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Author(s)	Okada, Nobunaga; Matsuyama, Tasuku; Morita, Sachiko et al.
Citation	Circulation journal. 2020, 84(3), p. 445-455
Version Type	VoR
URL	<a href="https://hdl.handle.net/11094/78716">https://hdl.handle.net/11094/78716</a>
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## Osborn Wave Is Related to Ventricular Fibrillation and Tachycardia in Hypothermic Patients

Nobunaga Okada, MD; Tasuku Matsuyama, MD, PhD; Sachiko Morita, MD;  
Naoki Ehara, MD; Nobuhiro Miyamae, MD; Yohei Okada, MD; Takaaki Jo, MD;  
Yasuyuki Sumida, MD; Makoto Watanabe, MD; Masahiro Nozawa, MD; Ayumu Tsuruoka, MD;  
Yoshihiro Fujimoto, MD; Yoshiki Okumura, MD; Kunio Hamanaka, MD;  
Tetsuhisa Kitamura, MD; Kei Nishiyama, MD, PhD; Bon Ohta, MD, PhD

**Background:** The Osborn wave (OW) is often observed in hypothermic patients; however, whether OW in hypothermic patients is related to the development of fatal ventricular arrhythmia, including ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT), remains undetermined. This study aimed to estimate the association between OW and the incidence of fatal ventricular arrhythmias.

**Methods and Results:** This retrospective study used the Japanese Accidental Hypothermia Network registry database and included 572 hypothermic patients. Patients were divided into the OW group (those with OW) and non-OW group (those without OW). The relationship between the development of fatal arrhythmias and presence of OW was assessed using the chi-squared test. All patients who developed VF/VT (n=10) had OW on electrocardiogram upon hospital arrival. The presence of OW had a sensitivity of 100%, specificity of 47.8%, positive predictive value of 4.0%, and negative predictive value of 100% for VF/VT development. The in-hospital mortality rate was 22.3% in the OW group and 21.2% in the non-OW group (P=0.781).

**Conclusions:** OW was observed in all hypothermic patients with VF/VT. The occurrence of ventricular arrhythmias is highly unlikely in the absence of OW on the electrocardiogram. Although the presence of OW might be used to predict these fatal arrhythmias in hypothermic patients, there was no association between the presence of OW and in-hospital mortality.

**Key Words:** Hypothermia; J wave; Osborn wave; Sudden cardiac death; Ventricular arrhythmia

Hypothermia, which occurs at a body temperature of 35°C, is a deleterious condition associated with a significant risk of mortality.<sup>1,2</sup> Hypothermia can cause cardiovascular instability, ventricular fibrillation (VF), and ventricular tachycardia (VT), leading to sudden cardiac death.<sup>3</sup> The incidence of VF/VT in hypothermic patients is unexpectedly low (0–2%),<sup>4,5</sup> but once arrhythmia has occurred, it is often fatal.<sup>2,6</sup> Hypothermic patients with ventricular arrhythmias who often do not survive with traditional rewarming (e.g., hemodialysis, ventral body cavity lavage) have become increasingly salvageable with extracorporeal life support (ECLS) using veno-arterial

extracorporeal membrane oxygenation (VA-ECMO) or cardiopulmonary bypass (CPB).<sup>1,2</sup> Currently, there is no accurate predictor of VF/VT development in hypothermic patients. If we can identify high-risk patients with fatal ventricular arrhythmias, we can effectively triage patients in need of critical care, including ECLS.

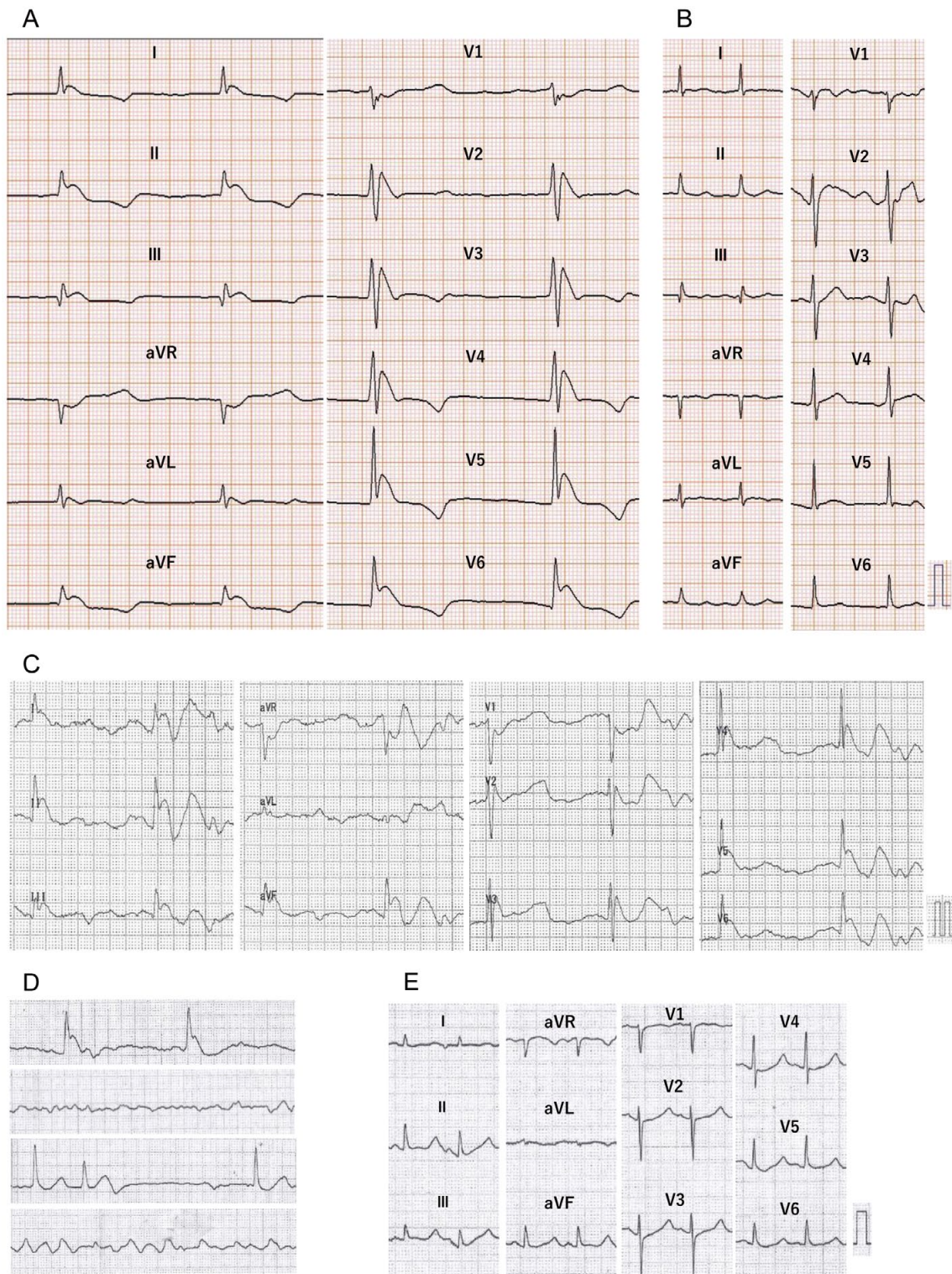
The Osborn wave (OW), also known as the J wave, on electrocardiograms (ECG) is frequently observed in hypothermic patients.<sup>7</sup> Recent studies reported that some J wave patterns such as early repolarization and Brugada syndrome are associated with an increased risk of fatal arrhythmias.<sup>8–10</sup> However, previous studies reported no correlation between

Received September 30, 2019; revised manuscript received November 25, 2019; accepted December 18, 2019; J-STAGE Advance Publication released online January 30, 2020 Time for primary review: 22 days

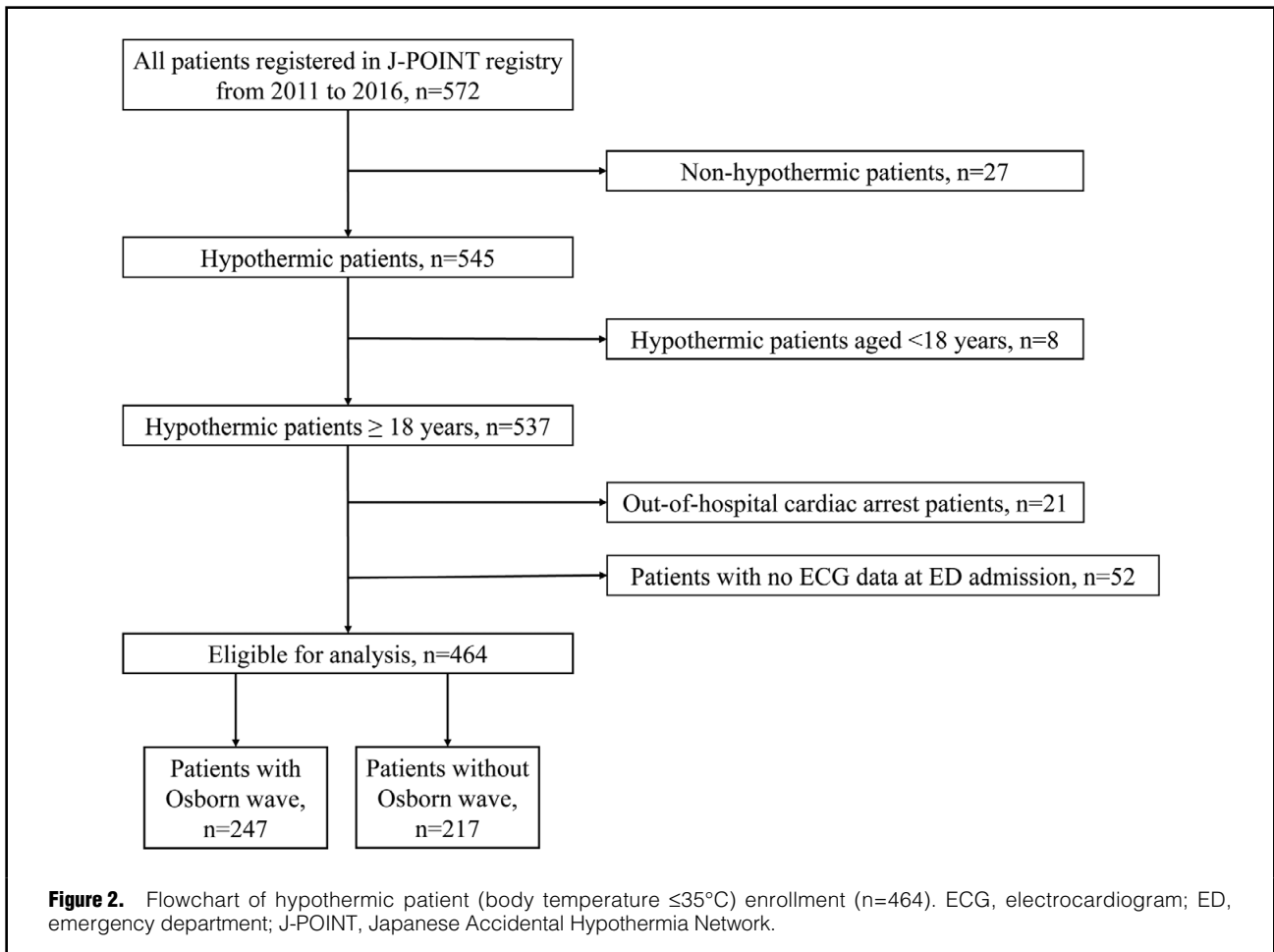
Department of Emergency Medicine, Kyoto Prefectural University of Medicine, Kyoto (N.O., T.M., M.W., B.O.); Senri Critical Care Medical Center, Saiseikai Senri Hospital, Suita (S.M.); Department of Emergency, Japanese Red Cross Society Kyoto Daiichi Red Cross Hospital, Kyoto (N.E., Y.F.); Department of Emergency Medicine, Rakuwa-kai Otowa Hospital, Kyoto (N.M.); Department of Primary Care and Emergency Medicine, Kyoto University, Kyoto (Y. Okada); Department of Emergency Medicine, Uji-Tokushukai Medical Center, Uji (T.J.); Department of Emergency Medicine, North Medical Center, Kyoto Prefectural University of Medicine, Kyoto (Y.S.); Department of Emergency and Critical Care Medicine, Saiseikai Shiga Hospital, Ritto (M.N.); Emergency and Critical Care Medical Center, Osaka City General Hospital, Osaka (A.T.); Department of Emergency Medicine, Fukuchiyama City Hospital, Fukuchiyama (Y. Okumura); Department of Emergency and Critical Care Medicine, National Hospital Organization Kyoto Medical Center, Kyoto (K.H., K.N.); and Division of Environmental Medicine and Population Sciences, Department of Social and Environmental Medicine, Osaka University Graduate School of Medicine, Suita (T.K.), Japan

Mailing address: Tasuku Matsuyama, MD, PhD, Department of Emergency Medicine, Kyoto Prefectural University of Medicine, Kamigyo-ku, Kyoto 602-8566, Japan. E-mail: task-m@koto.kpu-m.ac.jp

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**Figure 1.** Representative 12-lead electrocardiograms (ECG) from 2 hypothermic patients at the time of admission to the emergency department and after rewarming showing a typical Osborn wave (OW). Case 1. **(A)** OWs were present in nearly every lead on the ECG recorded at body temperature 21.8°C. **(B)** The OWs disappeared on the ECG after the patient was rewarmed until the body temperature reached 35.0°C. Case 2. **(C)** The ECG shows atrial fibrillation with bradycardia and OWs. The hypothermic patient's body temperature was 24.6°C at the emergency department arrival. **(D)** ECGs in the emergency department. From top to bottom: ECG recorded 4 min before ventricular fibrillation (VF) episode, ECG after the return of spontaneous circulation, and the second episode of VF. **(E)** ECG recorded from the patient supported with veno-arterial extracorporeal membrane oxygenation (body temperature=35.5°C).



OW and VF in hypothermic patients;<sup>11,12</sup> thus, the association between the presence of OW in hypothermic patients and the incidence of fatal arrhythmias including VF/VT remains unclear. The primary aim of this study was to estimate the association between OW and the incidence of fatal ventricular arrhythmias for identifying high-risk patients with these arrhythmias. The secondary aim was to assess the clinical significance of OW and its association with in-hospital mortality in hypothermic patients.

## Methods

A multicenter retrospective cohort study was conducted, and epidemiological and clinical data from the Japanese Accidental Hypothermia Network (J-POINT)<sup>13</sup> registry database were extracted. This registry and the study protocol were approved by the ethics committee of each institution, and written informed consent was waived given the retrospective study design. Guideline on the opt-out consent was posted on the bulletin board of the emergency department (ED) or the website of each participating institution. Patients were excluded from the registry if they or their family members had refused to be part of the registry.

### Data Source

The J-POINT registry database was based on a retrospective review of patients with body temperature  $\leq 35^{\circ}\text{C}$  visiting

the ED of 12 institutions. The J-POINT consists of eight critical care medical centers (CCMCs) and four non-CCMCs with an ED across Kyoto, Osaka, and Shiga prefectures in Japan. The ED of participating institutions had a median annual visit number of 19,651 (interquartile range [IQR]: 13,281–27,554).

The J-POINT registry included 572 patients who were retrospectively identified using the International Classification of Diseases, Tenth Revision (ICD-10) code for T68: Hypothermia, and who were diagnosed at each institution during the study period, from April 1, 2011, to March 31, 2016.

Epidemiological and clinical data were extracted from patients' medical records using a predefined data extraction sheet by emergency physicians who were trained in appropriate data extraction during face-to-face or web meetings.

### Participants

The inclusion criteria were hypothermia diagnosed in a participating ED, body temperature  $\leq 35^{\circ}\text{C}$  at ED admission, and age  $\geq 18$  years. Patients with out-of-hospital cardiac arrest, as well as those without ECG data, body temperature data, or outcome data (presence of VF/VT or in-hospital mortality), were excluded.

### Data Collection

Patient characteristics were defined as sex, age, past medical

<b>Table 1. Patients Characteristics, In-Hospital Data, and Outcomes According to the Presence or Absence of Osborn Waves</b>					
	<b>All patients (n=464)</b>	<b>Missing</b>	<b>Osborn wave (n=247)</b>	<b>Non-osborn wave (n=217)</b>	<b>P-values*</b>
<b>Men</b>	238 (51.3)	0 (0)	142 (57.5)	96 (44.2)	0.004 <sup>‡</sup>
<b>Age, years</b>	79 (68–87)	0 (0)	77 (66–86)	81 (71–88)	0.020 <sup>‡</sup>
<b>BMI</b>	19.6 (17.1–22.2)	117 (25.2)	19.8 (17.4–22.1)	19.4 (16.6–22.6)	0.900
<b>Medical history</b>		7 (1.5)			
Cardiovascular diseases	207 (44.6)		95 (38.5)	112 (51.6)	0.005 <sup>‡</sup>
Neurological diseases	88 (18.9)		43 (17.3)	45 (20.7)	0.362
Endocrine diseases	117 (25.1)		49 (19.8)	68 (31.3)	0.004 <sup>‡</sup>
Psychiatric diseases	79 (17.0)		42 (16.9)	37 (17.1)	0.989
Malignant diseases	45 (9.7)		27 (10.9)	18 (8.3)	0.338
Dementia	97 (20.9)		38 (15.3)	59 (27.2)	0.002 <sup>‡</sup>
Others	91 (19.6)		52 (21.0)	39 (18.0)	0.579
<b>Activities of daily living</b>		3 (0.6)			0.144
Independent	319 (69.2)		179 (73.1)	140 (64.8)	
Not independent	142 (30.8)		66 (26.9)	76 (35.2)	
<b>Associated condition</b>		0 (0)			
Cold exposure	364 (78.4)		206 (83.4)	158 (72.8)	0.018 <sup>‡</sup>
Internal diseases	203 (43.9)		107 (43.3)	96 (44.2)	0.842
Trauma	63 (13.5)		36 (14.6)	27 (12.4)	0.503
Alcohol intoxication	46 (9.9)		31 (12.5)	15 (6.91)	0.175
Drowning	21 (4.5)		6 (2.4)	15 (6.9)	0.020 <sup>‡</sup>
Self-harm	20 (4.3)		8 (3.2)	12 (5.5)	0.225
Others	185 (39.8)		95 (38.5)	90 (41.5)	0.508
<b>GCS</b>	11 (8–14)	70 (15.1)	11 (8–13)	13 (9–14)	<0.001 <sup>‡</sup>
<b>SBP (mmHg)</b>	119 (93–141)	30 (6.5)	111 (87–136)	122 (100–147)	<0.001 <sup>‡</sup>
<b>HR (beats/min)</b>	66 (52–82)	0 (0)	61 (49–78)	71 (56–90)	<0.001 <sup>‡</sup>
<b>Respiration rate (breaths/min)</b>	18 (14–21)	151 (32.5)	17 (14–21)	18 (13–22)	0.492
<b>BT (°C)</b>	30.8 (28.4–32.5)	0 (0)	29.4 (27.4–31.6)	32 (30.2–33.2)	<0.001 <sup>‡</sup>
<b>Laboratory data</b>					
pH	7.31 (7.25–7.37)	56 (12.1)	7.31 (7.22–7.36)	7.33 (7.26–7.38)	0.011 <sup>‡</sup>
PaO <sub>2</sub> (mmHg)	116 (79.6–174.5)	67 (14.4)	122.2 (84.9–191.5)	103.5 (72.9–148.5)	0.002 <sup>‡</sup>
HCO <sub>3</sub> (mEq/L)	21.2 (15.9–25.7)	59 (12.7)	20.7 (15.7–25.7)	21.5 (15.9–25.6)	0.478
Sodium (mEq/L)	140 (135–143)	6 (1.3)	140 (135–143)	139 (135–143)	0.909
Potassium (mEq/L)	4 (3.6–4.6)	6 (1.3)	4 (3.5–4.6)	4.1 (3.6–4.7)	0.183
Calcium (mg/dL)	8.9 (8.4–9.3)	52 (11.2)	8.8 (8.4–9.3)	8.9 (8.3–9.3)	0.887
Creatinine (mg/dL)	1 (0.6–1.8)	6 (1.3)	1 (0.6–1.8)	1 (0.6–1.8)	0.780
Albumin (mg/dL)	3.5 (2.9–4)	77 (16.6)	3.4 (2.9–3.9)	3.6 (3.0–4.1)	0.022 <sup>‡</sup>
Total bilirubin (mg/dL)	0.6 (0.4–1)	8 (1.7)	0.6 (0.4–1)	0.6 (0.4–1.6)	0.903
White blood cell (10 <sup>3</sup> /mm <sup>3</sup> )	8.3 (5.4–12.8)	5 (1.1)	8.6 (5.16–12.8)	8.1 (5.60–12.7)	0.950
Hematocrit (%)	35.9 (30.8–40.5)	5 (1.1)	35.6 (31.4–40.7)	36.2 (30.3–40.3)	0.760
Platelets (10 <sup>3</sup> /mm <sup>3</sup> )	178 (129–237)	5 (1.1)	176 (125–239)	189 (131–237)	0.463
<b>SOFA score<sup>†</sup></b>	4 (2–6)	98 (21.1)	5 (3–7)	4 (2–6)	<0.001 <sup>‡</sup>
<b>ECG characteristics</b>					
Rhythm		0 (0)			0.631
SR	310 (66.9)		162 (65.6)	148 (68.2)	
Af	98 (21.1)		51 (20.7)	47 (21.7)	
Other	41 (8.8)		24 (9.7)	17 (7.8)	
Unclassified	15 (3.2)		10 (4.1)	5 (2.3)	
RR interval (ms)	909 (732–1,154)		984 (769–1,224)	845 (667–1,081)	<0.001 <sup>‡</sup>
PR interval (ms)	169 (146–200)	167 (35.9)	167 (145–200)	172 (146–200)	0.967
QRS interval (ms)	108 (97–128)	1 (0.2)	112 (100–137)	104 (92–119)	<0.001 <sup>‡</sup>
QT interval (ms)	459 (404–520)	7 (1.5)	480 (424–537)	440 (398–501)	<0.001 <sup>‡</sup>
QTc interval (ms)	473 (440–510)	8 (1.7)	482 (444–517)	468 (437–497)	0.013 <sup>‡</sup>
QT prolongation	222 (48.7)	8 (1.7)	133 (55.0)	89 (41.6)	0.004 <sup>‡</sup>

(Table 1 continued the next page.)

	All patients (n=464)	Missing	Osborn wave (n=247)	Non-osborn wave (n=217)	P-values*
<b>Active internal rewarming</b>	68 (14.7)	0 (0)	49 (19.8)	19 (8.8)	<0.001 <sup>†</sup>
Lavage	35 (7.5)		27 (10.9)	8 (3.7)	0.003 <sup>†</sup>
Intravascular	3 (0.7)		2 (0.8)	1 (0.5)	0.640
Hemodialysis	23 (5.0)		14 (5.7)	9 (4.2)	0.452
VV-ECMO rewarming	2 (0.4)		2 (0.8)	0 (0)	0.003 <sup>†</sup>
VA-ECMO rewarming	9 (1.9)		6 (2.4)	3 (1.4)	0.283
<b>Patient in critical care medical center</b>		0 (0)	202 (81.8)	156 (71.9)	0.011 <sup>†</sup>
<b>Outcomes</b>		0 (0)			
VF or pulseless VT	10 (2.2)		10 (4.0)	0 (0)	0.003 <sup>†</sup>
Death	101 (21.8)		55 (22.3)	46 (21.2)	0.781
<b>Cause of death</b>		33 (7.1)			0.351
Sepsis	13 (2.8)		7 (2.8)	6 (2.8)	
Stroke	6 (1.3)		3 (1.2)	3 (1.4)	
Heart disease	4 (0.9)		1 (0.4)	3 (1.4)	
Respiratory disease	22 (4.7)		11 (4.5)	11 (5.1)	
Unintentional injuries	4 (0.9)		4 (1.6)	0 (0)	
Malignant diseases	2 (0.4)		0 (0)	2 (0.9)	
Others	17 (21.8)		8 (3.2)	9 (4.2)	

Values are presented as n (%) or median (interquartile range: quartile 1–quartile 3). Percentages (%) were calculated excluding missing values from denominator. Af, atrial fibrillation; BMI, body mass index; BT, body temperature; ECG, electrocardiogram; GCS, Glasgow Coma Scale; HCO<sub>3</sub>, bicarbonate; HR, heart rate; PaO<sub>2</sub>, partial pressure of arterial oxygen; SBP, systolic blood pressure; SOFA, sequential organ failure assessment; SR, sinus rhythm; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; VF, ventricular fibrillation; VT, ventricular tachycardia; VV-ECMO, veno-venous extracorporeal membrane oxygenation. <sup>†</sup>Calculated with patients who were admitted to intensive care units. \*Comparisons between the 2 groups were evaluated with the Mann-Whitney U-test for continuous variables and chi-squared test or Fisher's exact test for categorical variables. <sup>†</sup>P<0.05 is considered statistically significant.

histories (cardiovascular diseases [ischemic heart disease, heart failure, arrhythmia, hypertension, and others], neurological diseases [stroke, epilepsy, Parkinson's disease or syndrome, and others], endocrine diseases [diabetes mellitus, thyroid disease, adrenal insufficiency, and others], psychiatric diseases [depression, schizophrenia, and others], malignant diseases, dementia, and other diseases), activities of daily living (ADL) before the hypothermia event (independent, not independent), and conditions associated with hypothermia. Conditions associated with hypothermia were classified into internal diseases (stroke, seizure, Parkinson's disease, thyroid disease, hypoglycemia, infectious disease, acute pancreatitis, uremia, malignant disease, bowel ischemia, rhabdomyolysis, and others), traumatic injury (fall, motor vehicle accident, and others), alcohol intoxication, drowning (indoor, outdoor), self-harm (drug, external), and others (iatrogenic, mountain incident, burn, malnutrition/infirmity, and others). The ICD-9 or ICD-10 coding protocol was used to indicate the acute medical illness in each patient in the final medical summary or medical records.

Patients' in-hospital data characteristics were defined as vital signs at hospital arrival (Glasgow Coma Scales [GCS], systolic blood pressure, heart rate, respiratory rate, and body temperature) and biological data from blood samples that were drawn at hospital arrival (pH, partial pressure of arterial oxygen; sodium, potassium, calcium, creatinine, and albumin levels; and complete blood count), alongside sequential organ failure assessment (SOFA) score.

We used the first ECG on record for each patient admitted to the ED for our analysis. All ECGs were read and interpreted by 2 emergency medicine specialists blinded to the body temperature of the patient at the time of ECG recording. All ECG readings were also reviewed by an

experienced cardiologist. Analyzed ECG parameters were cardiac rhythm (sinus rhythm, atrial fibrillation, others including junctional rhythm, paced rhythm and atrioventricular block, unclassified rhythm), R-R interval, PR interval, QRS interval, QT interval, QTc interval, and QT prolongation (QTc  $\geq$ 470ms in men and  $\geq$ 480ms in women).<sup>14</sup> In our study, OW was defined as a height elevation  $\geq$ 1 mm above the isoelectric line (i.e., amplitude  $\geq$ 0.1 mV) in the terminal part of the QRS complex (Figure 1).<sup>7</sup>

In patients with OW, we evaluated the following characteristics for this wave: amplitude above the isoelectric line, location (classified into high lateral [I, aVL], inferior [II, III, aVF], septal [V1, V2], anterior [V3, V4], and lateral [V5, V6]), lead with the highest amplitude, and number of leads showing OW. Active internal rewarming methods included ventral body cavity lavage (i.e., stomach, chest, bladder), intravascular rewarming technique, hemodialysis, veno-venous ECMO, and VA-ECMO.<sup>1</sup>

### Outcome

The primary outcome was defined as the development of fatal arrhythmias such as VF/VT in hypothermic patients during rewarming. The secondary outcome was in-hospital death in hypothermic patients. We also assessed the causes most associated with death.

### Statistical Analysis

The hypothermic patients were allocated into 2 groups based on their respective ECG findings: 247 patients with OW (OW group) and 217 patients without OW (non-OW group). Patient characteristics, in-hospital information, and outcomes for the 2 groups were compared using the Mann-Whitney U-test for continuous variables and the chi-squared

Table 2. Information on Patients With VF or Pulseless VT					
Case	1	2	3	4	5
Fatal arrhythmia	VF (electrical storm)	VF (electrical storm)	VF	VF	VF
Sex and age (years)	F, 48	F, 86	M, 70	F, 89	M, 68
Independent life*	+	–	+	+	+
BT (°C)	24.6	24	29.2	24.3	31.4
pH	6.745	7.188	7.32	7.032	7.163
Potassium (mEq/L)	5.4	4.6	4.3	4.9	4.2
HR (beats/min)	40	28	63	29	89
SBP (mmHg)	40	Unmeasurable	Unmeasurable (radial pulse present)	111	Unmeasurable
Rhythm	Unknown	SR	SR	Other	SR
QT prolongation†	+	+	–	+	–
Amplitude of the Osborn wave (mV)	0.7	1.5	0.5	1.4	0.3
Number of the Osborn wave leads	9	11	8	8	3
Admission ward	ICU	ICU	ICU	ICU	ICU
Treatment of hypothermia	Intubation, warm IV fluids, blanket, gastric lavage, VA-ECMO	Intubation, heating pads, bladder lavage, VA-ECMO	Intubation, warm IV fluids, heating pads, warm bath	Warm IV fluids, heating pads, bladder lavage, VA-ECMO	Warm IV fluids, blanket, warm bath
CAG	Intact	No CAG	No CAG	No CAG	No CAG
Conditions associated with hypothermia	Cold exposure, alcohol intoxication	Unknown	Cold exposure, stroke, trauma, sepsis	Cold exposure, sepsis, uremia	Cold exposure
ROSC after VF/VT‡	+	–	+	+	+
Cause of death	Hypoxic ischemic encephalopathy caused by VF, alcohol dependence	VF	Traumatic brain injury		
Outcome	Dead	Dead	Dead	Alive	Alive

CAG, coronary angiography; F, female; ICU, intensive care unit; IV, intravenous; M, male; PCI, percutaneous coronary intervention; ROSC, return of spontaneous circulation. Other abbreviations as in Table 1. \*Patients' activities of daily living before the Hypothermic events (Plus sign indicates independent, minus sign indicates needing some assistance.). †Detection of QT prolongation on the first electrocardiogram recorded in the emergency department. ‡Plus sign indicates the presence of ROSC of the patient who experienced VF/VT events. Cases 3–10 had only one episode of fatal arrhythmia.

(Table 2 continued the next page.)

test or Fisher's exact tests for categorical variables.

We calculated odds ratios by using multivariate logistic regression analysis to determine whether the presence of OW was independently associated with in-hospital mortality. We selected the following potential confounding variables that were considered to be associated with in-hospital mortality: sex (men, women), age categories (18–64 years, 65–74 years, ≥75 years), ADL (independent, not independent, unknown), number of comorbidities identified in the medical history (none, one, multiple, unknown), systolic blood pressure (unmeasurable, 40–90 mmHg, <90 mmHg), body temperature (32–35°C, 28–31°C, <28°C), presence of acute medical illness (yes, no), active internal rewarming (yes, no), and hospital type (CCMC, non-CCMC). We treated the missing data for each variable as an “unknown category.” Potential confounding variables were selected and classified with reference to the models defined in a previous paper.<sup>13</sup> We then assigned the patients with OW to the VF/VT group (10 patients who developed VF/VT during rewarming) and non-VF/VT group (237 patients who did not develop VF/VT during rewarming) and assessed the characteristics of OW associated with the occurrence of VF/VT.

All tests were 2-tailed, and a P-value <0.05 was consid-

ered statistically significant. All statistical analyses were performed using the JMP 14.0 software (SAS Institute Inc., Cary, NC, USA).

## Results

A total of 572 patients were registered in the J-POINT registry during the study period. After excluding 27 non-hypothermic patients, 8 patients aged <18 years, 21 patients who experience out-of-hospital cardiac arrest, and 52 patients with no ECG data at ED admission, 464 patients (81.1%) were eligible for this study (Figure 2).

### Patients' Characteristics and In-Hospital Data

Patients' characteristics and in-hospital data are shown in Table 1. OW was observed in 53.2% (247/464) of all patients. Compared with the non-OW group, patients in the OW group were more often men (57.5%, P=0.004). The median age of the patients in the OW group and those in the non-OW group were 77 and 81 years, respectively. Compared with the non-OW group, patients in the OW group had a lower prevalence in presenting with 3 past medical histories (cardiovascular diseases, endocrine diseases, and dementia). Approximately 70% of patients

Case	6	7	8	9	10
Fatal arrhythmia	VF	Pulseless VT	VF (electrical storm)	VF	VF
Sex and age (years)	F, 89	F, 73	M, 55	M, 86	M, 94
Independent life	+	+	+	+	-
BT (°C)	24	28	26	32.7	29.4
pH	7.261	7.356	7.27	6.76	7.348
Potassium (mEq/L)	4.3	3.9	4.4	4.7	4.7
HR (beats/min)	55	68	53	55	63
SBP (mmHg)	170	104	75	91	119
Rhythm	SR	Af	SR	SR	SR
QT prolongation	+	+	+	+	+
Amplitude of the Osborn wave (mV)	0.1	0.2	0.7	0.2	0.1
Number of the Osborn wave leads	4	5	9	2	3
Admission ward	ICU	ICU	ICU	ICU	General ward
Treatment of hypothermia	Warm IV fluids, VA-ECMO	Warm IV fluids, blanket	Intubation, warm IV fluids, blanket	Intubation, warm IV fluids, VA-ECMO	Warm IV fluids, blanket
CAG	No CAG	No CAG	No CAG	No significant lesion (Previous PCI)	No CAG
Conditions associated with hypothermia	Cold exposure, spinal cord injury	Cold exposure, trauma, sepsis	Cold exposure, pancreatitis, alcohol intoxication	Cold exposure, alcohol intoxication	Cold exposure, stroke, sepsis, hypoglycemia
ROSC after VF/VT	+	+	+	+	+
Cause of death	Respiratory impairment following traumatic spinal cord injury			Cirrhosis, Alcohol intoxication (alcoholic ketoacidosis)	Cerebral infarction, pneumonia
Outcome	Dead	Alive	Alive	Dead	Dead

**Table 3. Secondary Outcome: Association With In-Hospital Death and Presence of Osborn Waves**

	Total	Death (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Non-Osborn wave	217	46 (21.2)	Ref.	Ref.*
Osborn wave	247	55 (22.3)	1.06 (0.68–1.66)	1.04 (0.60–1.78)

CI, confidence interval; OR, odds ratio. \*Adjusted for Osborn wave, sex, age, activity daily living, the number of comorbidities, systolic blood pressure, body temperature, presence of acute medical illness, active internal rewarming, and hospital type.

reported independence in performing ADL.

The proportion of cold exposure was higher in the OW group. Patients in the OW group were more likely to present with unstable vital signs such as low GCS, low blood pressure, and low heart rate (all  $P < 0.001$ ). The median body temperature was 29.4°C (IQR, 27.4–31.6°C) in the OW group and 32°C (IQR, 30.2–33.2°C) in the non-OW group, and the difference was significant ( $P < 0.001$ ). With regard to laboratory data, pH, PaO<sub>2</sub>, and albumin levels differed significantly between the 2 groups ( $P = 0.011$ , 0.002, and 0.022, respectively). No difference in other laboratory data was found between the 2 groups. The median SOFA score was 5 (IQR, 3–7) in the OW group and 4 (IQR, 2–8) in the non-OW group, and the difference was significant ( $P < 0.001$ ).

The ECG characteristics in the OW group had longer RR, QRS, QT, and QTc intervals than those in the non-OW group. The number of patients with QT prolongation was

higher in the OW group (133/242, 55.0%) than in the non-OW group (89/214, 41.6%) ( $P = 0.004$ ).

### Outcomes

The VF/VT events occurred in 10 individuals (4%) within the OW group and none within the non-OW group. Among the 10 patients with VF/VT, only 1 patient had pulseless VT, and 9 patients had VF. Of these 9 patients with VF, 2 patients developed VF during a central venous line placement, 2 patients before the start of ECMO, and 2 patients during ECMO (Table 2). To exclude the VF/VT due to acute ischemic heart disease, 2 patients with VF/VT events had undergone immediate coronary angiography (CAG). The other 8 patients, who did not undergo CAG, were evaluated by an experienced cardiologist using ECG, cardiac biomarkers, and cardiac ultrasonography. No obvious signs of ischemia were observed in any of the above tests. Spontaneous circulation returned in 9/10



patients after cardiac arrest caused by VF/VT and 1 patient died. The surviving patients had no further episodes of VF/VT after rewarming and did not require an implantable cardioverter-defibrillator. The presence of OW had a sensitivity of 100% (95% confidence interval (CI), 58.7–100%), specificity of 47.8% (95% CI, 43.1–52.5%), positive predictive value of 4.0% (95% CI, 2.0–7.3%), and negative predictive value of 100% (95% CI, 97.5–100%) for VF/VT development.

The overall rate of in-hospital deaths was 21.8% (101/464), with no significant difference between the OW group and non-OW group (22.3% [55/247] vs. 21.2% [46/217], respectively,  $P=0.781$ ) (Table 1). After adjustment for sex, age category, ADL, number of comorbidities, systolic blood pressure category, body temperature category, presence of acute medical illness, active internal rewarming, and hospital type, the OW group was not associated with a high risk of death compared to the non-OW wave group; the adjusted odds ratio for in-hospital death was 1.04 (95% CI 0.60–1.78) (Table 3).

We were able to access information on the cause of death in 68/101 patients who died in-hospital. The causes

of death were classified into sepsis, stroke (ischemic and hemorrhagic strokes), heart disease (ischemic heart disease, arrhythmias, and heart failure), respiratory disease (bacterial pneumonia, interstitial pneumonia, and alveolar hemorrhage), unintentional injuries (spinal cord injury and fracture), any malignancy, and others (multiple organ failure, renal disease, cirrhosis, mesenteric ischemia, gastrointestinal bleeding, frailty due to old age, and other). These causes were listed in Table 1. Almost half died of infections such as bacterial pneumonia (17/22 patients with respiratory disease) and sepsis (13 patients).

#### Factors Associated With VF/VT in Hypothermic Patients With OW

In the OW group, factors associated with the development of VF/VT are shown in Table 4. Compared to the non-VF/VT group, the VF/VT group had lower pH and higher potassium levels, and longer QTc interval ( $P=0.029$ ). Although the association with OW characteristics and VF/VT was evaluated, no difference was found between the groups in the amplitude of OW, location of OW, lead of the highest amplitude, and number of OW leads ( $P$  for all

Table 4. Factors Associated With VF/VT Among Hypothermic Patients With Osborn Wave					
	Total (n=247)	Missing	VF/VT (n=10)	Non-VF/VT (n=237)	P-values*
<b>Men</b>	142 (57.5)	0 (0)	5 (50.0)	137 (57.8)	0.625
<b>Age, years</b>	77 (66–86)	0 (0)	79 (65–89)	77 (66–86)	0.988
<b>BMI</b>	19.8 (17.4–22.1)	60 (24.3)	20.4 (17.1–22.3)	19.8 (17.4–22.1)	0.779
<b>Past medical history</b>		0 (0)			
Cardiovascular diseases	95 (38.5)		3 (27.3)	92 (39.0)	0.575
Alcohol use disorder	27 (10.9)		2 (20.0)	25 (10.6)	0.348
<b>Associated condition</b>		0 (0)			
Alcohol intoxication	31 (12.6)		3 (30)	28 (11.8)	0.089
<b>Admission ward</b>		0 (0)			<0.001†
Death in the emergency room	1 (0.4)		1 (10.0)		
No admission	8 (3.2)		0 (0)	8 (3.4)	
General ward	103 (41.7)		2 (20.0)	101 (42.8)	
Intensive care unit	135 (54.7)		8 (80.0)	127 (53.8)	
<b>GCS</b>	11 (8–13)	37 (15.0)	8 (7–11)	11 (8–13)	0.141
<b>SBP (mmHg)</b>	111 (87–136)	22 (8.9)	104 (75–119)	111 (87–136)	0.397
<b>BT (°C)</b>	29.4 (27.4–31.6)	0 (0)	27 (24.2–29.9)	29.5 (27.4–31.7)	0.057
<b>Laboratory data</b>					
pH	7.31 (7.22–7.36)	27 (10.9)	7.22 (6.96–7.33)	7.31 (7.23–7.36)	0.043‡
PaO <sub>2</sub> (mmHg)	122.2 (84.9–191.5)	30 (12.1)	143 (106.1–259.4)	121 (84–190.3)	0.235
Potassium (mEq/L)	4 (3.5–4.6)	2 (0.8)	4.5 (4.3–4.8)	4 (3.5–4.6)	0.021‡
<b>ECG characteristics</b>		0 (0)			
HR (beats/min)	61 (49–78)		55 (37–64)	61 (50–79)	0.178
Rhythm					0.679
SR	162 (65.6)		7 (70.0)	155 (65.4)	
Af	51 (20.7)		1 (10.0)	50 (21.1)	
Other	24 (9.7)		1 (10.0)	23 (9.7)	
Unclassified	10 (4.1)		1 (10.0)	9 (3.8)	
PR interval (ms)	167 (145–200)	97 (39.3)	195 (164–275)	166 (144–200)	0.155
RR interval (ms)	984 (769–1,224)	0 (0)	1,091 (935–1,642)	984 (764–1,212)	0.178
QRS interval (ms)	112 (100–137)	1 (0.4)	110 (95–138)	114 (100–137)	0.580
QT interval (ms)	480 (424–537)	4 (1.5)	540 (448–730)	479 (424–535)	0.029‡
QTc interval (ms)	482 (444–517)	5 (1.6)	521 (474–575)	480 (443–516)	0.030‡
QT prolongation	133 (55.0)	5 (1.6)	8 (80.0)	125 (53.9)	0.104

(Table 4 continued the next page.)

	Total (n=247)	Missing	VF/VT (n=10)	Non-VF/VT (n=237)	P-values*
<b>Amplitude of the Osborn wave (mV)</b>	0.2 (0.2–0.4)	0 (0)	0.4 (0.2–0.9)	0.2 (0.2–0.4)	0.213
<b>Location of the Osborn wave</b>		0 (0)			
I	85 (34.4)		5 (50.0)	80 (33.8)	0.290
II	194 (78.5)		7 (70.0)	187 (78.9)	0.502
III	166 (67.2)		7 (70.0)	159 (67.1)	0.848
aVR	2 (0.8)		0 (0)	2 (0.8)	0.771
aVL	45 (18.2)		3 (30.0)	42 (17.7)	0.355
aVF	164 (66.4)		4 (40.0)	160 (67.5)	0.082
V1	35 (14.2)		2 (20.0)	33 (13.9)	0.589
V2	67 (27.1)		6 (60.0)	61 (25.7)	0.017 <sup>†</sup>
V3	110 (44.5)		6 (60.0)	104 (43.9)	0.315
V4	163 (66.0)		7 (70.0)	156 (65.8)	0.785
V5	199 (80.6)		7 (70.0)	192 (81.0)	0.389
V6	203 (82.2)		8 (80.0)	195 (82.3)	0.854
High lateral	40 (16.2)		2 (20.0)	38 (16.0)	0.739
Inferior	148 (59.9)		4 (40.0)	144 (60.8)	0.190
Septal	34 (13.8)		2 (20.0)	32 (13.5)	0.559
Anterior	103 (41.7)		6 (60.0)	97 (40.9)	0.231
Lateral	193 (78.1)		7 (70.0)	186 (78.5)	0.525
<b>Lead of the highest amplitude</b>		0 (0)			0.121
I	3 (1.2)		0 (0)	3 (1.3)	
II	36 (14.6)		2 (20.0)	34 (14.4)	
III	33 (13.4)		0 (0)	33 (13.9)	
aVR	0 (0)		0 (0)	0 (0)	
aVL	5 (2.0)		1 (10.0)	4 (1.7)	
aVF	5 (2.0)		0 (0)	5 (2.1)	
V1	4 (1.6)		0 (0)	4 (1.7)	
V2	16 (6.5)		0 (0)	16 (6.8)	
V3	30 (12.2)		2 (20.0)	28 (11.8)	
V4	45 (18.2)		5 (50.0)	40 (16.9)	
V5	39 (15.8)		0 (0)	39 (16.5)	
V6	31 (12.6)		0 (0)	31 (13.1)	
<b>Number of the Osborn wave leads</b>	6 (4–7)	0 (0)	7 (3–9)	6 (4–7)	0.722

Values are presented as n (%) or median (interquartile range: quartile 1–quartile 3). Percentages (%) were calculated excluding missing values from denominator. Abbreviations as in Table 1. \*Comparisons between the 2 groups were evaluated with the Mann-Whitney U-test for continuous variables and chi-squared test or Fisher's exact test for categorical variables. <sup>†</sup>P<0.05 is considered statistically significant.

the abovementioned variables was >0.05).

Among patients in the OW group, 6 patients were provided VA-ECMO rewarming, including 4 of 10 (40%) patients in the VF/VT group and 2 of 236 (0.8%) patients in the non-VF/VT group, and the difference was significant (P<0.001). With regard to mortality, the VF/VT group (6/10, 60%) had a significantly higher mortality rate than the non-VF/VT group (49/236, 20.7%) (P=0.003).

## Discussion

The results of this multicenter study of hypothermic patients demonstrated that the risk for experiencing VF or pulseless VT during rewarming was higher in patients with OW than in patients without OW. In this study, all patients who developed VF/VT had OW on ECG at ED arrival; thus, the absence of OW on ECG may allow the exclusion of VF/VT events (sensitivity of 100%).

Some reports<sup>9,10,15,16</sup> indicate that hypothermic patients with OW have experienced VF, pulseless VT, or cardiac arrest. However, to the best of our knowledge, no major

studies affirm the significant relationship between the presence of OW on ECG and VF/VT development in hypothermic patients. Our findings provide important clues into predicting the risk of developing fatal arrhythmias in patients with hypothermia.

Although the cause of death in patients with hypothermia may reportedly be a combination of many factors,<sup>13,17</sup> death in these patients was related to the severity of any underlying disease, rather than the severity of hypothermia or the fatal arrhythmia associated with it. Even in our study, the main causes of in-hospital deaths were related to the underlying disease, including infection. However, once the severely hypothermic patient had led to ventricular arrhythmia, the defibrillation from ventricular arrhythmia is usually difficult until the core body temperature has exceeded 30°C. Therefore, it is necessary to avoid sudden death due to rare and unpredictable arrhythmia or circulatory failure before starting the treatment of the underlying disease.

In a hypothermic patient with severe circulatory instability, active internal and invasive rewarming with ECLS

should be performed to immediately restore circulation.<sup>1</sup> However, given the increased risk of complications with rewarming using ECMO or CPB, including infection, hemorrhage, or thrombosis, as well as the absence of enough evidence that these methods improve the outcome, the initiation of rewarming in hypothermic patients who are not at a high risk of unstable circulation or cardiac arrest may be unwarranted.<sup>17,18</sup>

Based on recent recommendations in some guidelines or reviews, in both pre- and in-hospital settings, patients identified as having cardiac instability (e.g., systolic blood pressure of <90 mmHg, ventricular arrhythmias, or cardiac arrest) and those with a core temperature below 28°C should be considered for transfer to a hospital offering the possibility of ECLS rewarming with ECMO or CPB.<sup>1,2</sup>

Given the diverse causes of VF/VT, it is difficult to accurately predict the development of these arrhythmias. Electrolyte abnormalities, acidosis, and hypoxia, among others<sup>19</sup> are reported as classic risk factors of VF/VT. In our study, the patients in the VF/VT group had more severe acidosis and higher potassium levels than those in the non-VF/VT group. Surprisingly, in this study, 40% of the patients who developed VF/VT had stable circulation at ED arrival and body temperature of  $\geq 28^\circ\text{C}$  (**Table 2**); thus, it is necessary to consider the risk of VF/VT even in patients with stable vital signs at ED arrival.

Recently, increased attention has been given to the “J-wave syndrome” including early repolarization and Brugada syndrome. The J-point elevation observed on ECG was reported to be associated with a higher risk of VF.<sup>7</sup> OW (J wave) is a deflection at the junction point of the QRS wave with the ST segment on ECG, and it is considered the result of increased outward flow of potassium called “Ito K” in the ventricular epicardium, but not the endocardium.<sup>7</sup> This mechanism creates a transmural voltage gradient resulting in the development of phase 2 reentry, and a short QTc interval, which may cause ventricular arrhythmias including VF and VT. In patients with early repolarization, the amplitude of OW  $\geq 0.2\text{mV}$ , presence of OW in inferior leads, short QTc interval, presence of Brugada syndrome pattern on ECG, and a positive family history of sudden death have been identified as risk factors associated with idiopathic VF.<sup>7</sup> In this study, hypothermic patients with OW, especially patients in the VF/VT group, had long QTc intervals on ECG. The amplitude of the OW tended to be higher in patients in the VF/VT group than those in the non-VF/VT group, although no statistically significant difference was found. Moreover, we did not observe any difference in the location of OW on ECG between the groups. This result is different from the characteristics (i.e., a relatively short QTc interval, high amplitude of OW, and OW in inferior leads) of the more fatal J wave syndrome (or early repolarization syndrome) mentioned above. Thus, as Higuchi et al<sup>20</sup> has also shown, we would consider that OW in hypothermic patients may have partially different electrophysiological and arrhythmogenic characteristics from those in early repolarization and Brugada syndromes.

Patients in the OW group presented with longer RR, QRS, and QT (QTc) intervals, more severe acidosis, lower blood pressure, and lower body temperature than those in the non-OW group. Furthermore, in the OW group, patients in the VF/VT group experienced lower body temperature, more severe acidosis, and more prolonged QT (QTc) interval than those in the non-VF/VT group.

Thus, the development of fatal arrhythmias may be associated with prominent hypothermia, intense myocardial damage (as reflected in ECG findings), and acidosis. QT prolongation was observed in 80% of patients (8/10) with VF/VT (**Table 2**). As the number of VF/VT events were not adequate to allow the use of multivariate logistic regression analysis, we could not determine whether OW or prolonged QT (QTc) interval is independently related to VF/VT.

Moreover, the presence of OW is reportedly associated with mortality in hypothermic patients.<sup>21</sup> We could not determine any significant relationship between the presence of OW and in-hospital mortality, despite adjusting for potential confounders in this study.

Hypothermic patients with OW had higher scores on GCS, hemodynamic instability (i.e., bradycardia and hypotension), and higher SOFA scores than patients without OW. Hence, OW might be regarded as a sign or indicator of organ failure due to hypothermia.

### Study Limitations

Despite the importance of our findings, this study had several limitations. First, this study has the inherent limitations of possible bias due to residual confounding factors and missing data due to its retrospective design. However, most variables used for adjustment, other than “systolic blood pressure,” had <5% missing data, which did not affect our results significantly. Second, the exact incidence rates of fatal arrhythmic events and OW are still uncertain, because hypothermic patients who suffered from out-of-hospital cardiac arrest were excluded from this study. Third, as ECG is evaluated only when the patient has hypothermia, it is unclear whether OW disappeared after rewarming. Thus, there is a possibility that J wave humps, which are a common incidental finding in normal individuals, were regarded as OW related to hypothermia. Fourth, our sample size may not have been adequate to allow the detection of significant differences in the rates of VF/VT events because of their low frequency. Future studies including a heterogeneous population and larger cohorts are needed to detect any significant differences. Fifth, our study was conducted using data from Japan, a country in East Asia. Further studies including different multiple medical centers in different countries will provide more generalized information and external validity. Sixth, although the relationship between the presence of OW and in-hospital mortality could not be estimated in this study, the participating institutions were hospitals that provided intensive care, including ECLS, for severe conditions caused by circulatory failure. Thus, the mortality rate of patients with OW at a facility with limited treatment facilities is undetermined. Expanding the study to other medical facilities with limited options to provide intensive care will give more precise information. Finally, this study was based on data from a hospital-based registry and a comprehensive analysis on the epidemiology of hypothermia was not performed. Such an approach might have resulted in selection bias (e.g., we selected study subjects based on ICD-10 code and may have missed patients with body temperature  $\leq 35^\circ\text{C}$ ).

### Conclusions

In summary, among patients without OW, none developed VF/VT during rewarming. The absence of OW on ECG dramatically reduces the risk of experiencing fatal

arrhythmias in patients with hypothermia.

However, we could not draw the conclusion whether occurrence of OW is independently related to VF/VT development because the number of VF/VT events was not adequate in this study. Further studies will be warranted to predict patients with hypothermia who are more at risk of suffering from fatal arrhythmias.

#### Acknowledgment

The authors thank the members of the J-POINT registry group for their contributions.

#### Disclosures

The authors have nothing to declare.

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