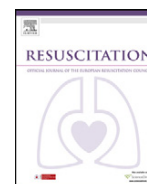




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Clinical paper

## Outcome of accidental hypothermia with or without circulatory arrest Experience from the Danish Præstø Fjord boating accident<sup>☆</sup>

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## ABSTRACT

**Background:** Resuscitation guidelines for the treatment of accidental hypothermia are based primarily on isolated cases. Mortality rates are high despite aggressive treatment aimed at restoring spontaneous circulation and normothermia.

**Methods:** The present report is based on a boating accident where 15 healthy subjects (median age 16 (range 15–45) years) were immersed in 2 °C salt water. Seven victims were recovered in circulatory arrest with a median temperature of 18.4 °C (range 15.5–20.2 °C). They were all rewarmed with extracorporeal membrane oxygenation (ECMO) and were subsequently evaluated with advanced neuroradiological and functional testing. The remaining 7 had established spontaneous circulation without the use of ECMO. One victim drowned in the accident.

**Results:** The victims that survived the accident without circulatory arrest were predominantly females with a higher body mass index. Victims with circulatory arrest pH on arrival was a median of 6.61 (range 6.43–6.94), with ECMO being established a median of 226 (178–241) min after the accident. Magnetic resonance spectroscopy showed neuronal dysfunction in five. In five victims initial normal white matter spectra progressed to show evidence of abnormal axonal membranes. Based on the seven-level Functional Independence Measure test functional outcome was good in six circulatory arrest victims and in all without circulatory arrest. Mild to moderate cognitive dysfunction was seen in six and severe dysfunction in one circulatory arrest victim.

**Conclusion:** Seven patients with profound accidental hypothermic circulatory arrest were successfully resuscitated using a management approach that included extracorporeal rewarming, followed by successive periods of therapeutic hypothermia and sedated normothermia and intensive neurorehabilitation. Seven other hypothermic victims (core temperature as low as 23 °C) that did not suffer circulatory arrest also survived the accident.

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Profound hypothermia, defined as a core temperature of less than 30 °C<sup>1</sup> is associated with a significant risk of circulatory arrest. Even with aggressive treatment including circulatory support and rewarming mortality rates due to progressive uncontrollable

systemic oedema, pulmonary insufficiency and cerebral oedema is high. Successful management of deep hypothermia with restoration of circulation and normal body temperature has been achieved using extracorporeal membrane oxygenation (ECMO) in selected victims. However, the understanding and management of accidental deep hypothermia has been largely based on isolated retrospective cases and reviews, whereas data based on controlled studies are not available for obvious ethical reasons.<sup>2–7</sup>

The present report is based on a boating accident that occurred in February 2011 where a dragon boat carrying 13 teenagers and 2 adult teachers from a continuation high school capsized on a fjord

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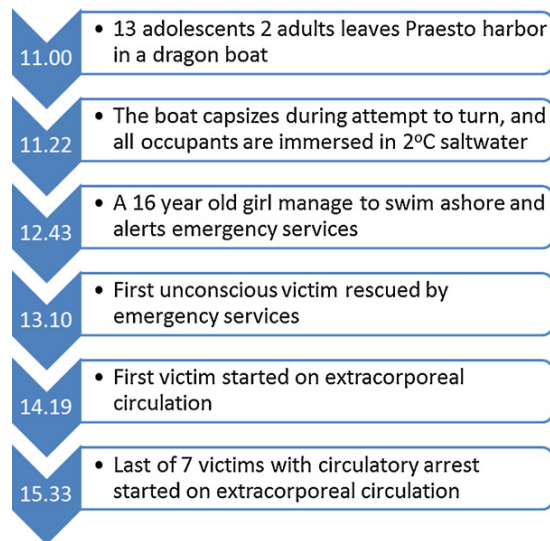


Fig. 1. Time course of accident.

in the southern part of Denmark. All 15 persons fell overboard and were immersed in 2°C salt water and subsequently suffered varying degrees of hypothermia. Of the 15 subjects, 7 were recovered after prolonged circulatory arrest with extreme hypothermia, 7 survived the disastrous event with spontaneous circulation and moderate to profound hypothermia and one victim drowned. This population therefore offers a unique possibility to compare two groups (with and without circulatory arrest), and to assess the immediate outcome and 6 month outcome of profoundly hypothermic victims.

## 1. Methods

The study is based on 13 healthy (7 boys, 6 girls aged 15–17 years) students at a continuation high school, and two adult teachers (a 33 year old female that survived the accident and a 44 year old male who drowned). Victims and/or victim's parents provided informed consent to publication of this report.

The accident occurred February 11, 2011 on a 20 km<sup>2</sup> fjord with a depth of 2–5 m. On the day of the accident the air temperature was 4°C, the wind speed was 7 m/s, the water temperature was 2°C, and the visibility was good. The party was wearing swim-vests and had been paddling for 22 min when their teacher ordered the boat back to shore due to a sudden weather change. As they tried to turn the boat they created a wave which capsized the boat. All attempted to swim to the nearest shore 500 m away. Three of the teenagers and the female teacher succeeded in reaching the shore. A 16 year old female reached the nearest town 2.1 km away and made the first emergency call 81 min after the accident (Fig. 1). Three teenagers with spontaneous circulation were recovered from the water by boat or helicopter. One subject was unconscious (victim #9 Table 1) and received a brief period of chest compressions and mask ventilation with subsequent return of spontaneous breathing and circulation. All seven victims were taken by ambulance to four nearby hospitals.

The remaining seven victims were found with their heads submerged in salt water, and recovered by boat or helicopter. Once diagnosed with circulatory arrest basic life support was started. The first victim brought ashore (#7, Table 1) was taken by ambulance to a nearby hospital that did not have the resources necessary for extracorporeal rewarming. Six victims (#1–6, Table 1) were transferred by helicopter to the nearest cardiothoracic facility in

Copenhagen for extracorporeal rewarming. Four victims (#3–6) were intubated on site, ventilated and given chest compressions and two victims (#1–2) were given chest compressions during transportation, and intubated on arrival at the hospital. Data on rescue and transfer to hospital were recorded according to the Ustein style.<sup>8</sup>

### 1.1. Treatment of victims in circulatory arrest

Veno-arterial ECMO was established surgically within 30 min (14–72 min) of arrival to hospital in victim #1–6 (Table 1). Once the core temperature of the victims reached 32–34°C, all six victims were weaned from ECMO and decannulated, and the patients were transferred to a specialised cardiothoracic intensive care unit. In victim #7 life support was continued at the local hospital until the arrival of a helicopter carrying emergency medical staff and a portable ECMO system. Rewarming was started 233 min after immersion and the victim was subsequently transferred to a cardiothoracic intensive care unit. At the accepting intensive care units a core temperature of 32–34°C was maintained for 24 h with subsequent gradual rewarming 0.5°C/h until 37.0°C according to guidelines for adult life support.<sup>9</sup> To avoid increased metabolic demands due to hyperthermia, pain and agitation it was decided to maintain sedation and normothermia for another 48 h before extubating the victims. During the following days fever was actively treated. Vasoactive support was provided as needed using norepinephrine and/or dopamine. All victims were sedated with propofol, and either remifentanyl or fentanyl.

Following intensive care treatment all seven victims were transferred to the same neurorehabilitation centre.

### 1.2. Neurophysiological tests and serum markers of neuronal damage

In victims #1–6 (Table 1) electroencephalographic recordings were performed using a standard system and protocol. Somatosensory evoked potentials were registered from both hemispheres with bipolar electrical stimulation applied to the median nerves, bilaterally.

Neuron specific enolase (NSE) and protein S100B were sampled after 24, 48, and 72 h as markers of neuronal damage.<sup>10,11</sup> NSE was analysed using Liaison® NSE (DiaSorin AB, Sundbyberg, Sweden), with a reference level of <12.5 g/L. Protein S100B level was measured using the immunoluminometric assay method (Elec-sys 2010, Roche Diagnostics, Switzerland), with a reference level of <0.105 µg l<sup>-1</sup>.

### 1.3. Imaging of the brain

In all cardiac arrest cases cerebral computer tomography and neuro-magnetic resonance imaging (MRI) including proton magnetic resonance spectroscopy was carried out during initial hospitalisation and was then repeated 6 months later. MRI of the brain and spine and short echo time proton magnetic resonance spectra<sup>12</sup> of three volumes of interest in the brain were acquired at three Tesla. Spectral locations were an occipitoparietal region predominantly containing white matter, and regions comprising grey matter in the occipital midline and in the nucleus lentiformis. Metabolite quantification involved fully automated and user independent spectral evaluation by linear combination modelling combined with reference to data from healthy volunteers. Deviation exceeding 2 standard deviations in the ratios were considered abnormal.<sup>13</sup> Ratios to total creatine of the neuronal marker N-acetylaspartate, of the membrane integrity marker total

**Table 1**  
Ustein style report of 14 victims. Victims #1–7 were recovered with circulatory arrest, victims #8–14 with spontaneous circulation.

Patient	Age (years)	Gender	Body mass index (kg/m <sup>2</sup> )	Water temperature (°C)	Time to first EMS contact (min)	Glasgow coma scale	Airway intubation	Duration chest compression	Core temperature (°C)	First recorded rhythm
#1	15	Male	21.8	2	121	3	N	57	16.0	VF
#2	16	Male	18.4	2	121	3	N	56	20.2	VF
#3	15	Male	21.6	2	168	3	Y	65	18.4	Asystole
#4	16	Female	17.3	2	153	3	Y	88	15.5	PEA
#5	15	Female	24.0	2	168	3	Y	58	19.4	VF
#6	16	Male	22.7	2	108	3	Y	120	17.5	VF
#7	17	Male	21.6	2	108	3	Y	125	20.0	Asystole
Median (range)	16 (15–17)		21.1 (17.3–24.0)		121 (108–169)	3		65 (56–125)	18.4 (15.5–20.2)	
#8	16	Male	22.5	2	106	15	N	ND	34.2	Sinus
#9	16	Female	20.1	2	108	3	Y	1–2	23.0	PVC
#10	16	Female	24.7	2	91	15	N	ND	36.4	Sinus
#11	16	Female	22.9	2	104	12	N	ND	27.5	AFIB
#12	17	Female	26.8	2	96	15	N	ND	37.5	Sinus
#13	16	Female	27.7	2	113	15	N	ND	35.9	Sinus
#14	33	Female	22.5	2	96	12	N	ND	28.0	Sinus
Median (range)	16 (16–33)		23.8(20.1–27.7) <sup>*</sup>		104 (91–113) <sup>*</sup>	15 (3–15) <sup>*</sup>			28.0 (23.0–37.5) <sup>*</sup>	
Patient	Time to ECMO (min) <sup>†</sup>	pH	Lactate (mmol/l)		Temperature at ECMO termination	Duration of ECMO (min)	pH at ECMO stop	Length of hospital stay (days)	Glasgow coma scale at hospital discharge	
#1	178	6.59	21.0		4.0	33.8	161	7.19	12	
#2	179	6.62	18.0		3.6	32.9	149	7.15	10	
#3	233	6.43	23.0		3.6	31.9	120	7.12	11	
#4	241	6.61	24.0		4.0	36	245	7.30	10	
#5	226	6.90	9.3		2.3	34	127	7.09	17	
#6	228	6.52	22.0		3.6	35.4	109	7.18	11	
#7	233	6.94	11.3		4.0	36.5	2614	7.38	10	
Median (range)	226 (178–241)	6.61 (6.43–6.94)	21.0 (9.4–24)		3.6 (2.3–4.0)	34.0 (31.9–36.5)	149 (109–2614)	7.18 (7.09–7.38)	10 (10–17)	
#8	ND	ND	ND		3.5	ND	ND	2	15	
#9	ND	7.00	4.7		4.2	ND	ND	4	15	
#10	ND	ND	ND		4.2	ND	ND	2	15	
#11	ND	7.27	0.9		4.3	ND	ND	2	15	
#12	ND	ND	ND		3.9	ND	ND	1	15	
#13	ND	7.33	0.9		3.8	ND	ND	3	15	
#14	ND	ND	ND		3.9	ND	ND	2	15	
Median (range)		7.27 (7.00–7.33)			3.9 (3.5–4.3)			2 (1–4) <sup>*</sup>	15	

ECMO, extracorporeal membrane oxygenation; EMS, emergency medical services; N, no; ND, not done; PEA, pulseless electrical activity; PVC, premature ventricular contractions; VF, fine ventricular fibrillation; Y, yes.

<sup>†</sup> p < 0.02.

choline, of the glial marker myo-Inositol, and of lactate (an indicator of hypoxic damage) were evaluated.

#### 1.4. Assessment of cognitive and physical disability

Functional impairment was assessed after 6 months using the 7-level Functional Independence Measure (FIM) score based on 18 items each rated from 1 to 7 resulting in a total score between 18 and 126; a FIM-score exceeding 108 is considered good outcome.<sup>14</sup> The Extended Glasgow Outcome Scale was also performed.<sup>15</sup>

#### 1.5. Treatment of victims with spontaneous circulation

Seven victims were taken by ambulances to four different nearby hospitals for rewarming and observation (Table 1).

#### 1.6. Statistical analysis

Unless otherwise stated, values are expressed as median and ranges. Comparisons between the groups with and without circulatory arrest were done with the nonparametric Mann–Whitney rank test for continuous variables and chi square test for categorical variables. A  $p$ -value  $< 0.05$  was considered statistically significant. Statistical analyses were carried out using IBM SPSS version 20.

## 2. Results

Among the seven victims with circulatory arrest the first recorded temperature was a median of 18.4 °C (15.5–20.2 °C). All victims were pulseless with dilated pupils unresponsive to light (Table 1). Arterial blood gases analysed according to the Alpha-Stat principle demonstrated severe metabolic acidosis in all with a median pH of 6.61 (6.43–6.94), and lactate concentration a median of 21.0 mmol/l (9.4–24.0 mmol/l) (Table 1 and Fig. 2A). Six victims were weaned from ECMO when return of spontaneous circulation had been established and the core body temperature was a median of 33.5 °C (31.4–35.4 °C) (Table 1). No victims had hyperkalemia on admission. Several of the victims had a moderate increase of creatine kinase, creatine kinase MB, S-creatinine, P-alanine transaminase, and anti-thrombin III (Table 2). The increase was generally transient with near normalisation in most within 1 week. No victims needed dialysis, and no victims developed multiple organ failure. Two victims developed respiratory failure. One (victim #7) was maintained on ECMO for two days for this reason, the other needing prolonged ventilatory support and tracheostomy.

The victims that survived the accident without circulatory arrest were predominantly females and had a higher body mass index, and a higher first recorded body temperature of a median of 34.2 °C (23.0–37.5 °C) (Table 2). One victim (#9) arrived unconscious with a core temperature of 23.0 °C and in respiratory distress with a  $p\text{CO}_2$  of 9.98 kPa. The victim was sedated, intubated and subsequently extubated following 6.5 h of ventilation and rewarming, and was discharged from hospital after three days. Several of the victims without circulatory arrest had elevations of creatine kinase and myoglobin (Table 2).

#### 2.1. Neurophysiological testing and neuroimaging in the circulatory arrest victims

Though electroencephalography was severely abnormal in all, none of the investigations suggested status epilepticus and no focal abnormalities were described. Somatosensory evoked potentials were bilaterally present in all though cortical transit times were prolonged (median 27.3 ms (range 25.0–36.0 ms)).

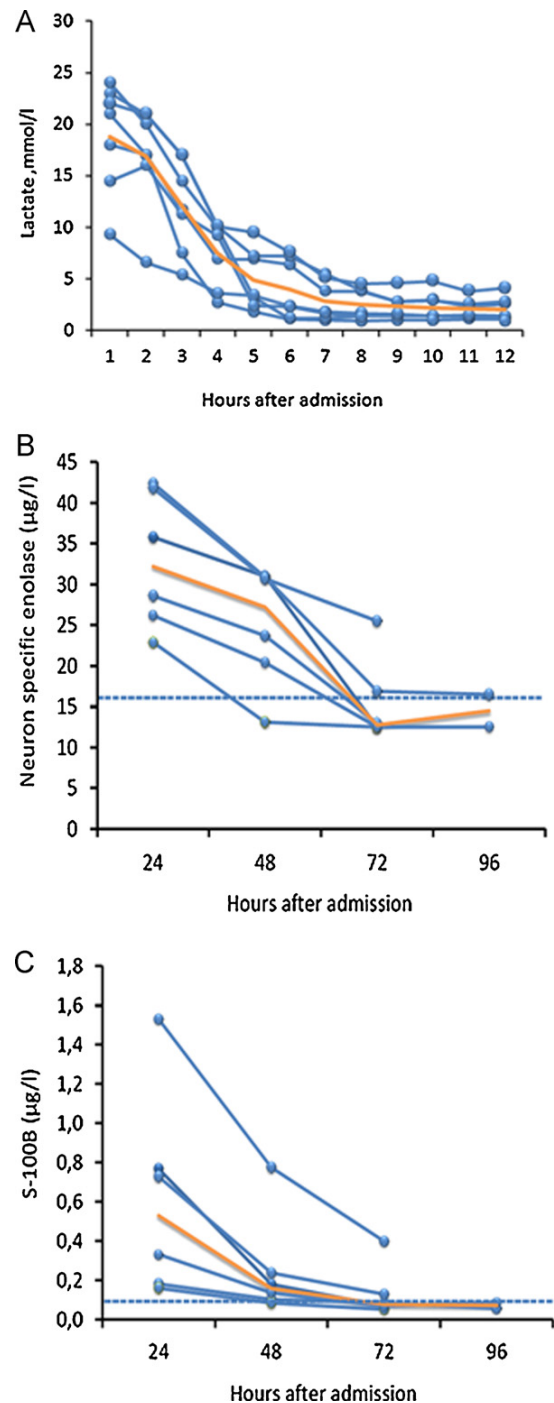


Fig. 2. Time course of (A) arterial blood lactate admission in the group with prolonged circulatory arrest; (B) neuron specific enolase; and (C) protein S100B (B) in 6 victims with circulatory arrest. Dotted lines denote upper limits of normal, orange line median.

Biomarkers for neural damage were increased in all subjects with an early peak NSE of  $33 \mu\text{g l}^{-1}$  ( $23\text{--}42 \mu\text{g l}^{-1}$ ) and a peak S100B of  $0.75 \mu\text{g l}^{-1}$  ( $0.18\text{--}1.53 \mu\text{g l}^{-1}$ ) (Fig. 2B). All cerebral computed tomography scans were normal. MRI performed 7 (7–26) days after admission was normal in three victims. The remaining had hyperintense signal in the nucleus lentiformis (two victims), in the crus posterior of capsula interna (one victim), and in the nuclei

**Table 2**

Time course of creatine kinase, creatine kinase MB, myoglobin, S-creatinine, P-alanintransaminase, and anti-thrombin III during hospitalisation in the group with and without circulatory arrest.

Test	Day 1	Day 2	Day 5	Day 7
Creatine kinase, $\mu\text{g l}^{-1}$				
No circulatory arrest	208 (119–286)	5178 (1730–11720)	ND	ND
Circulatory arrest	1590 (783–1934)	3189 (1750–3973)	1863 (649–1881)	758 (140–1917)
Creatine kinase MB, $\mu\text{g l}^{-1}$				
No circulatory arrest	ND	ND	ND	ND
Circulatory arrest	40 (15–68)	79 (35–144)	8 (5–9)	7 (4–8)
Myoglobin, $\mu\text{g l}^{-1}$				
No circulatory arrest	949 (584–4254)	209 (105–1306)	ND	ND
Circulatory arrest	3008 (1072–7146)	1330 (448–2361)	289 (156–423)	168 (64–220)
S-creatinine, $\mu\text{mol/l}$				
No circulatory arrest	55 (48–73)	64 (55–108)	ND	ND
Circulatory arrest	57 (38–66)	75 (41–111)	67 (51–144)	48 (38–127)
P-alanintransaminase, U/l				
No circulatory arrest	25 (20–56)	51 (23–191)	ND	ND
Circulatory arrest	407 (260–788)	334 (194–626)	190 (93–230)	142 (88–228)
Anti thrombin III, $\times 10^3$ IU/l				
No circulatory arrest	0.74 (0.73–0.99)	0.88 (0.75–1.18)	ND	ND
Circulatory arrest	0.72 (0.51–0.84)	0.66 (0.59–0.73)	0.67 (0.50–0.81)	1.06 (0.97–1.18)

Data are median and range. ND, not done.

lentiformis-caudatus, and in the thalami (one victim). This latter victim (#1 Table 1) demonstrated progressive abnormalities and atrophy on follow-up MRI; all other abnormalities in the remaining victims had resolved at follow-up (Fig. 3). MRI of the spine revealed a transient hyperintensity in two victims.

Magnetic resonance spectroscopy was normal in the two victims who had no or very minor cerebral imaging abnormalities. The remaining five victims demonstrated a pattern of partially transient neuronal injury, followed 6 months later by signs of membrane injury and gliosis (Table 3). Lactate or other signs of severe global diffuse tissue injuries were absent at the initial examination, but two victims showed elevated lipids and macromolecules in the nucleus lentiformis at follow-up consistent with partial necrosis.

After transfer to neurorehabilitation all seven victims suffered disturbed day/night cycles, one developed a psychosis and one developed epilepsy. Initial physical disabilities were primarily due to a distal symmetric sensorimotor polyneuropathy in the extremities, and all suffered severe neuropathic pain. With rehabilitation, all regained truncal stability and walking ability. One victim had a percutaneous endogastric feeding tube inserted due to impairment of swallowing reflexes. At discharge after 3–7 months physical disabilities mainly of the upper extremities persisted in all. One victim has started high-school with special support and 5 victims receive intensive cognitive training before restarting school. One victim requires neurorehabilitation in a 24 h institution.

Median FIM-score after 6 months was 115 (range 51–121) and was more than 108 in six victims. Extended Glasgow Outcome

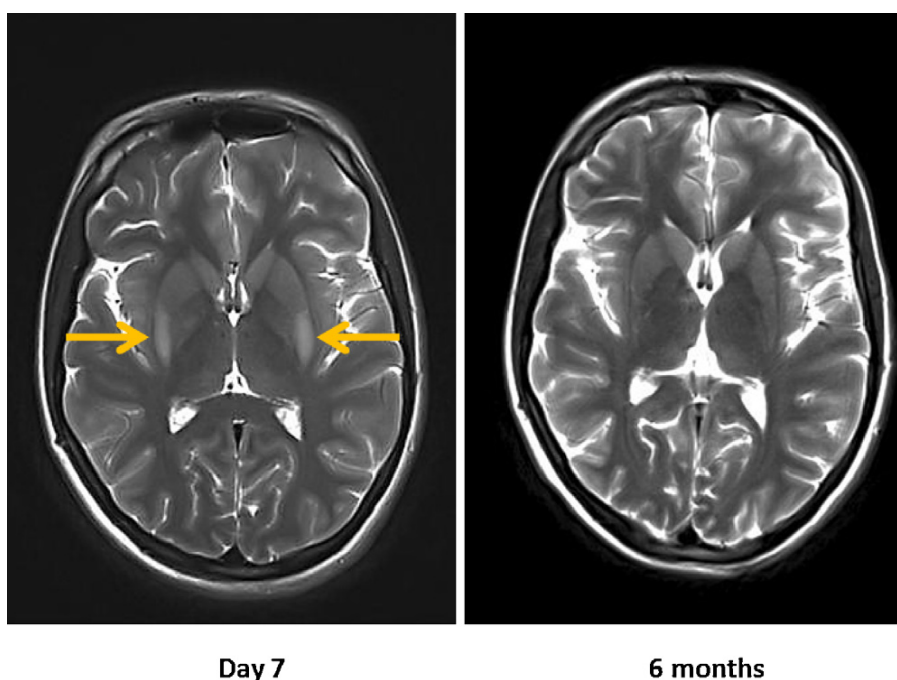


Fig. 3. Representative example of hyperintensities on magnetic resonance in basal ganglia that resolved at 6 months follow-up.



**Table 3**

Results of proton magnetic resonance spectroscopy at baseline and at follow-up in the seven patients with initial circulatory arrest.

	Baseline (n = 7)	Half year follow-up (n = 7)
Parietal white matter		
NAA/tCr decreased	1	0
tCho/tCr increased	0	4 <sup>a</sup>
ml/tCr increased	0	2
Lip + MM	0	0
Occipital gray matter		
NAA/tCr decreased	4 <sup>b</sup>	0
tCho/tCr increased	1	0
ml/tCr increased	0	1
Lip + MM	0	0
Nucleus lentiformis gray matter		
NAA/tCr decreased	3	1
tCho/tCr increased	0	2
ml/tCr increased	0	3
Lip + MM	0	2

Typical abnormalities after insults are counted. Decreased N-acetylaspartate to total creatine ratio (NAA/tCr) suggest neuronal damage or dysfunction, elevated total choline to total creatine ratio (tCho/tCr) signifying loss of membrane integrity, elevated myo-Inositol to total creatine ratio (ml/tCr) suggest gliosis, and elevated lipids and macromolecules (Lip + MM) indicating necrosis.

<sup>a</sup> Median 29% increased, range 12–40% increased.

<sup>b</sup> Median 20% decreased, range 16–25% decreased.

Scale score median was 4 (range 3–7). The subject (#1, Table 1) with worst outcome had a FIM-score of 51 and Extended Glasgow Outcome Scale score of 3 after 6 months.

In the group that did not develop circulatory arrest initial confusion and transient muscle pain was frequently seen. Two victims had minor symmetric and distal sensorineural polyneuropathies. No major cognitive deficits were seen at follow-up, although several developed posttraumatic stress syndrome.

### 3. Discussion

The present analysis of a boating accident involving 13 teenagers and 2 adults provides a unique insight into the development of accidental profound hypothermia and 6-month outcomes. As opposed to previously reported individual case reports/case series, this report is able to describe an entire population, minimizing publication bias. In the group with circulatory arrest a regimen of extracorporeal rewarming followed by therapeutic hypothermia and normothermia with sedation and supportive ventilation, led to an acceptable clinical outcome in more than 80% of cases with no deaths despite profound hypothermia and circulatory arrest for as long as 2.5 h in several victims.

Although all victims were immersed at the same time, the degree of hypothermia varied significantly. Previous studies, often dating several decades back have demonstrated that immersion in cold water is associated with “cold shock” where the immediate cooling of the skin is associated with uncontrollable hyperventilation, panic and lack of coordination with an immediate risk of drowning.<sup>16–18</sup> After respiration has adapted, further cooling will depend on a complex interplay of water temperature, water convection, body fat, body surface area, clothing, and fitness level.<sup>19</sup> If swimming is attempted in cold water heat loss will be accelerated due to increased blood flow, especially in the upper extremities where tissue insulation is poor.<sup>20</sup> In this reported population, fitness level and clothing were similar, and all attempted to swim ashore. However, there was a striking difference in the gender mix and outcome, with predominantly males developing profound hypothermia with circulatory arrest, while females seemed to be less susceptible to developing profound hypothermia. The higher body fat percentage in females likely protected against extreme

hypothermia. This is further supported by the higher body mass index in the group that did not develop circulatory arrest. It has been generally assumed that healthy subjects only are able to swim for a short time in water below 5 °C before being incapacitated by the cold.<sup>16,17</sup> It is therefore remarkable that four individuals managed to swim 500 m in the 2 °C cold water before reaching the shore and that one subsequently was able to alert the emergency services.

The management of victims with extreme hypothermia and circulatory arrest is generally based on expert consensus rather than evidence from trials. In all of our victims with circulatory arrest extracorporeal rewarming was performed according to recommendations.<sup>1</sup> When return of spontaneous circulation was achieved therapeutic hypothermia was maintained for 24 h, followed by a further 48 h of sedation and supportive ventilation at normothermia. This was done in an attempt to avoid increased metabolic demands due to hyperthermia, pain, and agitation, which in theory could further aggravate hypoxic brain damage. Although no definite conclusions can be drawn from the present study it is remarkable that none of the victims managed this way developed multiple organ failure or generalised oedema. This suggests that circulatory arrest was most likely due to hypothermia rather than asphyxia (due to saltwater aspiration).

The physical and cognitive effects of hypothermia described in this report are a result of its effects on peripheral nerves, and of cerebral anoxia. Victims with moderate to profound hypothermia but without circulatory arrest all complained of transient muscle pains possibly as a result of rhabdomyolysis. In the group with circulatory arrest, all had clear signs of peripheral nerve lesions especially in the upper extremities. This was likely due to hypothermia's effects on relatively unprotected superficial nerves in the upper extremities, exacerbated by increased heat loss from limb use during swimming, which may have led to more extreme cooling of limbs and consequently peripheral nerve lesions.

MRI and spectroscopy at baseline were remarkably close to normal considering the extended duration of circulatory arrest. None of the findings were consistent with unquestionable poor outcomes. The magnetic resonance spectroscopy provided insights to the initial and more permanent neuro metabolic changes due to circulatory arrest. In the acute phase reversible neuronal abnormalities in grey matter and the nucleus lentiformis dominated. Mild white matter abnormalities that were suggestive of membrane changes and gliosis were noted at follow-up imaging at 6 months. The pattern of NSE and S100B release suggested cerebral damage, although the concentrations were generally lower than what has been reported in victims resuscitated from out of hospital cardiac arrest.<sup>10,11</sup> These findings support the concept of hypothermia's protective effects on the hypoxic brain.

Prognostication in this small group of seven patients proved to be difficult. MRI and spectroscopy during hospitalisation did identify patients with normal or near normal examinations and a good cerebral outcome as well as the patient with abnormal imaging results and ultimately severe mental disability. There was significant overlap however; no baseline investigation performed during the initial phase of intensive care treatment predicted 6-month outcome.

In summary the present report demonstrates that despite severe metabolic derangement, extreme hypothermia and circulatory arrest for up to 2.5 h, a management regimen including extracorporeal rewarming followed by therapeutic hypothermia, 48 h normothermia with sedation and supportive ventilation and intensive neurorehabilitation led to 100% survival and only 1/7 victims with severe cognitive impairment. Furthermore seven hypothermic victims with core temperature as low as 23 °C (predominantly females) survived without having experienced circulatory arrest. It must be stressed, however, that this report is based on a tragic

accident with the loss of one life and various degrees of deficits in the survivors, including an on-going need for support for some.

### Conflict of interest statement

No conflict of interest exists for any of the authors.

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*Contributors:* Michael Wanscher contributed for the drafting of manuscript, participation in the collection of data; analysis and interpretation of data; critical revision of manuscript for important intellectual content; and final approval of the manuscript submitted. Lisbeth Agersnap, Jørgen Feldbæk Nielsen, Christian Hassager and Else R. Danielsen contributed for the collection of data; analysis and interpretation of data; critical revision of manuscript for important intellectual content; and final approval of the manuscript submitted, and Jesper Ravn, Stig Yndgaard, Bertil Romner, Carsten Thomsen, Steen Barnung, Anne Grethe Lorentzen, Hans Høgenhaven, and Matthew Davis contributed for the collection of data; critical revision of manuscript for important intellectual content; and final approval of the manuscript submitted while Jacob Eifer Møller prepared the first draft of manuscript, collection of data; analysis and interpretation of data; critical revision of manuscript for important intellectual content; and final approval of the manuscript submitted.

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