Slide 1

Post-hypothermia fever is associated with increased mortality after out-of-hospital cardiac arrest☆

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2013/12/2

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Slide 2
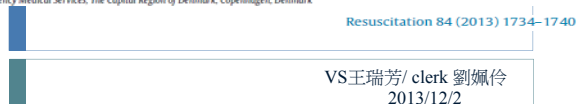
Objective

- Post-cardiac arrest fever →adverse outcome before therapeutic hypothermia (TH).
- the prognostic implications of post-hypothermia fever (PHF) has not been thoroughly investigated.
- To assess the prognostic implication of PHF in a large consecutive cohort of comatose survivors after out-of-hospital cardiac arrest (OHCA) treated with TH.

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Slide 3

Introduction

- TH plays a central role in post-resuscitation care after OHCA and is recommended in patients remaining comatose after ROSC.
- TH的好處:
  - 降低腦部的代謝→ 降低6-8%/ ℃ 代謝率
  - 降低半胱氨酸蛋白酶(caspase)的活動& 粒線體的失能→阻斷細胞凋亡。
  - 降低缺氧帶來的發炎反應, eg NO, 白血球帶來的發炎作用。

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Slide 4

Methods

- prospective observational cohort study
- 2004/6/1 – 2010/10/31 , OHCA在恢復自發性循環後保持昏迷的病人, Copenhagen University Hospital Rigshospitalet
- Inclusion criteria
  - (1) OHCA with presumed cardiac aetiology
  - (2) age ≥ 18 years
  - (3) sustained ROSC >20 min
  - (4) GCS ≤ 8
- Exclusion criteria → see flow chart
- treatment goals of post-resuscitation care
  - MAP > 65 mmHg, HR: 40–90/min, CVP: 10–15 mmHg, diuresis >1.5 mL/kg/h.

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Slide 5

Methods

- TH :
  - 降溫期: infusion of 30 mL/kg of 4∘C Ringer's solution and surface cooling.
  - 維持期:core temperature(食道,膀胱) < 34∘C, maintain 24h, 目標溫度: 33∘C
  - 回溫期: active rewarming by 0.5∘C/h until 36.5∘C.
- Post-hypothermia period:
  - 回溫後,中心體溫≥36.5∘C ,持續36h
- Post-hypothermia fever:
  - 回溫後36h內,中心體溫> median peak temperature(≥38.5∘C)

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Slide 6

Methods

- The population was stratified in two groups by median peak temperature (≥38.5 ∘C) within 36 h after rewarming: PHF and no-PHF.
- Primary endpoint
  - 30-days mortality
- Secondary endpoint
  - neurological outcome assessed by Cerebral Performance Category (CPC) at hospital discharge and follow-up, which was performed at least 6mo after OHCA.
    - CPC 1-2 → good neurological outcome

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Results

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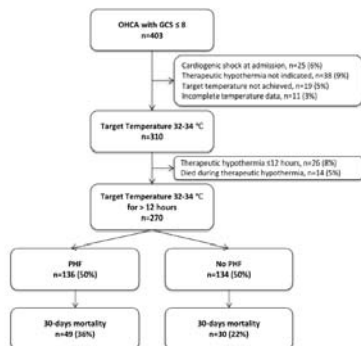
Fig. 1. Flow chart. This figure shows included and excluded patients admitted to Copenhagen University Hospital Rigshospitalet after OHCA in the period 2004–2010. GCS, Glasgow Coma Scale; OHCA, Out-of-Hospital Cardiac Arrest; PHF, Post-hypothermia fever.

Results

Table 1
Patient characteristics according to development of PHF.

	Overall n = 270	PHF n = 136	No PHF n = 134	p-value
Age, years (mean ± SD)	60 ± 14	59 ± 13	61 ± 14	0.13
Male sex (%)	223 (83)	111 (82)	112 (84)	0.67
Co-morbidities:				
Hypertension (%)	72 (27)	30 (23)	42 (32)	0.09
Diabetes mellitus (%)	34 (13)	18 (14)	16 (12)	0.73
Known IHD (%)	66 (25)	31 (23)	35 (27)	0.52
Heart failure	34 (13)	13 (10)	21 (16)	0.14
COPD	21 (8)	9 (7)	12 (9)	0.48
Initial rhythm:				
VF/VT (%)	233 (86)	119 (88)	114 (85)	0.56
PEA/asystole (%)	37 (14)	17 (13)	20 (15)	
Witnessed arrest (%)	235 (87)	116 (85)	119 (89)	0.39
Bystander CPR (%)	165 (61)	82 (60)	83 (62)	0.78
Time to MECU arrival, mins (25th and 75th percentile)	5 (4–7)	5 (4–8)	5 (4–7)	0.66
Time to ROSC, mins (25th and 75th percentile)	15 (10–23)	17 (10–24)	15 (11–22)	0.23
Acute Myocardial Infarction (%)	146 (54)	75 (55)	71 (53)	0.72
ST-elevation Myocardial Infarction (%)	94 (35)	50 (37)	44 (33)	0.50
Temperature at admission, °C	35.7 (34.6–36.4)	35.7 (35.0–36.5)	35.2 (34.1–36.3)	0.03
Time from OHCA to target temperature, min	290 (200–454)	305 (211–454)	270 (186–455)	0.17
Duration of TH, hours below 34 °C	27 (25–29)	27 (25–29)	27 (24–30)	0.94
Length of intensive care unit stay, hours	111 (77–182)	116 (81–189)	106 (76–173)	0.37

Data are presented as mean ± SD or median and interquartile range as appropriate. The p-value represents comparison between groups; development of post-hypothermia fever and no post-hypothermia fever. A significance level of p < 0.05 was chosen.
Abbreviations: PHF: post-hypothermia fever; IHD, ischaemic heart disease; COPD, chronic obstructive pulmonary disease; VF/VT, ventricular fibrillation/ventricular tachycardia; PEA, pulseless electrical activity; CPR, cardio-pulmonary resuscitation; MECU, mobile emergency care unit; ROSC, return of spontaneous circulation; TH, therapeutic hypothermia.

Results - Post-hypothermia temperature and outcome

- (CPC 3–5) vs. (CPC 1–2)
  - higher maximum temperature after rewarming
    38.7 °C (38.1–39.2) vs. 38.4 °C (38.0–38.7), p = 0.001
  - more frequent developed PHF
    61% vs. 45%, p = 0.02
- <u>Among those who developed PHF</u>
  (CPC 3–5) vs. (CPC 1–2)
  - later onset of PHF
    11 (6–20) vs. 6 (4–10) h, p = 0.001
  - Longer time from end of rewarming to peak temperature
    19 (8–29) vs. 6 (4–12) h, p < 0.0001

▸ 9

Results - Post-hypothermia temperature and outcome

- gender, age, initial rhythm, bystander CPR and time to ROSC
  → neither univariate nor multivariate associated to development of PHF
- AMI and clinical signs of pneumonia during ICU
  → not associated with development of PHF.

▸ 10

Results - Mortality

- 30-day mortality (Overall, 29%)
  - PHF vs. No PHF,
    36% vs. 22%, p = 0.02
- One-year mortality
  - PHF vs. No PHF,
    38% vs. 26%, p = 0.03
- PHF was independently associated with increased 30-day mortality.
  HR = 1.8 (95% CI: 1.1–2.7), p = 0.02

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Results - Mortality

- Maximum temperature and duration of PHF were both independent predictors of 30-days mortality.

Table 2
Cox proportional hazard models predicting 30-days mortality.

	Univariable		Model 1 Multivariable		Model 2 Multivariable	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Maximum temperature, per °C > 36.5 °C	2.0 (1.4–2.9)	0.0003	2.0 (1.4–3.0)	0.0005	-	
Duration of fever (>38.5 °C), per 8 h	1.5 (1.2–1.8)	<0.0001	-		1.6 (1.3–2.0)	<0.0001
Body Mass Index, per kg m⁻²	1.0 (1.0–1.1)	0.32				
Sex, male vs. female	0.5 (0.3–0.9)	0.01				
Age, per 5 years	1.1 (1.0–1.2)	0.005	1.2 (1.1–1.4)	<0.0001	1.2 (1.1–1.4)	<0.0001
Witnessed arrest, yes vs. no	0.5 (0.3–0.9)	0.01	0.5 (0.3–1.0)	0.05		
Bystander CPR, yes vs. no	0.5 (0.3–0.7)	0.0007	0.6 (0.3–0.9)	0.03	0.6 (0.4–0.9)	0.04
Initial rhythm, VF vs. no VF	0.4 (0.2–0.7)	0.001	0.5 (0.3–0.9)	0.01	0.5 (0.3–0.8)	0.004
Time to ROSC, per 5 min	1.1 (1.1–1.2)	0.001	1.1 (1.1–1.2)	0.0003	1.2 (1.1–1.3)	<0.0001

Results - Mortality

- Excluding 17 patients who died in the post-hypothermia period
  - maximum temperature
    HR = 3.6 per °C above 36.5 °C
    95% CI: 2.3–5.7
    p < 0.0001
  - duration of PHF
    HR = 2.0 per 8 h
    95% CI: 1.6–2.5
    p < 0.0001

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Results - Mortality

- GCS ≤8 throughout the observation period
  - maximum temperature
    HR = 2.2 per °C above 36.5 °C
    95% CI: 1.3–3.8, p = 0.003
  - duration of PHF
    HR = 1.4 per 8 h
    95% CI: 0.9–2.2, p = 0.12
- mortality rates due to neurological injuries
  - PHF vs. No PHF,
    32% vs. 19%, p = 0.02
  - maximum temperature
    HR = 2.3 per °C above 36.5 °C
    95% CI: 1.5–3.5, p = 0.0002
  - duration of PHF
    HR = 1.8 per 8 h
    95% CI: 1.5–2.3, p < 0.0001

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Results - Neurological outcome

- unfavourable neurological outcome (CPC 3–5)
  - maximum temperature
    OR = 2.5 per °C above 36.5 °C
    95% CI: 1.5–4.1, p = 0.0005
  - duration of PHF
    OR = 2.0 per 8 h
    95% CI: 1.4–2.9, p < 0.0001

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Results - Neurological outcome

- At hospital discharge,
  good outcome (CPC 1–2)
  - PHF vs. No PHF,
    61% vs. 75%, p = 0.02
- At follow-up 1 year after OHCA,
  good outcome (CPC 1–2)
  - PHF vs. No PHF,
    57% vs. 73%,
  unfavourable outcome (CPC 3–5)
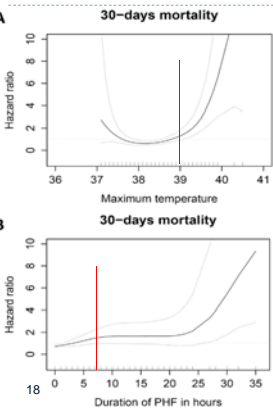 - PHF vs. No PHF,
    43% vs. 27%,
  p = 0.007

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Discussion

- 這項研究整體而言,30天的死亡率是29%,要小心解讀,必須確認在住院期間有發生cardiogenic shock的病人及在回溫期還沒結束前就死亡的病人給排除掉。
- 之前有研究報告,在還沒介入TH前,心臟停止後24-72h內發燒的發生率:20-83%
- 只有少數的Studies針對post-hypothermia period發燒進行研究,一般發燒的定義:中心體溫≥ 38.0–38.5°C , Incidence of PHF: 41-76%
- 在OCHA後的72h,才去評估病人的神經功能,對於目前的分析結果,可能會導致神經功能預後的結果有些偏差

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Discussion

- Maximum temperature and duration of PHF were not perfect linear predictors.
- The effect of PHF on mortality is modest below a threshold of approximately 39 °C or duration of PHF ≤ 7 h.

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Discussion

▶ 這篇研究跟過去的研究都一致認為➔維持數小時顯著的體溫增加,才會與預後有關聯,尤其是較晚發生的PHF及較長的duration,可能也會容易帶來較不好的神經功能預後。

▶ 造成心臟停止後發燒的可能原因:

　▶ 感染: pulmonary aspiration pneumonia or bacteraemia secondary to translocation of bacteria across ischaemic gut, but also translocation of endotoxins in absence of infections.

　　▶ 其他: injuries to the brain, seizures & acute myocardial infarction

▶ 心臟停止後,腦部的灌流減少,導致global cerebral ischaemia 及injuries to neurons ➔ neurotransmitters 釋放& cell apoptosis。

▶ hypothalamic & hippocampus area are sensitive to ischaemia and lesions in the anterior hypothalamus may affect the thermoregulatory system ➔ autoregulation 受損導致發燒

▶ 由於這是一個observational study, 無法確定PHF的發生是否因autoregulation 受損或是global cerebral ischaemia 而導致neuron injuries

Discussion

▶ 心臟停止後,全身有一段時間會缺血—開始會導致整體組織和器官的傷害,再灌流期間與之後也會發生更進一步的傷害,這時就會發生心臟停止症候群(PCAS),可能有助於PHF的發生

▶ PCAS clinical signs: fever, arterial hypotension➔需要用vasopressor去維持organ perfusion.

▶ 從這篇paper的Results來看,PCAS對PHF發生的影響是有限的

▶ age, bystander CPR, ventricular fibrillation and time to ROSC➔ are well-known predictors of outcome, but not predictive in development of PHF.

▶ PHF was found to be associated with increased mortality and unfavourable outcome after controlling for potential confounding factors,

Conclusion

▶ Development of PHF (≥38.5∘C) was frequent and associated with increased 30 days mortality and unfavourable neurological outcome

THANKS FOR YOUR ATTENTION!