BMJ Open

Intensive care with extracorporeal membrane oxygenation rewarming in accident severe hypothermia (ICE-CRASH) study: a protocol for a multicentre prospective, observational study in Japan

Shuhei Takauji [ID],[1] Mineji Hayakawa [ID] [2]

[1]Department of Emergency Medicine, Asahikawa Medical University Hospital, Asahikawa, Japan
[2]Department of Emergency Medicine, Hokkaido University Hospital, Sapporo, Japan

Correspondence to
Dr Shuhei Takauji;
s-takauji@asahikawa-med.ac.jp

ABSTRACT

Introduction Accidental hypothermia (AH) is a rare but critical disease, leading to death in severe cases. In recent decades, extracorporeal membrane oxygenation (ECMO) has been successfully used to rewarm hypothermic patients with cardiac arrest or circulation instability. However, data on the efficacy of rewarming using ECMO for patients with AH are limited. Therefore, a large-scale, multicentre, prospective study is warranted. The primary objective of this study will be to clarify the effectiveness of rewarming using ECMO for patients with AH. Our secondary objectives will be to compare the incidence of adverse effects between ECMO rewarming and non-ECMO rewarming and to identify the most appropriate management of ECMO for AH.

Methods and analyses The Intensive Care with ExtraCorporeal membrane oxygenation Rewarming in Accidentally Severe Hypothermia study is taking place in 35 tertiary emergency medical facilities in Japan. The inclusion criteria are patients ≥18 years old with a body temperature ≤32°C. We will include patients with AH who present to the emergency department from December 2019 to March 2022. The research personnel at each hospital will collect several variables, including patient demographics, rewarming method, ECMO data and complications. Our primary outcome is to compare the 28-day survival rate between the ECMO and non-ECMO (other treatments) groups among patients with severe AH. Our secondary outcomes are to compare the following values between the ECMO and non-ECMO groups: length of stay in the intensive-care unit and complications. Furthermore, in patients with cardiac arrest, the Cerebral Performance Category score at discharge will be compared between both groups.

Ethics and dissemination This study received research ethics approval from Asahikawa Medical University (18194 and 19115). The study was approved by the institutional review board of each hospital, and the requirement for informed consent was waived due to the observational nature of the study.

Trial registration number UMIN000036132.

Strengths and limitations of this study

► This study will be the first large-scale, prospective study of extracorporeal membrane oxygenation (ECMO) rewarming for patients suffering from accidental hypothermia.
► This study will evaluate the effectiveness of ECMO rewarming compared with non-ECMO rewarming for hypothermic patients with cardiac arrest or circulatory instability.
► This study will also collect blood samples to determine the relationship between coagulation fibrinolysis and ECMO-related complications and identify optimal ECMO rewarming management approaches for hypothermic patients.
► However, this study is not a randomised trial, which means that the adjustment for confounding factors is not complete.

INTRODUCTION

Accidental hypothermia (AH) is a rare condition but can be life-threatening in severe cases.[1 2] Thanks to technological advances over the past few decades, veno-arterial extracorporeal membrane oxygenation (V-A ECMO) has become a viable rewarming treatment for patients with severe hypothermia with cardiac arrest or severe circulatory instability.[3–6] Recently, the resuscitation guidelines from both the European Resuscitation Council and the American Heart Association have recommend the use of ECMO in AH patients with cardiac arrest.[7 8] However, there has been limited evidence concerning the utility of ECMO rewarming in patients with AH because of the low frequency of eligible patients. In addition, ethical implications restrict the utility of randomised controlled trials. Thus, previous studies on patients with

BMJ

AH rewarmed by ECMO have been case reports or single-centre retrospective analyses.[4–6]

A recent study using the nationwide Japanese Diagnosis Procedure Combination inpatients database showed that V-A ECMO was associated with a higher survival rate and more favourable neurological outcomes than conventional cardiopulmonary resuscitation (CPR) alone in hypothermic patients with cardiac arrest.[9] However, this study has several issues. First, whether or not ECMO should be initiated in hypothermic patients with circulatory instability remains unclear. Second, this study did not clarify whether ECMO or other rewarming methods should be used in patients with AH. At present, there are no clinical guidelines on this point. Third, this study did not describe the complications associated with ECMO rewarming in hypothermic patients. The use of ECMO for hypothermic patients with non-cardiac arrest is highly debatable, as ECMO is a highly invasive treatment with potentially serious complications.[5] Therefore, a large-scale, multicentre, prospective study is warranted to resolve these issues.

OBJECTIVES
The primary objective of this study will be to clarify the effectiveness of ECMO rewarming for hypothermic patients with cardiac arrest and those with unstable circulation. We hypothesised that the ECMO rewarming method is more beneficial in terms of survival than conventional rewarming methods. Our secondary objectives are to compare the incidence of adverse effects, such as bleeding, thrombosis and infectious disease between ECMO rewarming and non-ECMO rewarming. Furthermore, in this study, we will collect blood samples and perform additional tests related to coagulation and fibrinolysis to investigate the relationship between bleeding or thrombotic complications and anticoagulant use.

The results will help identify the most appropriate management approach with ECMO for patients with AH.

METHODS AND ANALYSES
Study design and setting
The Intensive Care with ExtraCorporeal membrane oxygenation Rewarming in Accidentally Severe Hypothermia (ICE-CRASH) study is a prospective, multicentre, observational study of patients with AH. The registry started in December 2019, with a planned 3 years of patient recruitment. The study is taking place at 35 tertiary emergency medical facilities that provide emergency and intensive care treatments to patients with AH in Japan.

Eligibility criteria
Inclusion criteria
The ICE-CRASH study consists of patients whose core body temperature measured at the emergency department (ED) is less than 32°C. Investigators will enrol consecutive patients ≥18 years old with AH, including those with cardiac arrest. We will include patients with AH who present to the ED from December 2019 to March 2022.

Exclusion criteria
The following patients will be excluded: patients <18 years old and those with cardiac arrest who are not eligible for resuscitation, according to the judgement of the emergency physician at each institution.

Data collection and quality control
A trained investigator or research assistant at each centre will collect the following data: age, sex, any pre-existing conditions, activities of daily living, causes underlying the hypothermia, alcohol intake, anticoagulants, Charlson Comorbidity Index, Glasgow Coma Scale, Sequential Organ Failure Assessment score,[10] laboratory data, core body temperature, temperature measurement site, blood pressure, heart rate, respiratory rate, ECG, cardiac arrest during prehospital, duration in the intensive care unit, length of hospital stay, mortality and Cerebral Performance Category (CPC) score at discharge, event days (ventilator, renal replacement therapy and catecholamine days), amount of transfusion and mortality at 28 days after admission (table 1). The laboratory data consist of the following: an arterial blood gas analysis, including the lactate level, blood count, biochemical tests and coagulation test. Measurement of the body temperature is based on the core body temperature. If for some reason the core body temperature cannot be measured, the peripheral body temperature will be measured and data on the measurement site (bladder, rectum, oesophagus, axilla and others) will be collected. These data will be recorded in the electronic data capture system (NorthNet; https://www.crmic-huhp.jp/northnet/edc/).

Rewarming methods will be divided into active external rewarming (warmed blanket and warmed bath) and active internal rewarming (warmed fluid infusion, lavage, haemodialysis, intravascular catheter and ECMO). The selection of the rewarming method will be decided based on the attending physician's judgement. When rewarming using ECMO is selected, the registry will also record additional information regarding ECMO as follows: the ECMO setting (venous–arterial or venous–venous), the size of the ECMO cannula, the ECMO flow, presence of distal perfusion, usage and types of anticoagulants, patient status at the start of ECMO (cardiopulmonary arrest (CPA) or non-CPA), time from the scene until ECMO initiation, duration using ECMO and presence of weaning from ECMO.

In addition, registry data will be collected concerning the incidence of complications (ventricular fibrillation, bleeding, pneumonia, acute pancreatitis, acute kidney injury) and complications due to ECMO (infection or thrombosis of cannula). Complications will include events that occur within 7 days after admission. Bleeding is defined as any amount requiring a transfusion.

Table 1 Variables collected in this study

Prehospital	In-hospital	Rewarming time/method	Outcome	Complications
Age, years	Core body temperature (measurement site)	Time required for rewarming	Length of ICU stay	Bleeding/thrombosis
Sex	GCS	Active external rewarming	Length of hospital stay	Pneumonia
Time from EMS alert to ED arrival	CPA or non-CPA	Warmed blanket	Mortality at discharge	Pancreatitis
Location (indoor or outdoor)	Blood pressure	Warmed bath	CPC score at discharge	Acute kidney injury
Causes underlying the hypothermia	Heart rate	Active internal rewarming	Event days	
ADL	ECG	Warmed fluid infusion	Ventilator	
Charlson Comorbidity Index	Respiratory rate	Lavage	Renal replacement therapy	
	Laboratory tests (blood counts, biochemical tests and coagulation test)	Haemodialysis	Catecholamine	
	Arterial blood gas analysis (including lactate)	Intravascular catheter	Transfusion	
	SOFA score	ECMO	Mortality at 28 days after admission	
		(Venous–arterial or venous–venous, cannula size, flow, distal perfusion, anticoagulant, time to initiate ECMO, duration, weaning)		

ADL, activities of daily living; CPA, cardiopulmonary arrest; CPC, Cerebral Performance Category; ECMO, extracorporeal membrane oxygenation; ED, emergency department; EMS, emergency medical service; GCS, Glasgow Coma Scale; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

Pneumonia is defined as an obvious shadow on chest radiography or CT. Pancreatitis is defined as cases meeting at least two of the following conditions: (1) abdominal pain, (2) elevation of pancreatic enzyme levels in the blood and (3) oedema of the pancreas or peripancreatic effusion on ultrasound/CT. Acute kidney injury is defined as acute kidney injury network classification stage ≥2.

Furthermore, the ICE-CRASH study will collect blood samples from patients with AH at each participating institution and perform additional tests related to coagulation and fibrinolysis.

OUTCOMES

Our primary outcome is the comparison of the survival rate between the ECMO and non-ECMO (other treatments) groups for severe hypothermic patients. Our secondary outcomes are to compare the CPC score at discharge between the ECMO and non-ECMO groups for hypothermic patients with cardiac arrest; to compare the incidence of complications (ventricular fibrillation, bleeding, thrombosis, pneumonia, acute pancreatitis,

lower limb ischaemia, acute kidney injury) between the ECMO and non-ECMO groups; and to clarify the relationship between the time to ECMO initiation and the prognosis in the ECMO group.

STATISTICAL PLAN
Sample size estimation

The sample size was calculated based on similar previous studies.[4–6] Based on the results of previous retrospective observational studies, we assumed proportions of surviving patients at 28 days after admission among hypothermic patients with cardiac arrest of 50% in the ECMO group and 15% in the non-ECMO group.[4 5] For a power of 80% and a type 1 error of 5%, the number of patients required is at least 33 in each group. Taking into account the sample of patients who dropped out during the process, the total number needed was calculated to be 70 patients. Similarly, we assumed proportions of surviving patients at 28 days after admission among hypothermic patients with circulatory instability (non-cardiac arrest) of 85% in the ECMO group and 55% in the non-ECMO

group.[5] Based on the same calculation, the number of patients required was determined to be at least 43 in each group, and the total number needed was calculated to be 90 patients.

This study is a registry study, so it will be conducted until at least March 2022, after which enrolment may continue in order to increase the number of cases.

Statistical analyses

Categorical variables will be presented as frequencies and percentages, and continuous variables will be presented as the means with the SD or medians with the IQR (25th to 75th percentile). Intergroup comparisons will be carried out using Fisher's exact test for categorical data and the Mann-Whitney U test for continuous data. We will use propensity matching between the ECMO and non-ECMO groups to adjust for the patient background as much as possible for statistical analyses. We will then compare the survival rates of the ECMO and non-ECMO groups.

Ethics and dissemination

This study will be conducted in accordance with the Declaration of Helsinki. It has received research ethics approval from Asahikawa Medical University (18194 and 19115) and is registered with the UMIN Clinical Trials Registry. It has also been approved by the Ethics Committee of each participating hospital. The need for informed consent will be waived due to the observational nature of the study. However, if blood samples are collected for additional studies, written informed consent will be obtained from each patient as appropriate.

The results of the study will be disseminated to the participating hospitals, submitted to peer-reviewed journals for publication and presented at scientific congresses.

DISCUSSION

Since the successful use of ECMO for AH with cardiac arrest has been reported, many studies have reported the efficacy of ECMO rewarming in patients with AH.[3–6] In recent years, the resuscitation guidelines from both the European Resuscitation Council and the American Heart Association have recommended the use of ECMO in AH patients with cardiac arrest.[7 8] However, at present, there are no global guidelines concerning the use of ECMO in AH patients with circulatory instability. The present findings may support the creation of guidelines concerning the use of ECMO in AH patients with circulatory instability.

Previous studies have shown that severe hypothermia inhibited the platelet function and coagulation.[11 12] However, few retrospective studies have focused on complications associated with ECMO usage, especially haemorrhagic and thrombotic complications. Thus, the incidence of these complications from using ECMO rewarming in patients with AH remains unclear. In this study, we will collect blood samples and perform additional coagulation and fibrinolysis tests to evaluate the relationship between thrombotic and bleeding complications during and after rewarming. These results may lead to the development of a new management approach for hypothermia specific to ECMO.

According to studies regarding extracorporeal resuscitation (ECPR) for out-of-hospital CPA patients, the longer it takes to initiate ECPR, the poorer the neurological prognosis.[13 14] However, this did not apply to patients with AH resulting in cardiac arrest.[15 16] A recent study showed that the parameter 'un-witnessed cardiac arrest' was not associated with a worse outcome.[17] However, the maximum permissible time until the initiation of ECMO remains unclear. In the present study, we will collect data on the time to the initiation of ECMO and CPR to clarify the relationship between the time to ECMO and the prognosis. These results may provide evidence supporting the feasibility of long-distance transport for the introduction of ECMO for patients with AH in the future.

Furthermore, a recent retrospective study showed that a slower ECMO rewarming rate was associated with a better survival rate,[18] while another study showed the opposite result.[19] The optimal ECMO rewarming rate thus remains unclear. The present study will collect data associated with the ECMO rewarming rate. The results may help establish safer and more optimal ECMO management methods for patients with severe hypothermia.

ORCID iDs
Shuhei Takauji http://orcid.org/0000-0001-5794-7586
Mineji Hayakawa http://orcid.org/0000-0001-8341-7626

REFERENCES

1 Silfvast T, Pettilä V. Outcome from severe accidental hypothermia in Southern Finland--a 10-year review. *Resuscitation* 2003;59:285–90.
2 van der Ploeg G-J, Goslings JC, Walpoth BH, *et al*. Accidental hypothermia: rewarming treatments, complications and outcomes from one university medical centre. *Resuscitation* 2010;81:1550–5.
3 Dunne B, Christou E, Duff O, *et al*. Extracorporeal-assisted rewarming in the management of accidental deep hypothermic cardiac arrest. *Heart, Lung and Circulation* 2014;23:1029–35.
4 Ruttmann E, Weissenbacher A, Ulmer H, *et al*. Prolonged extracorporeal membrane oxygenation-assisted support provides improved survival in hypothermic patients with cardiocirculatory arrest. *J Thorac Cardiovasc Surg* 2007;134:594–600.
5 Morita S, Inokuchi S, Yamagiwa T, *et al*. Efficacy of portable and percutaneous cardiopulmonary bypass rewarming versus that of

conventional internal rewarming for patients with accidental deep hypothermia. *Crit Care Med* 2011;39:1064–8.

6 Kosiński S, Darocha T, Jarosz A, *et al*. Clinical course and prognostic factors of patients in severe accidental hypothermia with circulatory instability rewarmed with veno-arterial ECMO - an observational case series study. *Scand J Trauma Resusc Emerg Med* 2017;25:46.

7 Truhlář A, Deakin CD, Soar J, *et al*. European resuscitation Council guidelines for resuscitation 2015: section 4. cardiac arrest in special circumstances. *Resuscitation* 2015;95:148–201.

8 Lavonas EJ, Drennan IR, Gabrielli A, *et al*. Part 10: special circumstances of resuscitation: 2015 American heart association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2015;132:S501–18.

9 Ohbe H, Isogai S, Jo T, *et al*. Extracorporeal membrane oxygenation improves outcomes of accidental hypothermia without vital signs: a nationwide observational study. *Resuscitation* 2019;144:27–32.

10 Vincent JL, de Mendonça A, Cantraine F, *et al*. Use of the sofa score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European society of intensive care medicine. *Crit Care Med* 1998;26:1793–800.

11 Levi M. Hemostasis and thrombosis in extreme temperatures (hypo- and hyperthermia). *Semin Thromb Hemost* 2018;44:651–5.

12 Wolberg AS, Meng ZH, Monroe DM, *et al*. A systematic evaluation of the effect of temperature on coagulation enzyme activity and platelet function. *J Trauma* 2004;56:1221–8.

13 Chen Y-S, Lin J-W, Yu H-Y, *et al*. Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis. *Lancet* 2008;372:554–61.

14 Massetti M, Tasle M, Le Page O, *et al*. Back from irreversibility: extracorporeal life support for prolonged cardiac arrest. *Ann Thorac Surg* 2005;79:178–83.

15 Darocha T, Kosiński S, Jarosz A, *et al*. The chain of survival in hypothermic circulatory arrest: encouraging preliminary results when using early identification, risk stratification and extracorporeal rewarming. *Scand J Trauma Resusc Emerg Med* 2016;24:85.

16 Hilmo J, Naesheim T, Gilbert M. "Nobody is dead until warm and dead": prolonged resuscitation is warranted in arrested hypothermic victims also in remote areas--a retrospective study from northern Norway. *Resuscitation* 2014;85:1204–11.

17 Pasquier M, Hugli O, Paal P, *et al*. Hypothermia outcome prediction after extracorporeal life support for hypothermic cardiac arrest patients: the hope score. *Resuscitation* 2018;126:58–64.

18 Saczkowski R, Kuzak N, Grunau B. Extracorporeal life support rewarming rate is associated with survival with good neurological outcome in accidental hypothermia. *Eur J Cardiothorac Surg* 2020 (published Online First: 2020/11/25).

19 Austin MA, Maynes EJ, O'Malley TJ, *et al*. Outcomes of extracorporeal life support use in accidental hypothermia: a Systematic Review. *Ann Thorac Surg* 2020;110:1926–32.