ADVERSE EVENTS AND THEIR RELATION TO MORTALITY IN OUT-OF-HOSPITAL CARDIAC ARREST PATIENTS TREATED WITH THERAPEUTIC HYPOTHERMIA

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Objectives

- Out-of-hospital cardiac arrest patients treated with therapeutic hypothermia.
- Critical care
- Adverse events vs Mortality

Design:

- Prospective
- Observational
- Registry-based study.

Setting &Patients:

- Twenty-two hospitals in Europe and the United States.
- Between October 2004 and October 2008
- 765 patients were included.
- Some centers joined the registry later than October 2004

Patients

- The participating centers reported consecutively all unconscious (Glasgow Coma Scale score 8) adult (18 yrs) OHCA patients with ROSCadmitted to their critical care units and who were eligible for active post-cardiac arrest care with TH.

Measurements and Main Results:

- Common
- Pneumonia (48%),
- Metabolic and electrolyte disorders (5%–37%)
- Seizures (24%)
- Arrhythmias (7%–14%)

Measurements and Main Results:

- **Less frequent**
  - **sepsis (4%)**
  - **bleeding (6%)**

Measurements and Main Results:

- **Associated with increased mortality**
  - **Sustained hyperglycemia(blood glucose > 144 mg/dl for >4 hrs)**
  - **Seizures treated with anticonvulsants**

Measurements and Main Results:

- **Bleeding and sepsis**
- **Invasive procedures會增加機會 : coronary angiography, intravascular devices for cooling, intraaortic balloon pump**
- **Not associated with increased mortality**

Conclusions:

- **Out-of-hospital cardiac arrest**
- **Adverse events were common**
- **Sustained hyperglycemia and seizures treated with anticonvulsants ⇨ increased Mortality**

Therapeutic hypothermia (TH)

- As part of routine care
- adverse events, their incidence, and the impact on important outcomes
- Affect many physiologic processes and responses and may contribute to the development of adverse events, especially infections, bleeding, and electrolyte disorders

Therapeutic hypothermia (TH)

- Research trials and meta-analyses have reported a trend toward more adverse events with TH treatment but suggested *an overall beneficial effect on survival and neurologic outcome*

Therapeutic hypothermia (TH)

- The overall incidence of bleeding is low in OHCA patients treated with TH (16 –18), but we have previously reported an increased risk of bleeding when coronary angiography or percutaneous coronary intervention (PCI) was performed (18).

Main objective of this study

- **Incidence of adverse events** recorded during critical care treatment VS **Mortality** #
- #6 months after the insult in a large international cohort of OHCA patients treated according to modern therapeutic principles as part of routine care

Data Set

- Bleeding was defined as an adverse event if it was intracerebral or required transfusion.
- Arrhythmias were categorized as VT,Vf,Af, bradycardia of 40 beats/min, or tachycardia of 130 beats/min.
- Metabolic and electrolyte disorders included sustained hyperglycemia (8mmol/l=144 mg/dL for 4 hrs), hypoglycemia (3mmol/l=54 mg/dL) hypokalemia (3.0 mEq/L), hypophosphatemia (0.7 mmol/L=2.18mg/dl), and hypomagnesemia (0.7 mmol/L=1.7mg/dl).

Data Set

- Seizures were diagnosed either clinically or by electroencephalogram.
- Sepsis was defined using standard criteria and categorized as severe sepsis or septic shock
- Pneumonia was defined with four requirements: new or progressive consolidation on the chest radiograph, fever, leukocytosis, and the presence of purulent tracheobronchial secretions.

Data Set

- Renal replacement therapy was defined as the use of either continuous renal replacement therapy or intermittent hemodialysis.
- Anticonvulsants were medications, other than protocol sedation, administered to treat seizures.
- Antibiotic : prophylactic or treatment
- EEG
- Brain CT

Outcome

- Primary outcome was mortality at 6 months after the initial hospital admission.

Outcome: Cerebral performance category (CPC)

CPC		
1	conscious, with no or minor neurologic disability	Good neurologic outcome.
2	conscious, moderate neurologic disability, and able to work	Good neurologic outcome.
3	conscious, severe neurologic disability, and dependent	
4	coma or vegetative state	
5	dead	

RESULTS

- Eleven patients (1.4%) were lost to
- follow-up
- At 6 months, 391 patients (52%) were dead.
- Among the 363 patients (48%) alive

RESULTS

CPC	363 patients (48%) alive
1	268(74%)
2	66 (18%)
3	25(7%)
4	4(1%)

RESULTS

Table 2. Univariate analysis of patient characteristics among those alive or dead at follow-up, categorized by background, prehospital and inhospital factors

Factor	Alive at Follow-up n = 363 (48%)	Dead at Follow-up n = 391 (52%)	p
Background factors			
Age	60 (49–68)	67 (54–74)	<.001
Female	75 (21)	128 (33)	<.001
Previously healthy	117 (32)	60 (15)	<.001
Coronary disease	118 (32)	151 (39)	.081
Congestive heart failure	59 (16)	90 (23)	.022
Hypertension	109 (30)	140 (36)	.10
Diabetes	30 (8)	78 (20)	<.001
Pulmonary disease	28 (8)	72 (18)	<.001
Renal impairment	7 (2)	24 (6)	.005
Neurologic disease	23 (6)	53 (14)	.001
Prehospital factors			

RESULTS

Table 2. Univariate analysis of patient characteristics among those alive or dead at follow-up, categorized by background, prehospital and inhospital factors

Factor	Alive at Follow-up n = 363 (48%)	Dead at Follow-up n = 391 (52%)	p
Prehospital factors			
Witnessed arrest	330 (91)	311 (80)	<.001
Bystander cardiopulmonary resuscitation	252 (69)	227 (58)	.002
Cardiac cause of arrest	334 (92)	279 (71)	<.001
First monitored rhythm	Ventricular tachycardia/ventricular fibrillation = 304 (84); asystole = 41 (11); pulseless electrical activity = 11 (3)	Ventricular tachycardia/ventricular fibrillation = 214 (55); asystole = 128 (33); pulseless electrical activity = 40 (10)	<.001
Time from emergency call to arrival of emergency medical services team	5 (4–8)	7 (5–10)	<.001
Time from arrest to cardiopulmonary resuscitation	7 (5–10)	9 (6–12)	<.001
Time from arrest to defibrillation	10 (7–12)	11 (10–13)	<.001
Time from arrest to return of spontaneous circulation	16 (11–23)	28 (19–35)	<.001

RESULTS

Table 2. Univariate analysis of patient characteristics among those alive or dead at follow-up, categorized by background, prehospital and inhospital factors

Factor	Alive at Follow-up n = 363 (48%)	Dead at Follow-up n = 391 (52%)	p
Inhospital factors			
Initial temperature	36.0 (35.3–36.6)	35.7 (34.8–36.4)	<.001
Shock at admission	58 (16)	70 (18)	.50
Time from arrest to initiation of hypothermia	90 (60–180)	90 (60–160)	.89
Time from arrest to core temperature <34°C	300 (200–440)	240 (145–360)	<.001
Glasgow Coma Scale at admission	3 (3–5)	3 (3–3)	<.001
Thrombolysis performed	21 (6)	18 (5)	.51
Angiography performed	237 (65)	140 (36)	<.001
Percutaneous coronary intervention performed	149 (41)	76 (19)	<.001
Coronary artery bypass grafting performed	6 (2)	3 (1)	.32
Pacemaker used	18 (4)	11 (3)	.13
Intra-aortic balloon pump	62 (17)	53 (14)	.19
Acute myocardial infarction	229 (63)	225 (58)	.20
Inotropic/vasoactive drugs	282 (78)	315 (81)	.37
Renal replacement therapy	13 (4)	19 (5)	.47
Length of critical care unit stay	120 (73–201)	96 (48–146)	<.001

RESULTS

- Electroencephalogram 316 (41%)
- Cmputed tomography scan 382 (50%)

Univariate Analyses: Bleeding

- Intravascular devices for TH(OR 2.3, 95% CI 1.1–4.9)
- Thrombolysis (OR 3.5, 95% CI 1.1–9.1)
- Cardiogenic shock (OR 4.1, 95% CI 2.0–8.1)
- Intra-aortic balloon pump (OR 2.9, 95% CI 1.4–6)
- Coronary angiography (OR 1.9, 95% CI 0.97–3.9)
- No statistically significant VS Mortality
- Alive or dead at 6 months (5.5% vs. 5.8%, *p .76*).

Univariate Analyses: *Infections*

- Intravascular devices for TH: cooling devices (OR 2.6, 95 CI 1.2– 6.5) and IABP (OR 3.2, 95% CI 1.3–7.3).
- Coronary angiography (OR 4.4, 95% CI 1.7–13).
- Pneumonia (OR 0.48, 95% CI 0.36–0.65) and sepsis (OR 0.43, 95% CI 0.18–0.97) ,Antibiotic treatment (OR 0.39, 95% CI 0.29–0.53)

Univariate Analyses: *Metabolic and Electrolyte Disorders*

- Sustained hyperglycemia was common
- Sustained hyperglycemia (OR 2.5, 95% CI 1.8 –3.4)
- hypoglycemia (OR 2.3, 95% CI 1.1– 4.9)
- Hypokalemia (OR 1.5, 95% CI 1–2.2)

Univariate Analyses: *Arrhythmias*

- Not statistically significantly associated
- with mortality.

Univariate Analyses: *Seizures*

- 24% of the patients
- Seizures *per se (OR 4, 95% CI 2.7–5.9)*
- Seizures treated with anticonvulsant medication (OR 4.7, 95% CI 3–7.4)
- Had longer times from arrest to initiation of cardiopulmonary resuscitation and to return of spontaneous circulation (*p<0.001)*
- 常見Noncardiac cause of their arrest (*p=0.001)*
- 常見Asystole or pulseless electrical activity (*p =0.002*).

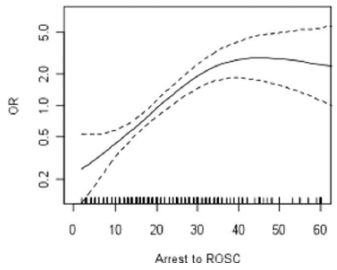
Univariate Analyses: *Seizures*

- Of the 182 patients with registered seizures, 31 (17%) were alive with a good outcome at 6-month follow-up.

Table 3. Number and frequency of adverse events with corresponding univariate and adjusted odds ratios for mortality

Adverse Event and Concomitant Treatment	Total, n (%)	Alive, n (%)	Dead, n (%)	Univariate Odds Ratio (Lower Confidence Limit–Upper Confidence Limit)	p	Adjusted Odds Ratio (Lower Confidence Limit–Upper Confidence Limit)	p
	754 (100)	363 (48)	391 (52)				
Bleeding requiring transfusion	43 (6)	20 (6)	23 (6)	1.1 (0.57–2.2)	.76	1.0 (0.43–2.5)	.94
Pneumonia	361 (48)	208 (56)	153 (39)	0.48 (0.36–0.65)	<.001	0.88 (0.57–1.37)	.58
Sepsis	31 (4)	21 (6)	10 (3)	0.43 (0.18–0.97)	.028	0.59 (0.20–1.8)	.47
Antibiotic prophylaxis	207 (27)	94 (26)	113 (29)	1.2 (0.83–1.6)	.37	1.3 (0.80–2.0)	.31
Antibiotic therapy	414 (55)	242 (67)	172 (44)	0.39 (0.29–0.53)	<.001	.62 (0.40–0.98)	.04
Bradycardia <40 bpm	108 (14)	61 (17)	47 (12)	0.68 (0.44–1)	.062	.79 (0.42–1.5)	.47
Tachycardia >130 bpm	50 (7)	21 (6)	29 (7)	1.3 (0.70–2.5)	.38	1.7 (0.74–4.0)	.21
Atrial fibrillation	70 (9)	37 (10)	33 (8)	0.81 (0.48–1.4)	.45	1.1 (0.56–2.1)	.82
Ventricular tachycardia	76 (10)	36 (10)	40 (10)	1 (0.63–1.7)	.90	1.7 (0.87–3.3)	.12
Ventricular fibrillation	58 (8)	26 (7)	32 (8)	1.2 (0.65–2.1)	.68	2.0 (0.88–4.6)	.09
Hypoglycemia <3.0 mmol/l	40 (5)	12 (3)	28 (7)	2.3 (1.1–4.9)	.022	1.3 (0.47–3.7)	.6
Hyperglycemia >8 mmol/L >4 hrs	277 (37)	95 (26)	182 (46)	2.5 (1.8–3.4)	<.001	2.6 (1.6–4.1)	<.001
Hypokalemia <3.0 mmol/L	134 (18)	54 (15)	80 (20)	1.5 (1.0–2.2)	.046	1.3 (0.76–2.4)	.31
Hypomagnesemia <0.7 mmol/L	128 (17)	61 (17)	67 (17)	1 (0.69–1.5)	.92	1.2 (0.73–2.1)	.41
Hypophosphatemia <0.7 mmol/L	141 (19)	74 (20)	67 (17)	0.81 (0.55–1.2)	.26	0.68 (0.40–1.1)	.15
Seizures	182 (24)	44 (12)	138 (35)	4 (2.7–5.9)	<.001	1.1 (0.5–2.4)	.78
Anticonvulsants	154 (20)	32 (9)	122 (31)	4.7 (3.7–6)	<.001	5.4 (3.2–9.3)	<.001
Renal replacement therapy	32 (4)	13 (4)	19 (5)	1.4 (0.63–3.1)	.47	3.6 (1.1–12)	.04

Multivariate Analyses:



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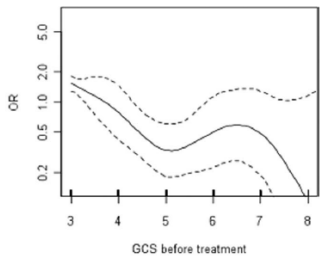

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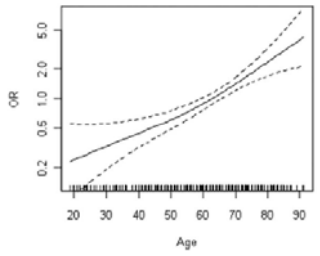
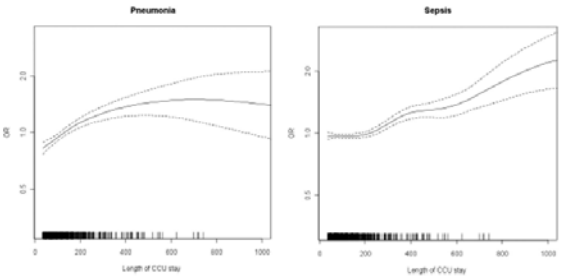


Multivariate Analyses:

Table 4. Results from the generalized additive multivariate model for mortality

Multivariate Model	Odds Ratio[a] or χ^{2b}	Confidence Limit (Upper–Lower)[a] or Degrees of Freedom[b]	p
Noncontinuous parameters[a]			
Intercept	0.96	(0.69–1.32)	<.3
Angiography	0.34	(0.23–0.52)	<.001
Seizures treated with anticonvulsants	4.8	(2.9–8.1)	<.001
Continuous parameters[b]			
Time from cardiac arrest to return of spontaneous circulation	40	4.6	<.001
Glasgow Coma Scale before initiation of hypothermia treatment	25	4.5	<.001
Age (yrs)	32	2.1	<.001

Multivariate Analyses:



Implications for Clinic Care and Research

- Modern intensive care after cardiac arrest involves an abundance of invasive procedures=>Increased bleeding and infections ; not associated with increased mortality
- Pneumonia and sepsis were not associated with increased mortality and should not be used as prognostic markers of a poor outcome.

Implications for Clinic Care and Research

- Seizures, although strongly associated with increased mortality, were not an irrevocable sign of bad outcome, because almost one-fifth(17%) of the patients survived with a good outcome.
- #Monitoring brain function (electroencephalogram) to improve the recognition and potential treatment of seizures.

Implications for Clinic Care and Research

- Hyperglycemia and seizures had the strongest association with outcome, and with the previously demonstrated benefit of coronary angiography/PCI comprise the three factors which may be the best parameters to target in future randomized trials with TH.

Limitations

- not designed to compare the incidence of adverse events with or without TH
- Population remains at risk for possible selection bias
- Registry-based
- Centers with stricter guidelines, regions and hospitals

CONCLUSIONS

- Sustained hyperglycemia and seizures treated with anticonvulsants were associated with increased mortality.
- Bleeding and infection, although more common after invasive procedures , were not related to increased mortality.
- Arrhythmias and electrolyte abnormalities also were not associated with mortality in our study.

- Thsnks for your attention!