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CLINICAL PAPER

# Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest<sup>☆</sup>

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Received 29 June 2006; received in revised form 10 August 2006; accepted 15 August 2006

## KEYWORDS

Heart arrest;  
Cardiopulmonary  
resuscitation;  
Therapeutic  
hypothermia;  
Angioplasty;  
Survival

## Summary

**Background:** Mortality among patients admitted to hospital after out-of-hospital cardiac arrest (OHCA) is high. Based on recent scientific evidence with a main goal of improving survival, we introduced and implemented a standardised post resuscitation protocol focusing on vital organ function including therapeutic hypothermia, percutaneous coronary intervention (PCI), control of haemodynamics, blood glucose, ventilation and seizures.

**Methods:** All patients with OHCA of cardiac aetiology admitted to the ICU from September 2003 to May 2005 (intervention period) were included in a prospective, observational study and compared to controls from February 1996 to February 1998.

**Results:** In the control period 15/58 (26%) survived to hospital discharge with a favourable neurological outcome versus 34 of 61 (56%) in the intervention period (OR 3.61, CI 1.66–7.84,  $p=0.001$ ). All survivors with a favourable neurological outcome in both groups were still alive 1 year after discharge. Two patients from the control period were revascularised with thrombolytics versus 30 (49%) receiving PCI treatment in the intervention period (47 patients (77%) underwent cardiac angiography). Therapeutic hypothermia was not used in the control period, but 40 of 52 (77%) comatose patients received this treatment in the intervention period.

**Abbreviations:** BE, base excess; ED, emergency department; IABP, intra-aortic balloon pump; ICU, intensive care unit; PCI, percutaneous coronary intervention; ROSC, return of spontaneous circulation; SEP, somatosensory evoked potentials; STEMI, ST-elevation myocardial infarction; Volume, colloids and cristalloids

<sup>☆</sup> A Spanish translated version of the summary of this article appears as Appendix in the final online version at [10.1016/j.resuscitation.2006.08.016](http://10.1016/j.resuscitation.2006.08.016).

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*Conclusions:* Discharge rate from hospital, neurological outcome and 1-year survival improved after standardisation of post resuscitation care. Based on a multivariate logistic analysis, hospital treatment in the intervention period was the most important independent predictor of survival.

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## Introduction

Despite science based guidelines for cardiopulmonary resuscitation (CPR),<sup>1</sup> the survival rate after out-of-hospital cardiac arrest (OHCA) has not improved much over the last decade.<sup>1,2</sup> The guidelines focus mainly on treatment until return of spontaneous circulation (ROSC), due to scarcity of studies on the post resuscitation period.<sup>1</sup> Therapeutic hypothermia is reported to improve survival and neurological outcome in patients with ventricular fibrillation.<sup>3,4</sup> Two non-intervention cohort studies reported significant inter-hospital differences in survival (for those admitted with ROSC) that could not be explained by pre-hospital factors.<sup>5,6</sup> In-hospital body temperature, seizures, blood glucose and base excess were related to outcome.<sup>6</sup>

In Oslo, survival of those admitted to the intensive care unit (ICU) with ROSC has stayed at 25–35%,<sup>6–8</sup> similar to the 30% reported in 22,105 patients in UK,<sup>9</sup> but lower than the 56% reported in Stavanger,<sup>6</sup> with the best reported survival rate in Europe.<sup>10</sup>

Based on the assumption that in-hospital factors could be important, we designed a standardised treatment protocol including therapeutic hypothermia, percutaneous coronary intervention (PCI) – if indicated – and standardised goals for factors such as blood glucose, haemodynamics, ventilation and handling of seizures. With focus on better care and improved survival for OHCA patients admitted to hospital, this was implemented into our hospital system. Since it was a multivariate systems approach, patients could not be randomised to either receive the required treatment or not in the emergency department (ED) and intensive care unit (ICU). The results were therefore compared to patients admitted to Ullevål University Hospital (Ullevål) in a recently published study from the preceding period.<sup>6</sup>

## Patients and methods

The Norwegian Board of Health, Norwegian Social Science Data Service and Regional Committee for Medical Research Ethics approved the study.

## Organisation

Oslo has approximately 540,000 inhabitants. The Oslo EMS system is described elsewhere.<sup>6–8</sup> Approximately 70% of cardiac arrest patients with ROSC from Oslo EMS are admitted to Ullevål. Ullevål has approximately 45,000 patients admitted per year. It has 40 ICU beds distributed amongst seven ICUs, of which five ICUs cared for cardiac arrest patients in 1996–1998 compared to two in 2003–2005. In 2003–2005 a PCI service was available 24 h a day.

## Patients

All patients with sustained ROSC in the ED after OHCA of cardiac aetiology (using the Utstein style definition),<sup>11</sup> and admitted to the ICUs of Ullevål between September 1st 2003 and May 18th 2005 were included in the study. Patients were identified from continuous ED and ICU registrations, and double checked via the computerised hospital register. Patients were followed until in-hospital death or discharge from the final hospital or institution. These patients were compared to all patients admitted to Ullevål in a previously published study of post resuscitation treatment from February 1996 to February 1998.<sup>6</sup> The previous files and records were carefully re-examined.

## Outcome

Primary outcome was survival to hospital discharge with favourable neurological outcome. This was defined as the cerebral performance category (CPC) 1 (good recovery) or 2 (moderate disability) assessed from discharge or death note in the final acute care hospital/institution.<sup>11</sup> Survival to hospital discharge required that transferred patients were alive when discharged from the final hospital/institution. Secondary outcome was 1-year survival, collected from the Norwegian National Register/Death Register.

The standardised intensive care management incorporated several specific treatment goals and strategies (Appendix A), including treating the cause of arrest (PCI if indicated), initiation of

early therapeutic hypothermia (as early as possible after arrival in the ED), and strict control of haemodynamics, blood glucose and ventilation (see [Appendix A](#)). A new data collection sheet, including documentation of complications, was designed and introduced. Standard in-hospital data were collected from patient records, including those from the final hospital or institution if the patient was transferred.

## Implementation

With the overall goal of improving patient survival and quality of life, a strategic implementation plan was constructed. Barriers and critical factors were identified, and important partnerships were built with the relevant doctors, ICU nurses and administrators. A standardised post resuscitation treatment protocol (see [Appendix A](#)) was created and handed out to all involved doctors and nurses, presented at internal meetings and implemented during spring/summer of 2003. The protocol and relevant important publications were available at the ICUs involved.

## Statistical analysis

Statistics were performed with SPSS (SPSS Inc, Chicago, IL, USA). Numerical data were analysed using Students *t*-test (presented as mean  $\pm$  S.D.), or if not normally distributed with the Mann–Whitney test (presented as median with interquartile range). Proportions were analysed by the Pearson  $\chi^2$  test with Yates continuity correction or, where appropriate (in the presence of small numbers in either group), Fisher's exact test. We present odds ratio (OR) with 95% confidence intervals (95% CI) for the difference between proportions, and the mean difference with 95% CI for parametric comparison between groups. *p*-Values less than 0.05 are regarded as significant.

Prognostic factors that were found to be significant in preliminary bivariate analyses were included in a multivariate logistic regression analysis (dependent variable – survival outcome 0 = unfavourable, 1 = favourable). All variables were entered into the equation simultaneously in order to control for the effects of confounding (a subsequent stepwise analysis provided similar results). The OR with 95% CI was used to indicate a significant association (95% CI that exclude the value 1.0 are considered statistically significant). The Hosmer–Lemeshow goodness-of-fit statistic indicates a poor fit if the resulting significance value is less than 0.05.

## Results

### Patients admitted to Ullevål ICU

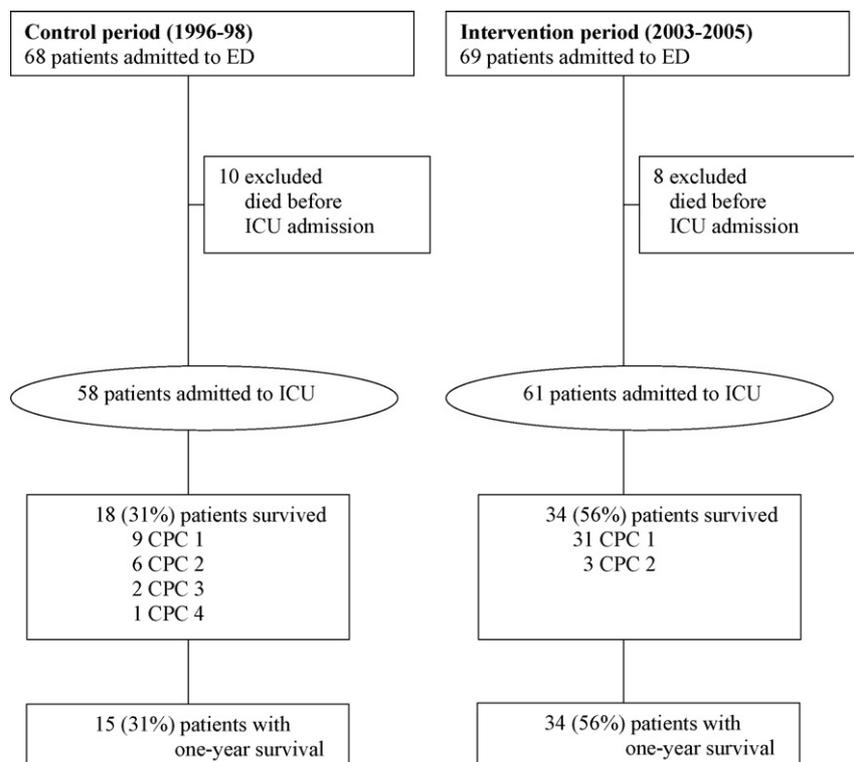
During the 20.5 months intervention period 61 patients with OHCA of cardiac aetiology were admitted to ICU with ROSC versus 58 in the 24 months control period ([Figure 1](#)). All survivors with a favourable neurological outcome in both groups were still alive 1-year after discharge ([Figure 1](#), [Table 1](#)).

Significantly more patients survived with a favourable outcome in the intervention period compared to the control period; 34 of 61 (56%) versus 15 of 58 (26%),  $p < 0.001$  ([Table 2](#)). Mean age ( $63 \pm 14$  versus  $68 \pm 12$ ,  $p = 0.008$ ) and proportion of patients younger than 70 years were lower in the intervention period than in the control period ([Table 1](#)) with no other significant differences in prognostic prehospital or admission variables ([Table 1](#)). Physiological variables on admission including body temperature, blood glucose, blood gases and blood pressure did not differ except there was a lower pulse rate in the intervention period ([Table 2](#)).

Of the in-hospital physiological variables ([Table 2](#)) and interventions ([Table 3](#)) the intervention group had a reduced level of blood glucose, temperature and pulse rate after 12 and 24 h, a more positive fluid balance and increased use of inotropic agents, intra-aortic balloon pump and insulin. There was no difference in the duration of mechanical ventilation or stay in ICU between the two periods ([Table 1](#)).

### Specific cardiac treatment

The proportion of patients with acute myocardial infarction (AMI) was similar in the two periods ([Table 1](#)). Only two control period patients (3%) received reperfusion treatment (with thrombolytics) ([Table 3](#)). In the intervention period 47 patients (77%) had coronary angiography and 30 (49%) received PCI with stent placement ([Table 3](#)). These 47 patients also received 300 mg acetylsalicylic acid (oral/rectal) and 5–10,000 IU heparin before angiography; 33 (54%) received clopidogrel and nine (15%) abciximab after the procedure. Three underwent acute coronary bypass surgery (all three survived) in the intervention period versus none in the control period. The main artery occluded was the left anterior descending in 16 patients, the right coronary artery in 10 and the circumflex in 11. Some patients had more than one artery involved. In 74% of the patients from the intervention period coronary artery disease was documented.



**Figure 1** Flow chart for patients admitted to Ullevål University Hospital with out-of-hospital cardiac arrest of cardiac aetiology in the control and intervention period.

### Therapeutic hypothermia

No control period patient was treated with therapeutic hypothermia compared to 40 of the 52 (77%) comatose patients in the intervention period (Table 3). Several cooling methods were used; 29 (73%) received endovascular cooling with Coolgard

(Alsius Corporation, CA, USA) alone or combined with initial ice cold fluids and ice packs. External cooling with Arctic Sun (Medivance, CO, USA) or just icepacks and wet, cold blankets was used if Coolgard was unavailable. The mean time from cardiac arrest until the target temperature was achieved ( $33^{\circ}\text{C}$ ) was  $5.5\text{ h} \pm 2.2\text{ h}$ . This was sig-

**Table 1** Univariate analysis of prognostic factors and outcome data for patients admitted to ICU of Ullevål University Hospital in the control (1996–1998) or intervention (2003–2005) periods, presented as absolute numbers (percentage) or median values with interquartile range

	Control period ( <i>n</i> = 58)	Intervention period ( <i>n</i> = 61)	OR (95% CI)	<i>p</i> -Value
Male	46 (79)	50 (82)	1.2 (0.5, 2.9)	0.89
Age < 70	28 (48)	43 (71)	2.6 (1.2, 5.4)	0.022
Witnessed	55 (95)	60 (98)	3.3 (0.33, 32.4)	0.36
Bystander CPR	43 (74)	43 (71)	0.8 (0.4, 1.9)	0.81
Initial VF	49 (84)	55 (90)	1.7 (0.6, 5.1)	0.51
Ambulance response time (min)	6 (4–9)	6 (4–8)		0.70 <sup>a</sup>
Time to ROSC (min)	18 (13–22)	18 (10–27)		0.98 <sup>a</sup>
Comatose on admission	52 (90)	52 (85)	1.2 (0.5, 2.8)	0.65
Myocardial infarction	33 (57)	36 (59)	1.1 (0.5, 2.3)	0.82
Mechanical ventilation (days)	2 (1–5)	2 (1–5)		0.70 <sup>a</sup>
Stay at ICU (days)	4 (3–6)	5 (2–8)		0.49 <sup>a</sup>
Survival to discharge	18 (31)	34 (56)	2.80 (1.32, 5.93)	0.007
Favourable outcome (CPC 1–2)	15 (26)	34 (56)	3.61 (1.66, 7.84)	0.001
1-Year survival	15 (26)	34 (56)	3.61 (1.66, 7.84)	0.001

<sup>a</sup> Two sided *p*-values for continuous variables from Mann–Whitney rank sum test.

**Table 2** Physiological variables on hospital admission and during the first 24 h in the control (1996–1998) and intervention (2003–2005) periods

	Control period (n = 58)	Intervention period (n = 61)	Mean difference (95 CI)	p-Value
Blood sugar (mmol/l)				
Admission	14.3 ± 4.5	14.3 ± 4.9	0.05 (−1.98, 2.08)	0.96
After 12 h	9.7 ± 3.3	8.0 ± 3.5	−1.69 (−3.25, −0.14)	0.033
After 24 h	7.5 ± 2.7	6.4 ± 1.6	−1.16 (−2.19, −0.15)	0.028
pCO <sub>2</sub> (kPa)				
Admission	5.3 ± 2.4	5.4 ± 1.5	0.09 (−0.78, 0.95)	0.84
After 12 h	5.6 ± 1.4	5.2 ± 0.7	−0.34 (−0.83, 0.14)	0.17
After 24 h	5.3 ± 0.9	5.3 ± 0.6	0.05 (−0.30, 0.40)	0.77
BE (mmol/l)				
Admission	−10.3 (−15.2, −5.5)	−8.5 (−12.3, −5.8)		0.20 <sup>a</sup>
After 12 h	−5.5 (−7.1, −3.0)	−3.2 (−6.7, −2.1)		0.077 <sup>a</sup>
After 24 h	−2.5 (−4.5, −0.4)	−3.2 (−6.4, −1.2)		0.10 <sup>a</sup>
Temperature (°C)				
Admission	35.9 ± 1.0	35.4 ± 1.3	−0.48 (−1.02, 0.07)	0.087
After 12 h	37.5 ± 1.1	33.9 ± 1.7	−3.64 (−4.21, −3.07)	<0.001
After 24 h	38.4 ± 1.3	34.0 ± 1.9	−4.41 (−4.99, −3.81)	<0.001
MAP (mmHg)				
Admission	90 ± 22	89 ± 23	−0.92 (−9.37, 7.53)	0.83
After 12 h	76 ± 10	73 ± 11	−3.54 (−7.80, 0.72)	0.10
After 24 h	77 ± 13	74 ± 10	−2.96 (−7.74, 1.81)	0.22
Pulse rate (min <sup>−1</sup> )				
Admission	101 ± 23	88 ± 22	−12.56 (−21.26, −3.85)	0.005
After 12 h	85 ± 14	67 ± 13	−18.91 (−24.45, −13.38)	<0.001
After 24 h	87 ± 16	68 ± 15	−19.08 (−25.33, −12.83)	<0.001

Data are presented as mean ± S.D., except for BE where median values with interquartile range is used; conversion factor for blood sugar concentration: 1 mmol/l = 18 mg/dl; conversion factor for pCO<sub>2</sub>: 1 kPa = 7.5 mmHg.

<sup>a</sup> Two sided p-values for continuous variables from Mann–Whitney rank sum test.

nificantly faster in the 25 patients (63%) who received cold fluids i.v. (mean 4.6 h ± 1.3 h versus 7.3 ± 3.0 h, *p* = 0.001). Twenty-seven (68%) of the cooled patients were paralysed.

### Factors associated with survival

Prognostic factors that were found to be significant in preliminary bivariate analyses (case/control, age, time to ROSC, ambulance response time,

initial VF) were included in the multivariate logistic regression analysis (Table 4). The Hosmer–Lemeshow goodness-of-fit statistic indicates a poor fit if the resulting significance value is less than 0.05. The model presented here achieved a  $\chi^2$  of 10.65 on 8 degrees of freedom, and a *p*-value of 0.22; thus the model adequately fits the data.

The logistic analysis revealed that favourable outcomes (an increased likelihood of survival) were

**Table 3** Inhospital treatment in the control (1996–1998) and intervention (2003–2005) periods, presented as absolute numbers (percentage) or mean ± S.D. (fluid balance)

	Control period (n = 58)	Intervention period (n = 61)	OR (95% CI)	p-Value
Reperfusion treatment	2 (3)	30 (49)	27.10 (6.06, 121.09)	<0.001 <sup>a</sup>
Therapeutic hypothermia	0	40 (66)	n.a.	<0.001 <sup>a</sup>
Inotropic agents	29 (50)	43 (80)	2.39 (1.13, 5.08)	0.022
Intra aortic balloon pump	0	8 (15)	n.a.	0.006 <sup>a</sup>
Glyceryl trinitrate	31 (53)	0	n.a.	<0.001 <sup>a</sup>
Fluid balance 1st day (ml)	2300 ± 1211	3455 ± 1594		<0.001 <sup>b</sup>
Insulin	4 (7)	27 (44)	10.72 (3.45, 33.33)	<0.001 <sup>a</sup>

Reperfusion treatment was only by PCI in the intervention period and by thrombolytics in the control period. n.a. not applicable.

<sup>a</sup> Fisher's exact test.

<sup>b</sup> Two sided *p*-values for continuous variables from Student's *t*-test.

**Table 4** Prognostic factors that were found to be significant in preliminary bivariate analyses were included in a multivariate logistic regression analysis to detect independent factors potentially affecting survival with favourable outcomes (CPC 1 and 2) from both the control (1996–1998) and intervention (2003–2005) periods

Prognostic factors	Adjusted odds ratio	95% CI
Intervention period	4.47	1.60–12.52
Age >70	0.48	0.17–1.37
Time to ROSC	0.91	0.85–0.96
Ambulance response time	0.91	0.78–1.07
Initial VF	1.84	0.33–10.41

All variables were entered into the equation simultaneously in order to control the effects of confounding (a subsequent stepwise analysis provided similar results).

associated with: being in the intervention group, being 70 years of age or younger, shorter time to ROSC, shorter ambulance response time, and an initial rhythm of VF. In addition to in-hospital treatment, age under 70 was the only factor that varied between the two periods (Table 1). However, only assignment to the intervention/control group and time to ROSC retained their statistical significance, controlling for the effects of the other prognostic variables.

## Complications

There was no difference in general or more specific complications between the two periods (Table 5). Bleeding was not looked for in the control period. Minor bleeding was reported in 5 (9%) patients in the intervention period (Table 5). Three of the 15 patients (20%) with arrhythmias from the intervention period had bradyarrhythmias (all cooled). One required a temporary pacemaker and another an isoprenaline infusion because of their sustained bradycardia (<40 min<sup>-1</sup>).

One patient in the intervention period survived (with CPC 1) despite severe status epilepticus that was treated with a barbiturate infusion from days 9 to 12 after his cardiac arrest.<sup>12</sup>

## Discussion

The 56% survival to hospital discharge with favourable neurological outcome and 1-year survival among OHCA patients admitted to ICU is high compared to our previous results<sup>6–8</sup> and those results reported from other institutions.<sup>5,9,13–16</sup> The value of the CPC score on hospital discharge as an indicator of quality of life and cognitive function later in life has been questioned,<sup>17</sup> but is still the standard evaluation tool recommended in the last ILCOR scientific statement for reports on cardiac arrest.<sup>18</sup> It was used identically in both study periods, and in the intervention period all hospital survivors were discharged to their homes, able to manage daily life activities or work on their own and were alive 1-year later.

It is unlikely that the control period was associated with an unrealistically poor outcome. The 31% survival of those admitted to ICU in the control period was better than the average of 25% during the preceding 30 years.<sup>8</sup> Patients from the intervention period were younger, reported by some to be associated with improved survival,<sup>6,13,19,20</sup> while others have failed to find such an association.<sup>14</sup> However, in both groups the mean age was below 70 years, which previously has been used as a age variable.<sup>6,13,14</sup>

Several new interventions and general treatment strategies were included in the new standardised post resuscitation care, and we would like to highlight six factors:

1. *Hawthorne effect*. Increased focus, enthusiasm, and introduction of new treatment strategies generally improve quality and outcome in emer-

**Table 5** Number of complications (%) in the control (1996–1998) and intervention (2003–2005) periods

	Control period (n = 58)	Intervention period (n = 61)	OR (95% CI)	p-Value
General complications	37 (64)	44 (72)	1.47 (0.68–3.19)	0.44
Pneumonia	33 (57)	29 (48)	1.28 (0.69–2.40)	0.43
Sepsis	1 (1)	2 (3)	2.33 (0.21–26.21)	0.60
Severe arrhythmias	9 (16)	15 (25)	1.90 (0.80–4.53)	0.14
Brady-arrhythmias	0	3		
Tachy-arrhythmias	9	12		
Seizures	16 (28)	11 (18)	0.63 (0.28–1.39)	0.34
Status epilepticus	3 (5)	5 (8)	1.98 (0.46–8.56)	0.47

Pulse rate >120 min or <40 min lasting for > 5 min was defined as severe arrhythmias.

gency medicine as in other fields of society.<sup>21</sup> Before we initiated this new approach patients were admitted to five ICUs with no standardised treatment plan. One of our goals was to place the patients in two specialised ICUs, increase focus and create enthusiasm for the treatment with a true team effort from all involved doctors and nursing staff. This made a randomised design impossible; focus cannot be turned on and off.

2. *Early reperfusion treatment with PCI.* Despite the same proportion of patients with AMI in the two periods, 53% received reperfusion treatment in the intervention period versus 3% in the control period. Patients were transported directly from the ED for angiography if clinically stable. Coronary thrombi are frequently found after sudden cardiac death<sup>22</sup> and most cardiac arrest patients have coronary artery disease. AMI caused the arrest in 68% in a Swedish clinical study<sup>13</sup> and 78% in a Finnish autopsy study.<sup>23</sup> As 73% of the patients in the intervention period had coronary artery disease, early PCI seems reasonable.<sup>24</sup> We have reported previously a 73% 2-year survival in selected patients with PCI after out-of-hospital cardiac arrest.<sup>25</sup> During that study period (1998–2001) we had no standardised treatment protocol or therapeutic hypothermia, and the proportion of discharged patients with a favourable neurological outcome was approximately 70% (not published, data from the author), the same as in the control period of the present study.<sup>6</sup>

Seventeen patients (28%) brought to angiography underwent no PCI, but received antiplatelets and anticoagulation. These could have their own positive effects because of the coagulation disorder occurring after cardiac arrest.<sup>26</sup> Beta blockers, which have been associated with improved outcome,<sup>27</sup> were hardly used in the acute phase because the patients were relatively bradycardic (creating a similar effect to beta blockers) during therapeutic hypothermia.

3. *Therapeutic hypothermia* is reported to improve neurological outcome for comatose patients with initial VF.<sup>3,4</sup> We cooled comatose patients regardless of rhythm. It has been suggested that the earlier hypothermia is initiated and target temperature reached, the greater the chance of positive outcome.<sup>28</sup> The mean time to the target temperature of 5.5 h compares well with the 8 h reported in the HACA study,<sup>3</sup> but is longer than reported when all patients receive a rapid infusion of ice-cold saline,<sup>29</sup> (which also increased the rate of temperature fall in the

present study). The final maintenance cooling technique was established after ICU arrival and stabilisation, thus after coronary angiography in the majority of the patients. We emphasised early cooling with ice-cold fluids and ice packs after arrival in the ED, thus, patients could easily be cooled during angiography and the PCI procedure. The method for therapeutic hypothermia was not standardised as only one endovascular device (Coolgard, Alsios Corporation, CA, USA) was available initially, and the different methods were not compared. The external device used (Arctic Sun, Medivance, CO, USA) was available from June 2004.

As in the HACA study,<sup>3</sup> no significant difference in general complications was present and no patients died because of complications. Interestingly, in spite of therapeutic hypothermia, the total stay in the ICU and total duration of mechanical ventilation did not differ between the two periods. The number of pneumonias in the present material (for both periods) is higher than reported from the HACA study,<sup>3</sup> which may be caused by our rather wide pneumonia definition. We recorded pneumonia if it was present as a diagnosis on the final hospital record on discharge (or at death) due to clinical signs, chest X-ray and/or blood test. Although there was a lower pulse rate in the intervention period, and a relative bradycardia in the majority of the cooled patients, severe bradycardia (< 40/min) was only present in three cooled patients and was easy to treat.

4. *A standardised treatment protocol* was devised which defined the goals for factors generally of importance for critically ill patients. This protocol addressed a number of factors, including those suggested previously to be important for cardiac arrest patients: blood glucose, temperature, seizure treatment, PaCO<sub>2</sub> (Appendix A, Tables 2 and 3). Except for therapeutic hypothermia no such factors have been tested in cardiac arrest intervention studies. Non-intervention studies have shown increased mortality among patients with cardiac arrest with high levels of blood glucose during reperfusion,<sup>6,27,30</sup> and a linear correlation between blood glucose level and infarct size for patients with coronary artery disease.<sup>31</sup> Moreover, aggressive insulin treatment in patients with acute myocardial infarction<sup>32</sup> or critical illness<sup>33</sup> reduced long-term mortality. We also stressed avoiding hyperventilation, which might reduce cerebral perfusion.<sup>34</sup> Despite limited scientific basis the protocol enabled doctors and nurses to focus on how to monitor and treat the

patients in different circumstances (Appendix A).

5. *Maintenance of an adequate arterial blood pressure* was attempted without placing undue strain on the myocardium by requiring too high arterial blood pressure. Cerebral hypoperfusion<sup>35</sup> and impaired autoregulation<sup>36</sup> occur during reperfusion. Disturbed microcirculation,<sup>26</sup> myocardial dysfunction<sup>37,38</sup> and a "sepsis-like-syndrome"<sup>39</sup> suggest that haemodynamics should be optimised in this critical early phase. There was more frequent use of inotropic drugs and increased positive fluid balance in the intervention period to maintain MAP > 65–70 mmHg for the first days after admission. There are no studies showing the optimal arterial blood pressure in the reperfusion phase, although a short period with hypertension based on animal experiments has been recommended.<sup>40</sup> A higher blood pressure with a MAP 90–100 have been used by others.<sup>4</sup> We decided to choose a MAP > 65–70 mmHg as this was common in other European comparable hospitals and should give an adequate brain and coronary circulation.
6. *Prehospital CPR.* It is difficult to ascribe the improved results to the pre-hospital treatment, although it cannot be excluded. Based on a recently published study,<sup>41</sup> the Oslo EMS has (since 2001) treated all non-EMS witnessed arrests with 3 min CPR before (CPRfirst) and between defibrillation attempts. Among the 104 CPRfirst patients with initial VF, 58 patients (56%) were admitted to ICU with ROSC and 20 were discharged alive with a favourable neurological outcome (34% of those admitted).<sup>41</sup> In the present study, with the same prehospital CPR algorithm, 32 of 55 (58%) patients admitted after initial VF were discharged with a favourable outcome (OR 2.64, CI 1.23–5.66,  $p=0.012$ ). Thus, with no changes in the prehospital algorithms since 2001, post resuscitation care appears to have improved survival. However, since the local guidelines differed between 1996–1998 and 2003–2005, the quality of CPR may have influenced on the improved results and could indeed be a confounding factor.

## Limitations

The patients in this study could not be randomised as we sought information on possible effects of a systems approach with a focus on many new factors in post resuscitation treatment. Increased awareness and intended enthusiasm for

the new approach cannot be turned on and off, neither the reduced number of ICUs. The study was therefore designed according to standards for studies without internal controls described by Bailar et al.<sup>42</sup> It was outcome-based with a prospectively identified hypothesis that the new standardised treatment should increase survival. Data analysis with historic controls was planned early and defined, and the results would be of interest whether positive or negative.<sup>42</sup> Observational studies are also important and do not overestimate the magnitude of treatment effects.<sup>43</sup>

Secondly, there could be other subtle effects that could have influenced outcome. The only major difference in the patients between the two groups was the younger age in the intervention group, and although not reaching statistical significance as an independent predictor, younger age seems to correlate with improved outcome<sup>6,13,19,20</sup> and therefore might be a confounding factor.

The improved survival may of course also be a result of a total improvement across the entire chain of survival, and especially an improved quality of CPR with the different CPR algorithms (as already discussed). Protocols for termination of care, both in the field and in the ED, however, have not been changed in the two cohorts, and should not have influenced on the results.

Finally, the results from this single institutional outcome study in a relative homogenous population may not be generalisable.

## Conclusions

Survival to hospital discharge with good neurological recovery, and 1-year survival, in patients admitted to the ICU after OHCA of cardiac aetiology, improved after implementation of a standardised post resuscitation care treatment protocol in our hospital. This protocol included therapeutic hypothermia, PCI, and a focus on goal-directed treatment for the reperfusion period. Due to the study design a cause-and-effect relationship cannot be firmly established, but the results are encouraging.

## Conflicts of interest disclosures

Dr. Sunde has received research grants from Laerdal Foundation for Acute Medicine and Professor Steen is a member of the Board of Laerdal Medical.

## Acknowledgments

We are greatly indebted to MSc Mitchell Loeb (Sintef, Health Research, Oslo) for skilful help with the statistical analyses. This study was supported by grants from Laerdal Foundation for Acute Medicine, Ulleval University Hospital Scientific Advisory Council and Health Region East.

## Appendix A

The standardised treatment protocol for Ulleval University Hospital and important treatment factors.

Inhospital standardised treatment plan after ROSC at Ulleval University Hospital

Goal: to reduce the vital organ injuries (brain, heart), through:

1. Initial optimising haemodynamics and oxygenation
2. (a) Treat the cause of arrest; reperfusion (PCI) after STEMI and  
(b) Therapeutic hypothermia (33 °C in comatose patients for 24 h)  
Start as early as possible after decision making in the ED  
Initially 1-3 l of ice-cold 0.9% NaCl i.v. together with icebags  
Endovascular cooling/external cooling for maintenance after arrival at the ICU
3. A standardised treatment protocol for the following days
  - 3.1.
 

Factor	Goal	Strategy
Reperfusion	Reperfusion	PCI in STEMI
Blood pressure	MAP > 65–70 mmHg	Volume, vasopressors, inotropic agents, IABP
Central venous pressure	8–12 mmHg	Volume, glyceryl trinitrate, diuretics
ECG, rate/ischaemia	60–100/min	Volume, sedation, glyceryl trinitrate, beta-blocker (normally not indicated when using therapeutic hypothermia because of relative bradycardia)
Temperature	33 °C for 24 h	Initially icecold (4 °C) NaCl 0.9% i.v. and icepacks, then internal/external cooling device
Ventilator	SpO <sub>2</sub> 95–98 pCO <sub>2</sub> 5–6 kPa	Respiratory control, FiO <sub>2</sub> , PEEP (NB! Avoid hyperventilation)
Blood glucose	5–8 mmol/l	Actrapid-infusion (NB! Avoid hypoglycemia/hypokalemia)
Electrolytes	Normal values	Replacement/specific treatment
Haemoglobin	>9–10 g/dl	Transfusion if necessary
Diuresis	>1 ml/kg/h	Volume, diuretics or pressors
Buffers	pH > 7.1, BE > –10	When indicated, trometamol 125–250 ml i.v.
Seizures	Prevent/treat seizures	Increase sedation, or specific anticonvulsive medication EEG when indicated (early contact with a neurologist)
  - 3.2. Sedation  
Fentanyl and propofol (paralysis when indicated with cisatracurium/pancuronium)
  - 3.3. Monitoring  
Arterial catheter  
O<sub>2</sub>-saturation  
Continuous ECG  
Central venous line with central venous pressure  
Temperature (bladder)  
Arterial blood gases (pH, BE, pCO<sub>2</sub>, pO<sub>2</sub>)  
Blood glucose and electrolytes  
Echocardiography, chest X-ray  
EEG and SEP

## 3.4. Vasopressors/inotropic agents

First choice: dopamine  
(2–10 µg/kg/min)

If tachycardia, check volume status, or change to noradrenaline (norepinephrine) (0.02–0.3 µg/kg/min)

If pump failure/cardiogenic shock

IABP  
Dobutamine (2–10 µg/kg/min) and if necessary adrenaline (epinephrine) (0.02–0.3 µg/kg/min) (levosimendan as last resort)

## 3.5. Awakening protocol/respirator weaning

After 24 h of cooling, patients should be slowly rewarmed (0.5 °C/h). Sedation may be stopped after the body temperature has reached 35.5 °C. Extubation using normal indications. Avoid long term ventilator treatment (if no complications are present)

## References

- International Liaison Committee on Resuscitation 2005 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Resuscitation* 2005;67:157–341.
- Kern KB, Valenzuela TD, Clarke LL, et al. An alternative approach to advancing resuscitation science. *Resuscitation* 2005;64:261–8.
- The HACA Study Group Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002;346:549–56.
- Bernard S, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002;346:557–63.
- Engdahl J, Abrahamsson P, Bång A, Lindquist J, Karlsson T, Herlitz J. Is hospital care of major importance for outcome after out-of-hospital cardiac arrest? Experience acquired from patients with out-of-hospital cardiac arrest resuscitated by the same Emergency Medical Service and admitted to one of two hospitals over a 16-year period in the municipality of Göteborg. *Resuscitation* 2000;43:201–11.
- Langhelle A, Tyvold SS, Lexow K, Hapnes SA, Sunde K, Steen PA. In-hospital factors associated with improved outcome after out-of-hospital cardiac arrest. A comparison between four regions in Norway. *Resuscitation* 2003;56:247–63.
- Sunde K, Eftestol T, Askenberg C, Steen PA. Quality assessment of defibrillation and advanced life support using data from the medical control module of the defibrillator. *Resuscitation* 1999;41:237–47.
- Naess AC, Steen PA. Long term survival and costs per life year gained after out-of-hospital cardiac arrest. *Resuscitation* 2004;60:57–64.
- European Resuscitation Council Guidelines for Resuscitation 2005: Section 4. Adult advanced life support, pages S39–S86.
- Herlitz J, Bahr J, Fischer M, Kuisma M, Lexow K, Thorgeirsson G. Resuscitation in Europe: a tale of five European regions. *Resuscitation* 1999;41:121–31.
- Chamberlain D, Cummins R. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the "Utstein style". *Resuscitation* 1991;22:1–26.
- Sunde K, Dunlop O, Rostrup M, Sandberg M, Sjöholm H, Jacobsen D. Determination of prognosis after cardiac arrest may be more difficult after introduction of therapeutic hypothermia. *Resuscitation* 2006;69:29–32.
- Herlitz J, Ekström L, Wennerblom B, Axelsson A, Bang A, Holmberg S. Hospital mortality after out of hospital cardiac arrest among patients found in ventricular fibrillation. *Resuscitation* 1995;29:11–21.
- Juchems R, Wahlig G, Frese W. Influence of age on the survival rate of out-of-hospital and in-hospital resuscitation. *Resuscitation* 1993;26:23–9.
- Hallstrom A, Cobb LA, Johnson I, Copass MK. Cardiopulmonary resuscitation by chest compression alone or with mouth-to-mouth ventilation. *N Engl J Med* 2000;342:1546–53.
- Cobb LA, Fahrenbruch CE, Walsh TR, et al. Influence of cardiopulmonary resuscitation prior to defibrillation in patients with out-of-hospital ventricular fibrillation. *JAMA* 1999;281:1182–8.
- Hsu JW, Madsen CD, Callahan ML. Quality-of-life and formal functional testing of survivors of out-of-hospital cardiac arrest correlates poorly with traditional neurologic outcome scales. *Ann Emerg Med* 1996;28:597–605.
- Jacobs I, Nadkarni V, Bahr J, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries. A statement for healthcare professionals from a task force of the international liaison committee on resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa). *Resuscitation* 2004;63:233–49.
- Herlitz J, Eek M, Engdahl J, Holmberg M, Holmberg S. Factors at resuscitation and outcome among patients suffering from out of hospital cardiac arrest in relation to age. *Resuscitation* 2003;58:309–17.
- Swor RA, Jackson RE, Tintinalli JE, Pirrallo RG. Does advanced age matter in outcomes after out-of-hospital cardiac arrest in community-dwelling adults? *Acad Emerg Med* 2000;7:762–8.
- Campbell JP, Maxey VA, Watson WA. Hawthorne effect: implications for prehospital research. *Ann Emerg Med* 1995;26:590–4.
- Davies MJ, Thomas A. Thrombosis and acute coronary-artery lesions in sudden cardiac ischemic death. *N Engl J Med* 1984;310:1137–40.
- Silfvast T. Cause of death in unsuccessful prehospital resuscitation. *J Intern Med* 1991;229:331–5.
- Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003;361:13–20.

25. Bendz B, Eritsland J, Nakstad AR, et al. Long-term prognosis after out-of-hospital cardiac arrest and primary percutaneous coronary intervention. *Resuscitation* 2004;63:49–53.
26. Bottiger BW, Motsch J, Bohrer H, et al. Activation of blood coagulation after cardiac arrest is not balanced adequately by activation of endogenous fibrinolysis. *Circulation* 1995;92:2572–8.
27. Skrifvars MB, Pettila V, Rosenberg PH, Castren M. A multiple logistic regression analysis of in-hospital factors related to survival at six months in patients resuscitated from out-of-hospital ventricular fibrillation. *Resuscitation* 2003;59:319–28.
28. Kuboyama K, Safar P, Radvosky A, Tisherman SA, Stezoski SW, Alexander H. Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: a prospective, randomized study. *Crit Care Med* 1993;21:1348–58.
29. Bernard S, Buist M, Monteiro O, Smith K. Induced hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: a preliminary report. *Resuscitation* 2003;56:9–13.
30. Mullner M, Sterz F, Binder M, Schreiber W, Deimel A, Laggner AN. Blood glucose concentration after cardiopulmonary resuscitation influences functional neurological recovery in human cardiac arrest survivors. *J Cereb Blood Flow Metab* 1997;17:430–6.
31. Kersten JR, Toller WG, Gross ER, Pagel PS, Warltier DC. Diabetes abolishes ischemic preconditioning: role of glucose, insulin, and osmolality. *Am J Physiol Heart Circ Physiol* 2000;278:H1218–24.
32. Malmberg K, Norhammar A, Wedel H, Ryden L. Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction: long-term results from the diabetes and insulin-glucose infusion in acute myocardial infarction (DIGAMI) study. *Circulation* 1999;99:2626–32.
33. Van Den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001;345:1359–67.
34. Buunk G, van der Hoeven JG, Meinders AE. Cerebrovascular reactivity in comatose patients resuscitated from a cardiac arrest. *Stroke* 1997;28:1569–73.
35. Snyder JV, Nemoto EM, Carrol RG, Safar P. Global ischemia in dogs: intracranial pressures, brain blood flow, and metabolism. *Stroke* 1975;6:21–7.
36. Sundgreen C, Larsen FS, Herzog TM, Knudsen GM, Boesgaard S, Aldersville J. Autoregulation of cerebral blood flow in patients resuscitated from cardiac arrest. *Stroke* 2001;32:128–32.
37. Kern KB, Hilwig RW, Rhee KH, Berg RA. Myocardial dysfunction after resuscitation from cardiac arrest: an example of global myocardial stunning. *J Am Coll Cardiol* 1996;28:232–40.
38. Laurent I, Monchi M, Chiche JD, et al. Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. *J Am Coll Cardiol* 2002;40:2110–6.
39. Adrie C, Adib-Conquy M, Laurent I, et al. Successful cardiopulmonary resuscitation after cardiac arrest as a "sepsis-like" syndrome. *Circulation* 2002;106:562–8.
40. Leonov Y, Sterz F, Safar P, Johnson DW, Tisherman SA, Oku K. Hypertension with hemodilution prevents multifocal cerebral hypoperfusion after cardiac arrest in dogs. *Stroke* 1992;23:45–53.
41. Wik L, Hansen TB, Fylling F, et al. Delaying defibrillation to give basic cardiopulmonary resuscitation to patients with out-of-hospital ventricular fibrillation: a randomized trial. *JAMA* 2003;289:1389–95.
42. Bailar III JC, Louis TA, Lavori PW, Polansky M. Studies without internal controls. In: Bailar, III, J.C., Mosteller, F., (Eds.), *Medical Uses of Statistics*. 2nd ed. Boston (MA) 1992; p. 105–23.
43. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med* 2000;342:1887–92.