80%)	0.11
Any Osborn by randomization allocation			
TTM at 36° C – n= 333 (%)	116 (35%)	217 (65%)	<0.01
TTM at 33° C – n= 347 (%)	158 (46%)	189 (54%)	
Cardiac arrest characteristics:			
Bystander witnessed arrest	246 (90%)	379 (93%)	0.09
Bystander Cardiopulmonary Resuscitation	204 (74%)	289 (71%)	0.35
Bystander defibrillation	28 (10%)	34 (8%)	0.41
Shockable initial rhythm	227 (83%)	302 (74%)	0.07
Time to return of spontaneous circulation – min (IQR)	25 (15-39)	25 (17-39)	0.15
Lactate at admission – mmol/L (\pm SD)	6.5 (\pm 4.4)	7.2 (\pm 4.6)	0.05
Acute coronary angiography	187 (68%)	242 (60%)	0.02
Percutaneous coronary intervention	133 (49%)	158 (39%)	0.01
Coronary artery bypass graft	0 (0%)	0 (0%)	
Left ventricular ejection fraction:			
Normal or preserved (>50%)	49 (18%)	54 (13%)	0.02
Moderately impaired (30-50%)	75 (27%)	120 (30%)	
Severely impaired (<30%)	34 (12%)	84 (21%)	
Not performed	107 (39%)	137 (34%)	
Pre-arrest comorbidities:			
Coronary artery disease	54 (20%)	135 (33%)	0.0001
Previous acute myocardial infarction	44 (16%)	96 (24%)	0.02
Previous coronary artery bypass graft	13 (5%)	48 (12%)	<0.01
Previous cardiac arrest	2 (1%)	12 (3%)	<0.05
Congestive heart failure	12 (4%)	29 (7%)	0.14
Arterial hypertension	96 (35%)	154 (38%)	0.44
Previous transitory cerebral ischemia/ stroke	15 (5%)	38 (9%)	0.06
Diabetes	45 (16%)	59 (15%)	0.55
Asthma/Chronic obstructive pulmonary disease	21 (8%)	45 (11%)	0.14
Alcoholism	9 (3%)	17 (4%)	0.54
Comorbidity – median (IQR)	1 (0-2)	2 (0-3)	<0.0001

Abbreviations: AMI: acute myocardial infarction. CABG: coronary artery bypass graft. CAG: coronary angiography. COPD: chronic obstructive pulmonary disease. CPR: cardiopulmonary resuscitation. IQR: interquartile range. LBBB: left bundle branch block. LVEF: left ventricular ejection fraction. n: number. PCI: percutaneous coronary intervention. RBBB: right bundle branch block. ROSC: return of spontaneous circulation. SD: standard deviation. STEMI: ST-elevation myocardial infarction. TCI: transitory cerebral ischemia. TTM: target temperature management. y: year, Osborn refers to Osborn wave present at any lead in any of the recorded ECGs

Table 2. Hazard ratio and odds ratios for 180-day mortality and unfavorable neurological outcome

	Hazard ratio for 180-day mortality			
	Univariable	p-value	Multivariable	p-value
	HR (95%CI)		HR (95%CI)	
Osborn waves	0.68 (0.54-0.86)	0.001	0.87 (0.68-1.11)	0.27
	Odds ratio for unfavorable neurological outcome 180 days after OHCA			
	Univariable	p-value	Multivariable	
	OR (95%C)		OR (95%C)	p-value
Osborn waves	0.58 (0.43-0.79)	0.0005	0.72 (0.49-1.06)	0.10

Abbreviations: CI: confidence interval. CPR: cardiopulmonary resuscitation. HR: hazard ratio. STEMI: ST-elevation myocardial infarction. OHCA: out-of-hospital Cardiac Arrest. OR: odds ratio. ROSC: return of spontaneous circulation. y: year. Multivariable model adjusted for: TTM 36° vs 33° group, age at arrest (5 year), sex (male), time to ROSC (5 min), witnessed arrest, bystander CPR, bystander defibrillation, shockable primary rhythm, lactate level at admission (per mmol/L), STEMI and comorbidity

FIGURES

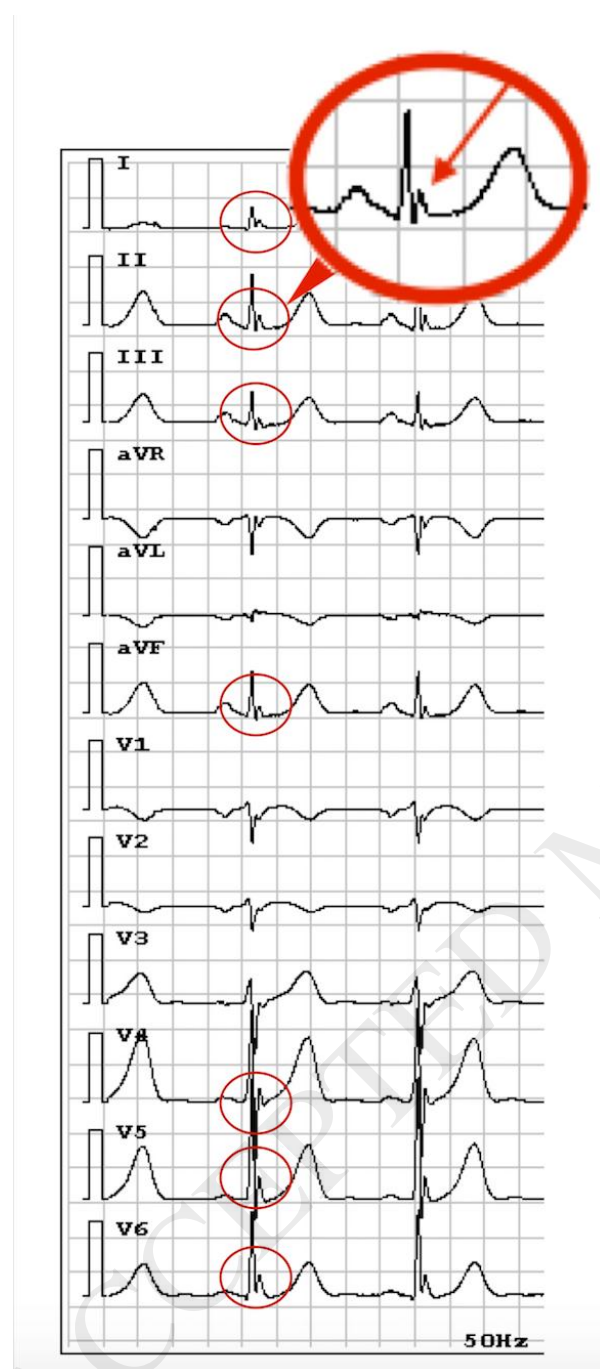


Figure 1 – Infero-lateral Osborn waves (red circles) during targeted temperature management following out-of-hospital cardiac arrest

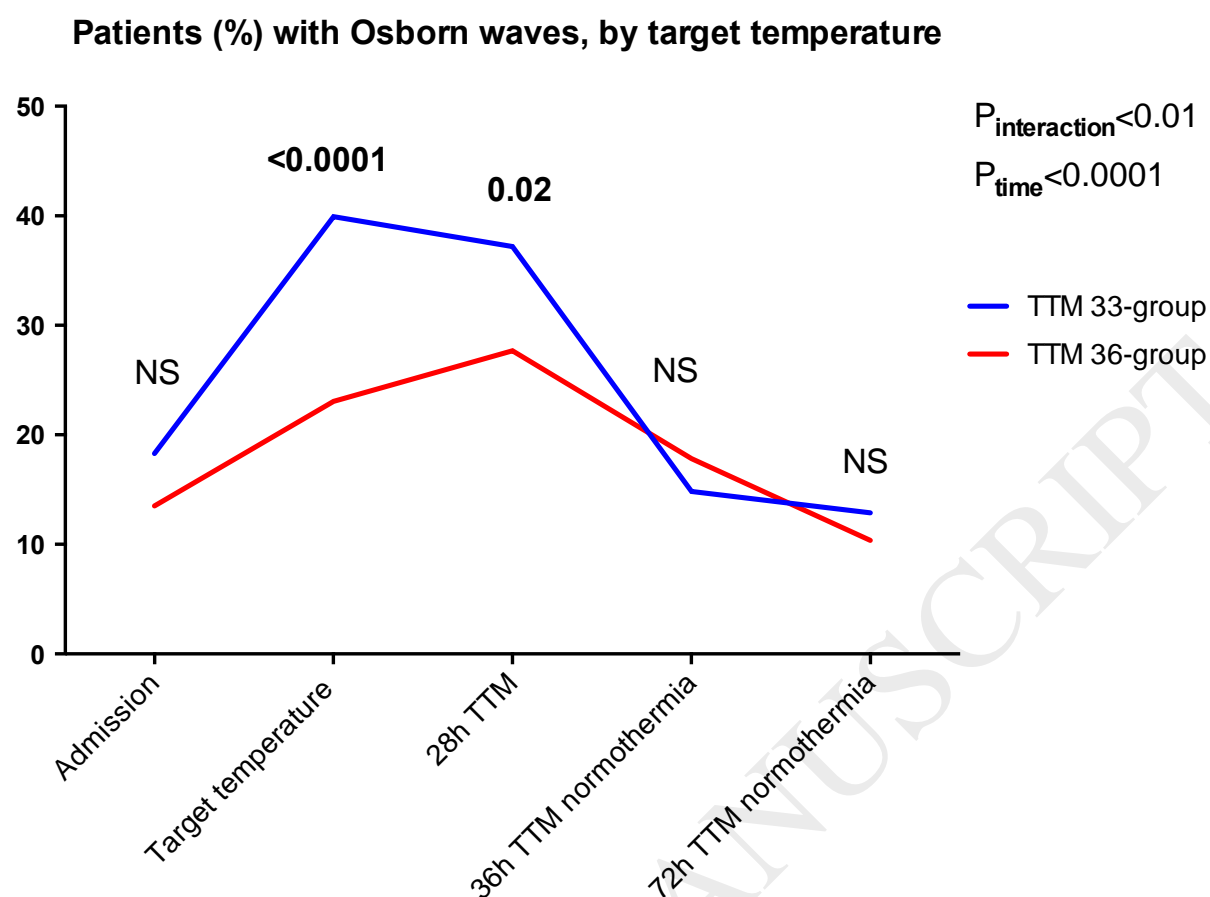
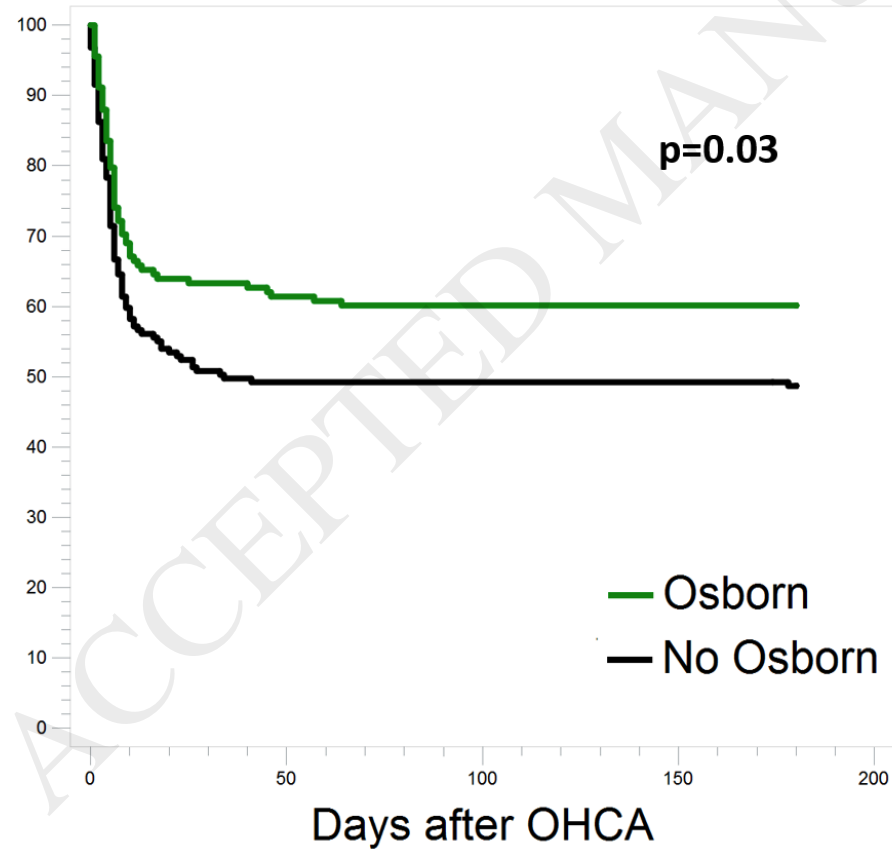


Figure 2 – The proportion of patients reported with Osborn waves in the 33°C-group (blue) and the 36°C (red) during the course of targeted temperature management. The p-value for the interaction term represents the effect of the temperature level over time between the groups.

180-day survival 33-group



180-day survival 36-group

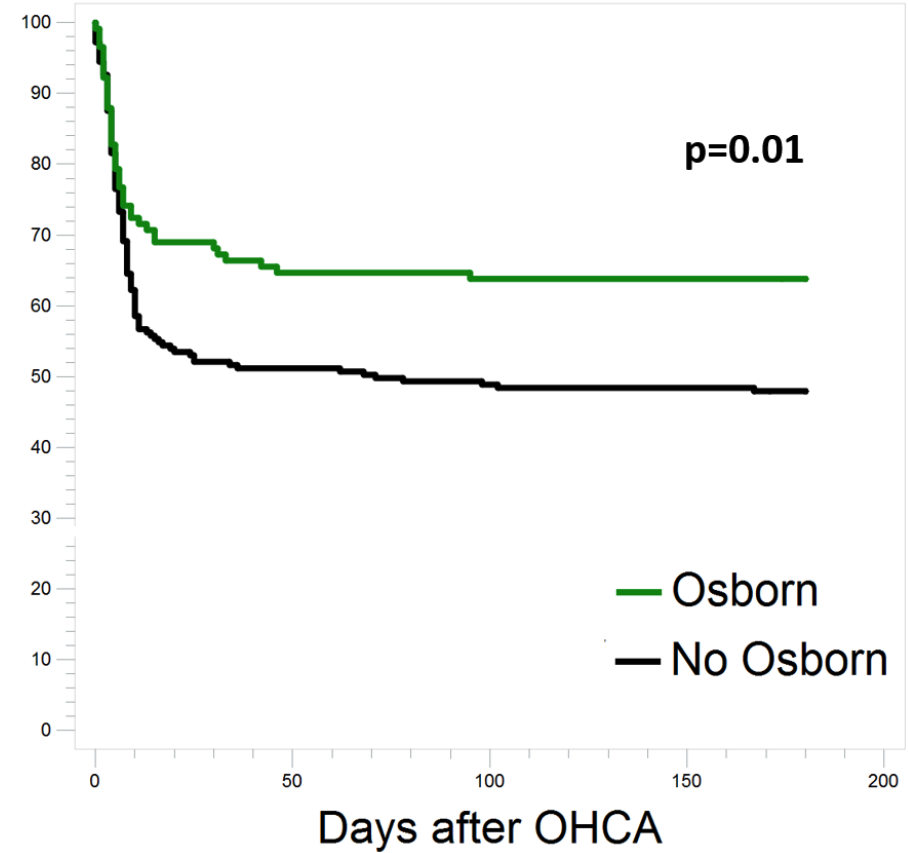


Figure 3 – 180-day survival rate stratified by TTM group and any Osborn waves during TTM. Left panel: 33°C-group. Right panel: 36°C-group

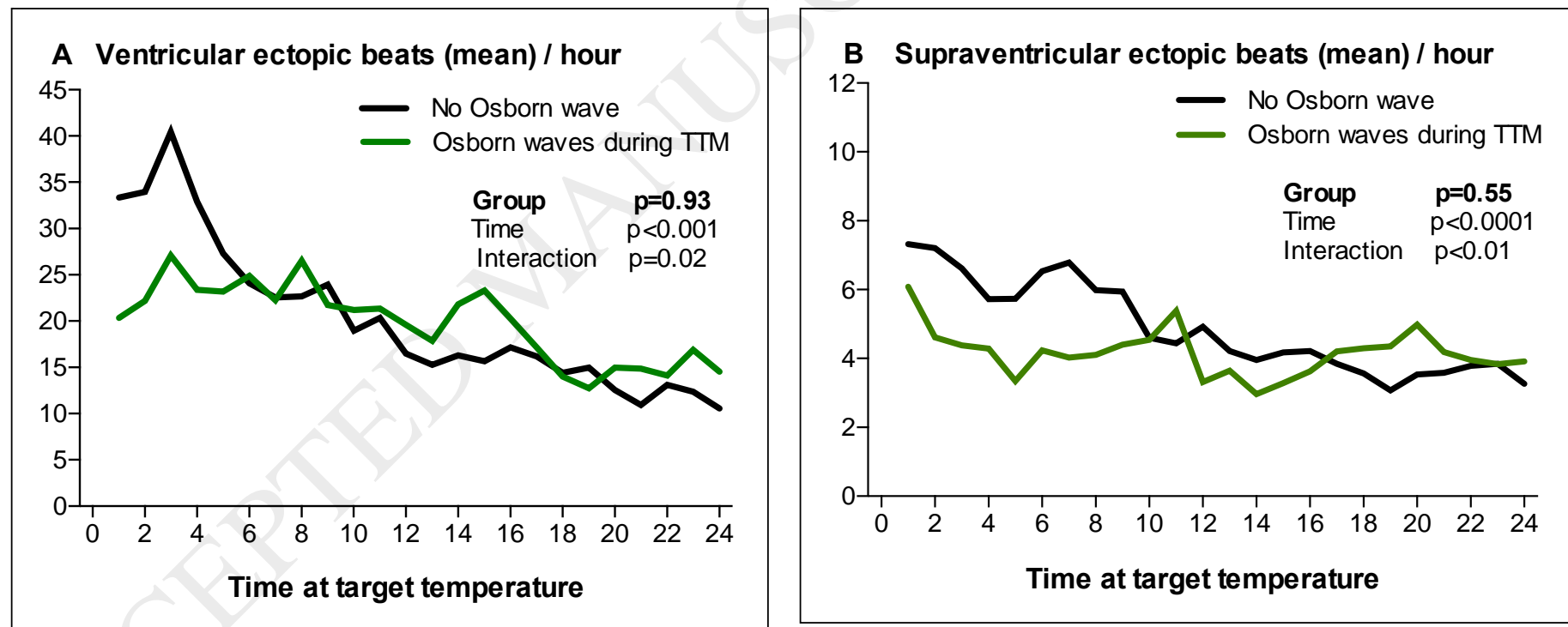


Figure 4 – Prevalence of ventricular and supraventricular ectopic beats during the TTM stratified by presence of Osborn waves in Holter-monitored subpopulation