Extracorporeal Life Support in Accidental Hypothermia with Cardiac Arrest—A Narrative Review

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Abstract: Severely hypothermic patients, especially suffering cardiac arrest, require highly specialized treatment. The most common problems affecting the recognition and treatment seem to be awareness, logistics, and proper planning. In severe hypothermia, pathophysiologic changes occur in the cardiovascular system leading to dysrhythmias, decreased cardiac output, decreased central nervous system electrical activity, cold diuresis, and noncardiogenic pulmonary edema. Cardiac arrest, multiple organ dysfunction, and refractory vasoplegia are indicative of profound hypothermia. The aim of these narrative reviews is to describe the peculiar pathophysiology of patients suffering cardiac arrest from accidental hypothermia.

We describe the good chances of neurologic recovery in certain circumstances, even in patients presenting with untreated cardiac arrest, asystole, and the absence of bystander cardiopulmonary resuscitation. Guidance on patient selection, prognostication, and treatment, including extracorporeal life support, is given. ASAIO Journal 2022; 68;153–162

Key Words: accidental hypothermia, advanced cardiac life support, cardiac arrest, cardiopulmonary resuscitation, extracorporeal membrane oxygenation, extracorporeal life support, rewarming

Hypothermia is defined as a core temperature below 35°C. In healthy young people, hypothermia does not cause cardiac arrest (CA) as a single reason unless the core temperature is below 30°C. However, in old multimorbid persons, hypothermia may contribute to CA below 32°C.1 Deep accidental hypothermia is a specific cause of CA associated with significant morbidity and mortality.2–4 Accidental hypothermia occurs in previously healthy patients exposed to excessive cold, mainly in hostile, harsh environments,2,5,6 induced by a variety of reasons, for example, cold-water immersion and submersion, avalanche burial, falling into a crevasse, overexertion, or prolonged sojourn in a cold or inadequately heated environment. However, accidental hypothermia is also common in urban areas and temperate zones. In such cases, other factors, commonly including alcohol intoxication, drug overdose, multimorbidities, and mental illness, may be causative.2,4,7,8 Especially in regions where the incidence of hypothermia is low, and the knowledge about the pathophysiology is not widespread, the diagnostic process may be underestimated, the treatment delayed and not in compliance with the guidelines.1,3,9,10

The outcome in normothermic unwitnessed out-of-hospital cardiac arrest (OHCA) is poor.11 Several terminations of resuscitation (TOR) rules suggest that after 20 minutes of resuscitation attempts in unwitnessed OHCA without bystander cardiopulmonary resuscitation (CPR), CPR may be terminated if no vital signs were detected and no shockable rhythm was found.12–15 Recommendations for extracorporeal CPR (ECPR) include only selected OHCA patients to sustain perfusion while percutaneous coronary intervention can be performed.16,17 The ECPR protocols include a set of criteria such as witnessed CA, immediate bystander CPR, short no-flow and low-flow time before ECPR, and a shockable rhythm.18,19 While the predictive value of TOR-rules in normothermic CA patients is high and withholding ECPR in these circumstances is sound, current ECPR guidelines do not apply in patients suffering CA from potentially reversible causes such as accidental hypothermia.2,17,19,20

Medical teams are faced with limited up-to-date triage and extracorporeal cardiac life support (ECLS) rewarming algorithms.21–23 It must be emphasized that if the patient is diagnosed and treated properly, an excellent neurologic outcome is often possible even after long-lasting hypothermic cardiac arrest.24 Although the advantage of ECLS over other ways of rewarming in severe hypothermia has been proven,25 it is still not implemented uniformly.7 Based on our experience, we believe that guidance should be provided for ECLS centers covering the eligibility, rewarming, and cardio-pulmonary stabilization of severely hypothermic patients. We would like to provide a concise, practical, and up-to-date recommendation focused on an optimal approach to perform triage and rewarm patients with cardiac arrest in severe accidental hypothermia at an ECLS center.

Pathophysiology

The human body cools gradually and with every fall in 1°C of the core temperature, brain oxygen requirements diminish...
6–7%.26 Thus, at 32°C hypothermic CA may be survivable for 10 minutes instead of 5 minutes in normothermia. This results in a metabolism of ~24% and ~16% at 18°C and 15°C, respectively, compared with that at normothermia.26,27 This phenomenon is well known and used commonly during cardiac surgery procedures, where deep hypothermic circulatory arrest is needed, for example, for aortic repair in acute aortic syndromes.28 In contrast, in normothermia, CA lasting for five or more minutes will result in severe brain damage or death.

Hypothermia diminishes vital function long before CA. Cooling will lead to an irritable myocardium, while arrhythmias will ensue below 35°C. Below 32°C, the elderly and multimorbid are at risk of hypothermic CA, while young, healthy people may suffer CA below 30°C.25,29–31 Few still have minimal vital signs below 24°C.25,29–31 The first presenting rhythm may be asystole in 30% of cases.30 Several parameters defined as exclusion criteria for ECPR in normothermic CA are not valid in hypothermic CA (Table 1).32–36 Essential differences between normothermic and hypothermic CA are outlined by Gordon et al.37 In severe hypothermia, end-tidal carbon dioxide (etCO2) is low due to a decreased metabolic rate while a correlation with the partial pressure of carbon dioxide in arterial blood (PaCO2) is lacking. Therefore, etCO2 can neither be used to assess blood flow and not the quality of CPR38 as in normothermic cardiac arrest.39–41 Many hypothermic CA patients suffer from an unwitnessed CA.

Hypothermic patients with asystole may be rewarmed with ECLS until the irritated myocardium resumes electrical activity (usually around 28–30°C), with shockable rhythm defibrillation being required to achieve the return of spontaneous circulations (ROSC). After ROSC, patients often develop multiple organ failure, with cardiac and respiratory failure as a prominent feature requiring advanced organ support such as ECLS.42 This strategy enables recovery while the pulmonary and cardiac functions are being supported.43

### Outcomes of Hypothermic CA After ECLS Rewarming

Although CA is likely to occur below 28°C, circulation may even persist below 24°C. Below 20°C, isoelectric ECG and EEG are likely but do not exclude successful ECLS rewarming. The lowest recorded temperature with neurologically intact survival following ECLS rewarming from accidental hypothermia in a pediatric survivor is 11.8°C, while the lowest in an adult survivor is 13.7°C.44,45 The lowest core temperature with neurologically intact survival from induced hypothermia was 4.0°C.46 The threshold of survival for core temperature has not yet been established.

For patients presenting to hospital with hypothermic CA and supported with ECLS, overall survival rates to hospital discharge between 20% and 100% are reported.3 Most notably 61–100% of survivors were neurologically classified as cerebral performance category 1–2.33,35,41,47,48 Respective survival rates are lower for lower hypothermic CA (from 0% to 17%)49 and drowning patients (from 10% to 42%).1,50,54

Apart from the protective effect of hypothermia itself, established protocols of treatment and novel rewarming techniques may influence the outcome.36,55–57 The coordination of the rescue procedures, immediate high-quality CPR (preferably using a mechanical chest compression system), recognition of hypothermia and veno-arterial (VA) ECLS cannulation for rewarming and cardiorespiratory support are crucial for achieving satisfactory survival rates44,35,58–62 and full neurologic recovery.10,61

### The Hypothermia Outcome Prediction After ECLS (HOPE) Score

The survival probabilities of in-patients can be determined according to the HOPE score.33 The HOPE score43 allows to perform an in-hospital prediction of the probability of survival after ECLS rewarming in a cardiac arrest patient with accidental hypothermia. The HOPE score is based on six covariates available at hospital admission (Table 2).36 The HOPE score has been externally validated with a cutoff of 10%.15 It showed good calibration as well as excellent discrimination (area under the receiver operating characteristic curve of 0.825) between patients who will survive from those who will die after ECLS rewarming.35 The negative predictive value (defined as the proportion of patients who died among those with a HOPE score <10%) was 97%.33,35

### Problems and Pitfalls in Patient Selection and Qualification for ECLS

There are several problems and pitfalls in qualification for ECLS rewarming and which are notably different from those in ECPR for CA in normothermic patients.45

ECLS rewarming is indicated in accidental hypothermic cardiac arrest with a potential for reversibility.31,50,61,64–67 Since hypothermic cardiac arrest is a rare medical emergency, EMS as well ED teams may be not familiar with its management. This can lead to fatal mistakes regarding the qualification of a patient for ECLS rewarming and finally patient’s death.68

Since the core temperature measurement is usually unavailable in prehospital settings, all details of patient’s

| Cardiac Arrest | Normothermic | Hypothermic |
|----------------|--------------|-------------|
| Temperature    | >35°C        | In healthy adults <30°C (in elderly <32°C) |
| Unwitnessed arrest | Usually, a contraindication for ECPR | Not a contraindication for ECLS |
| Initial rhythm | Shockable    | Not an independent predictor for survival |
| No flow time   | Shockable    | Not independently associated with worse outcome |
| Time to cannulation for ECPR | Usually important | Not an independent predictor for survival |
| Neurologic outcome in survivors | Usually less than 60 minutes | Asystole not independently associated with worse outcome |
|                | Variable     | Usually longer than 60 minutes |
|                |              | Full recovery likelier than in normothermia |

ECLS, extracorporeal cardiac life support; ECPR, extracorporeal cardiopulmonary resuscitation.
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Table 2. Hypothermia Outcome Prediction after ECLS (HOPE) Score

| HOPE score covariates at hospital admission |
|--------------------------------------------|
| - Age                                      |
| - Sex                                      |
| - Core temperature                         |
| - Serum potassium                          |
| - Presence of asphyxia (submersion with the head fully covered by water or snow avalanche accident AND in cardiac arrest at extrication) |
| - Duration of cardiopulmonary resuscitation (CPR); since CPR initiation until ECLS cannulation |

An online calculator of the HOPE score is available at: www.hypothermiascore.org

CPR, cardiopulmonary resuscitation; ECLS, extracorporeal cardiac life support.

history and clinical signs should be carefully analyzed. A cold trunk, a history of cooling that preceded CA, and the absence of fatal injuries suggest accidental hypothermia cardiac arrest (AHCA). Such patients should be transported directly from the scene to an ECLS center to shorten the low-flow time.

Key instructions may help to identify accidental hypothermia cases and initiate appropriate and adequate treatment. Local protocols in ECLS centers seem to be an ideal way to improve the quality of the initial treatment of hypothermic arrested patients. ECLS teams may support emergency teams, being aware of several limitations in equipment and skills in the out-of-hospital setting.

The complete absence of signs of life does not permit clinicians to declare an arrested hypothermic patient dead unless there is an associated fatal illness, fatal traumatic injury, or prolonged asphyxia. Fixed and dilated pupils, pallor, rigor mortis, and nonfixed dependent lividity alone are not reliable signs of death in the arrested severely hypothermic patient. The guiding principle is “no one is dead until they are warm and dead.”

However, the patient can be declared dead if the chest compressions are impossible to perform due to tissue freezing.

Besides the history of the patient, two important procedures have to be performed simultaneously at hospital admission: the measurement of the core (usually esophageal) temperature to diagnose or confirm significant hypothermia and blood sampling for blood gas analysis including potassium, which is one of the six variables used to calculate the HOPE survival probabilities to select patients for ECLS rewarming.

Indications for ECLS Rewarming

ECLS rewarming is indicated in AHCA with a mechanism/history compatible with AHCA AND HOPE survival probabilities of ≥10% (in adults)*

*Because children may have potentially higher chances of survival as well as a longer life expectancy if they survive, clinicians should exercise caution when using the HOPE survival probabilities with the proposed threshold of 10% to predict children’s outcomes.

An online calculator of the HOPE score is available at: www.hypothermiascore.org (Table 2).

ECLS rewarming should be carefully considered in the following circumstances due to low rates of survival and the high likelihood of major morbidity:

- Core temperature >30°C (consider other factors). CA that is solely caused by hypothermia does not occur in patients with a body temperature >30°C.
- Major trauma (Table 3)
- Futile comorbidities
- Chest compressions impossible due to tissue freezing

In such cases, the decision should be based on a multidisciplinary approach, which should also integrate the value of the HOPE survival probabilities.

The following parameters considered as exclusion criteria for ECPR in normothermic patients DO NOT contraindicate ECLS rewarming (Table 1, Figure 1):

- Asystole
- Unwitnessed CA
- The absolute value of the low-flow duration, provided rewarming with external and alternative internal rewarming if transport to ECLS/CPB is not available within 6 hours (survival with good neurologic outcome has been described with low flow up to 6 hours)
- The absolute value of the no-flow duration (survival with good neurologic outcome has been described with no flow >1 hour)
- Elderly
- Fixed and dilated pupils

End-tidal carbon dioxide (etCO₂) <10mm Hg

Contraindications for ECLS Rewarming

No absolute contraindications for ECLS rewarming in AHCA exist (Figure 1). However, the complications listed in the ELSO General Guideline for all ECLS cases are applicable and balancing the risks versus the potential benefits of the extracorporeal procedure is important, notably in elderly people.

Table 3. Problems and Pitfalls in Qualification for ECLS Rewarming

The clinical factors usually considered as contraindications for ECPR in normothermic CA (asystole, unwitnessed CA, unknown no-flow duration, prolonged CPR duration, advanced age) ARE NOT a contraindication for ECLS rewarming in AHCA patients. Blood sampling should avoid hemolysis, and minimize trauma to femoral vessels. Inclusion criteria for ECLS rewarming should not be based on a single potassium level. Extreme serum potassium levels are possible. A second blood sample obtained at a different site and verifying measurement may be reasonable. If some variables of the HOPE score are not clear (e.g., the presence or absence of asphyxia), taking into account the variable that will lead to the highest survival probabilities when calculating the HOPE score will offer the best chances of survival to the patient. Concomitant trauma, especially traumatic brain injury is not an absolute contraindication for ECLS rewarming.

Anticoagulation free ECLS run is possible.

AHCA, accidental hypothermia cardiac arrest; CPR, cardiopulmonary resuscitation; ECLS, extracorporeal cardiac life support.
Education of health care professionals in ED and ICU of participating institutions as well as efficient logistic coordination are mandatory for the successful treatment of hypothermic patients.79 As most countries designate specialized centers dedicated to hypothermia treatment using extracorporeal techniques, EMS providers transport potential candidates to these centers.6,10,58,59,61,79

Practical Information on the Management of Patient During ECLS Rewarming

ECLS Mode

Both cardiopulmonary bypass (CPB) and ECLS may be used to provide blood circulation, oxygenation, and warming to hypothermic cardiac arrest patients. ECLS is considered the preferred method due to its lower anticoagulation requirements than CPB and its potential to prolong circulatory support.20 Some patients who have sustained hypothermic cardiac arrest may require this support for several days due to temporary heart failure.42 In hypothermic CA, the VA ECLS mode is preferred.80,81

Initial Patient Management at ECLS Center Before ECLS Cannulation

1. Continue chest compressions with the best achievable level until sufficient ECLS flow is achieved. Chest compressions can then be terminated.17 In deeply hypothermic patients’ coagulation is impaired, and the risk of blood stasis-related thrombi is negligible (Figure 2).
2. etCO₂ is low due to decreased metabolic rate and cannot be used to assess the quality of CPR.
3. Core temperature assessment (see also Rewarming Goals)
4. Blood samples should be obtained with ultrasound-guided puncture or open puncture of the femoral vessels. Cardiopulmonary resuscitation (CPR) may be temporarily stopped.
5. Final decision to be made by HOPE score calculation (see also Hypothermia Outcome Prediction after ECLS - HOPE score) (Table 2)

Cannulation

ECLS cannulation in hypothermia-related CA may be challenging due to coagulopathy and a risk of bleeding. It is recommended to choose the method the person who will cannulate the patient is most used to:

1. the cut-down technique, preferred due to center-specific protocol or in vessels difficult to identify by ultrasound guidance.
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Specific Problems and Pitfalls of Cannulation

- Factors including alcohol intoxication, drug overdose, and mental illness may cause hypothermia commonly in urban areas. Patients coming from poor social conditions are at risk for hygiene neglect and infectious diseases. This makes them more vulnerable and puts them at risk for infectious complication on ECLS rewarming. Precautionary procedures and high-aseptic standards during cannulation are mandatory.

Circuit Management and Patient Monitoring

Blood flow. Once cannulation is achieved, blood flow during rewarming is controlled as recommended in the ELSO Guidelines, usually 2.2–2.4L/min/m² to provide adequate blood flow for optimal perfusion of the brain and other end organs. Blood flow ensures sufficient tissue perfusion targeted by $\text{SvO}_2 >70\%$. In hypothermia, due to reduced oxygen demand $\text{SvO}_2$ may be decided elevated. During the rewarming process, hypothermic patients suffer refractory hypotension due to vasoplegia and fluid shift. This condition may obscure the adequate blood flow. Fluid resuscitation with isotonic crystalloids and vasopressors are first line of treatment to maintain a mean systemic pressure between 50 and 70mm Hg and to ensure cerebral perfusion.

Fluids resuscitation. Patients with hypothermia frequently become disproportionately hypotensive during rewarming from severe dehydration and fluid shifts. High-volume fluid resuscitation with isotonic crystalloids is the first line of treatment. Fluids may be delivered via ECLS tubing in the absence of adequate vascular access.

Ventilation. Lung function may be deteriorated due to hypothermia, pulmonary vasoconstriction, low perfusion, or no-flow time. Ventilator settings should aim to allow lung protection. During rewarming, massive endothelial damage and lung edema may occur. An initial ventilator setting of $\text{FiO}_2$.0 may be required, adjusted to the lowest possible $\text{FiO}_2$ to avoid the risk of hyperoxia and additional alveolar damage.

Arterial blood gas analysis. Arterial blood gas analysis according to the alpha-stat-regulation should be repeated. Hypoglycemia, severe acid-base imbalance, and other problems requiring symptom-related treatment may occur.

Cardiac rhythm. Hypothermic ventricular fibrillation is resistant to pharmacotherapy and defibrillation. Defibrillation delivered in a patient with core temperature below 30°C may be successful if ECLS provides an adequate blood flow and stable rate of rewarming.

Internal cardiac pacing may be considered if bradycardia persists with cardiac instability after normothermia is achieved.

Sedation. Sedation and analgesia are required to avoid uncontrolled waking up, moving about or coughing. A score of –5 on the Richmond Agitation-Sedation Scale 5 is aimed. Sedation may be reduced and discontinued if normothermia, stable hemodynamic and pulmonary function are achieved.

Neurologic prognostication. Neurologic exams should be performed once sedation is discontinued. Collaboration with a neurologist is recommended.

Infection. Asepsis in the operative field during cannulation is a prerequisite to prevent bloodstream infections. Adherence to local protocols of antibiotic prophylaxis to prevent surgical site access for ECLS cannulation has the highest priority. Venous and arterial lines for drug administration and monitoring are deemed inferior.

Repeated attempts to provide blood sampling from femoral vessels may result in hemorrhage and emerged hematoma that aggravate difficult anatomical conditions for vascular access for ECLS.

There is a variability in potassium values between blood sampling sites. Central venous blood has been proposed as the preferred site for potassium sampling. It is crucial to avoid iatrogenic trauma to the femoral vessels. Blood samples should be obtained with an ultrasound-guided puncture or open puncture of the femoral vessels. Cardiopulmonary resuscitation (CPR) may be temporarily stopped. Hyperkalemia in deep hypothermia is a sign of a poor prognosis and may disqualify a patient from ECLS rewarming. Thus, it is essential to avoid hemolysis-induced pseudo-hyperkalemia. If a patient would not qualify for ECLS rewarming according to the first potassium measurement, a second blood sample may be obtained at a different site to verify the potassium level.

Inappropriate provision of external rewarming methods during prehospital rescue may result in possible skin damage and even burns. Heat pads placed in the groins increase the risk of difficult vascular access to the femoral vessels.

Determination of the body position before the rescue and tissue damage to the extremities.

Hypothermia increases blood echogenicity. Very slow flow of hyperechogenic blood in the heart cavities may mimic thrombus formations.

In cases of percutaneous cannulation, the following cannulas may be used: arterial 15–19 French, venous (drainage) 39–25 French. An ultrasound of the vessels, especially arteries, is recommended. Cannulation-related vessel injury may include unintentional puncture of unidentified vessels, saphenous-femoral junction cannulation, and transfixation of the inguinal ligament during cannulation. Femoral arterial cannulation may be associated with inadequate distal perfusion. A separate retrograde perfusion line (6–8 French) can be introduced in the distal superficial femoral artery by the direct cutdown or Seldinger techniques. Interruptions in chest compression may be aligned at key points of cannulation.

In patients with no contraindications for anticoagulation, unfractionated heparin is given as a bolus (50–100 units per kilogram) at the time of cannulation and by continuous infusion during ECLS. An activated clotting time (ACT) targeted at 150–200 seconds is recommended. In some centers, systemic anticoagulation is waived within the first 24 hours due to hypothermia-related coagulopathy.
infection is recommended. Antibiotics are indicated according to further signs of infection.

Rewarming goals. The optimal targets of rewarming are still unknown. A slow rewarming rate has an independent association with survival with good neurologic outcomes in hypothermic cardiac arrest. This is consistent with existing evidence and cardiac surgery guidelines suggesting that better neurologic outcome is inversely related to the rewarming rate. It is postulated that this may be due to a cerebral temperature overshoot that can occur when larger temperature gradients are required by a more rapid ECLS rewarming.

However, the ideal rate of rewarming of hypothermic ECLS patients remains unknown. The maintenance of the core temperature may be cautiously monitored by temperature measurements at several sites, such as the nasopharynx, pulmonary artery, carotid bubble, esophagus, urinary bladder, rectum, and tympanic membrane as well as the venous inflow and arterial outlet. However, no single site for measurement and

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Figure 2. Initial management in accidental hypothermia-related cardiac arrest before ECLS cannulation.
monitoring can be recommended. We do not exactly know how much difference there is between the body compartments during rewarming or how well the temperature of respective sites reflects the brain temperature. A common method of measuring core temperature in patients with hypothermic cardiac arrest is esophageal measurement.

The target position of the tip of the probe is the lower third of the esophagus. The esophageal temperature may not correspond to the core temperature, particularly when high gradients are applied (i.e., high-water bath settings). This may be due to a warmblood outflow in the vicinity of the tip of the esophageal probe.

Figure 3. Medical record template for patients suffering accidental hypothermia related cardiac arrest. Data of hypothermic CA patients may be collected according to this checklist template. These data are essential to allow a decision to be made whether the patient qualifies for ECPR. Required data include out-of-hospital and in-hospital data, namely: general and specific data of the patient, the mechanism leading to hypothermic CA, their present condition including core temperature, ECG, mode and duration of CPR and blood sampling results. These data are used to calculate the probability of survival according to the HOPE score. With a HOPE score of ≥ 10 ECPR is recommended.33,35
Therefore, the core temperature should be monitored in at least two sites simultaneously. A temperature gradient between the heat exchanger (water bath) and the core temperature is typically used to monitor the rewarming rate. Continuous oxygenator arterial outlet temperature monitoring is recommended, as well as maintaining a temperature gradient between the venous inflow and arterial outlet of ≤4°C. A maximum gradient between the arterial outlet and venous inflow of 10°C should not be exceeded. Failure to comply with these rules may cause serious neurologic complications and hemolysis of blood cells.

The target rewarming rate during ECLS in accidental hypothermia should be ≤5°C/h. It is recommended to start rewarming in 5–10 minutes time intervals after cannulation to ensure the accurate functioning of all devices. The heat exchanger should be set at a maximum of 37°C to prevent cerebral overheating. After ROSC, strict normothermia (35–36°C) is recommended during the first 24 hours. Faster rewarming rates of about 4–5°C per hours until normothermia (35–36°C) is recommended during the first 24 hours. Therefore, the core temperature should be monitored in at least two sites simultaneously. A favorable neurologic outcome is possible even in prolonged, unwitnessed cardiac arrest related to accidental hypothermia if the patient is diagnosed and treated properly.

A medical record card (Figure 3) is recommended to collect the data of hypothermic CA patients.

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