BODY TEMPERATURE REGULATION AND OUTCOME AFTER CARDIAC ARREST AND THERAPEUTIC HYPOTHERMIA

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INTRODUCTION

- Therapeutic hypothermia(TH) improves the outcome of comatose patients after cardiac arrest(CA)
- Body temperature(BT) regulation after CA has not been extensively stidied
- Altered thermoregulation frequently observed with acute brain conditions, mainly due to hypothalamic dysfunction
- Recently study suggested low spontaneous BT associate with increased in-hospital mortality
- No study has investigated regulation of BT in the early phase of post resuscitation care and during the various phase of induced cooling and examined the impact of BT variation on outcome

METHODS --- SUBJECTS

- Patients included in this study were part of a prospective observational database of comatose patients who were successfully resuscitated from CA and were treated with TH at the medical/surgical intensive care unit (ICU) of the University Hospital of Lausanne, Switzerland, over a 6-year period (2003–2009).
- All patients were initially admitted to the ER, and, after stabilization, were rapidly transferred to the ICU.
- 210 patients. A total of 33 patients were excluded: 14 patients were not treated with TH, 14 patients died within 48 h and 5 patients had incomplete data. Thus, a total of 177 patients were included in the present study.

TABLE 1 PATIENT BASELINE DEMOGRAPHICS

Patient baseline demographics.

	All patients (N = 177)	Survivors (N = 87) (49%)	Non-survivors (N = 90) (51%)	p value*
Median age, years	61 (18–85)	62 (18–85)	60 (18–84)	0.28
Female gender	39 (22%)	22 (25%)	17 (19%)	0.30
Initial arrest rhythm				
VF	123 (69%)	76 (62%)	47 (38%)	<0.0001
Non-VF (including asystole and PEA)	54 (31%)	11 (20%)	43 (80%)	
Time to ROSC, min	25 (5–75)	18 (5–45)	30 (8–75)	<0.0001

Data are expressed as median (range). *Abbreviations:* PEA: pulseless electrical activity; ROSC: return of spontaneous circulation; VF: ventricular fibrillation.
* p values for comparisons between survivors and non-survivors (Mann–Whitney U test).

METHOD --- THERAPEUTIC HYPOTHERMIA

- treated with TH to 32–34 ◦C for 24 h,
- started immediately after admission to the ICU using ice-cold packs and intravenous ice-cold fluids.(Arctic Sun SystemR, Medivance, Louisville, CO, US)
- protocol for sedation, analgesia and paralysis : Midazolam (0.1 mg/kg/h), fentanyl (1.5 g/kg/h), Vecuronium (0.1 mg/kg boluses)
- mean arterial blood pressure above 70 mmHg
- PaO2>90 mmHg and PaCO2 between 35 and 40 mmHg
- Rewarming was achieved passively by retraction of the surface cooling device, and sedation, analgesia and paralysis were stopped when patient BT was >35 ◦C.

METHOD --- DATA COLLECTION AND PROCESSING

- Spontaneous BT was recorded on hospital admission in the ER prior to ICU admission, using a rectal thermometer.
- Outdoor temperature at the time of CA, categorized in four : March–May, June–August, September–November and December–February.
- BT was measured continuously via a bladder thermometer or a central venous catheter and was recorded at least every 30 mins. (Metavision IMDsoft)
- Time to target temperature (TTT), defined as the time from admission to the hospital to achieve induced BT < 34 ◦C
- Cooling rate, defined as the difference between spontaneous BT and induced BT (34 ◦C) divided by the TTT
- Duration of passive rewarming, defined as the time from the end of cooling to achieve BT of 37 ◦C.
- Body temperature values (mean, min, max) during the stable maintenance phase of TH and the post-rewarming normothermic phase (NT) were also calculated.

METHOD --- OUTCOME ASSESSMENT

- Primary outcome endpoint --- in-hospital mortality
- Secondary endpoint --- CPC at discharge and at 3 months
- good (CPC 1 = full recovery and CPC 2 = moderate disability) vs. poor (CPC 3 = severe disability, CPC 4 = minimally conscious/vegetative state and CPC 5 = death).

METHOD --- STATISTICAL ANALYSIS

- Continuous variables --- median and interquartile range (IQR) --- Mann–Whitney U tests
- Categorical variables as numbers and percentage --- Fisher exact tests
- Univariate analyses were conducted with the JMP Software (SAS Institute Inc., Cary, NC, USA)
- Multivariable logistic regression was performed using Stata 9 software package (Statacorp LP, College Station, TX)
- Dependent variable was in-hospital mortality and admission BT, time to ROSC and initial arrest rhythm (dichotomized as VF vs. non-VF)
- Significance was assumed at a level of $p < 0.05$.

MANN–WHITNEY U TEST

- 檢定方法：
  將兩樣本資料混合，依數值由小排到大並標記排序分數，再將排序分數依兩樣本分別列出，分開加總兩樣本之排序分數得R_1、R_2。 檢定R_1、R_2與期望值差異情形以推測兩母群體統計量差異。
- 此無參數測定之目的，也是比較兩個隨機樣本之差異，然後推論到兩個母群間的差異

FISHER EXACT TESTS

- 這個方法並不需要假設資料母體的分布，Fisher's Exact Test 屬於一種無母數的檢定方法小樣本的檢定方法,方法的前提是固定邊際分布

	Men	Women	*Total*
Dieting	*a*	*b*	*a + b*
Non-dieting	*c*	*d*	*c + d*
Totals	*a + c*	*b + d*	*a + b + c + d (=n)*

$$p = \frac{\binom{a+b}{a}\binom{c+d}{c}}{\binom{n}{a+c}} = \frac{(a+b)!(c+d)!(a+c)!(b+d)!}{a!b!c!d!n!}$$

RESULT

- non-survivors had a lower spontaneous BT on hospital admission than survivors and time to target temperature was significant shorter
- no statistically significant associations were found between admission BT and neurological outcome both at hospital discharge and at 3 months
- non-survivors had lower spontaneous BT at all time of the year, except in warmest months (June 1st to August 31st),
- cooling rate was comparable between survivors and non-survivors
- the duration of passive rewarming following TH was significantly longer in non-survivors.
- no associations were found between outcome and BT values during TH maintenance and post-rewarming NT
- Fever (defined as BT > 38 °C) during NT was not associated with inhospital mortality.

- Admission BT was not independently associated with in-hospital mortality(odds ratio [OR] for mortality 1.22; confidence interval [CI] 0.92–1.61; p = 0.16)
- Adjusted for known predictors of mortality (OR 1.10; CI 1.05–1.14; p < 0.001 and non-VF rhythm OR 4.66; CI 1.97–11.03; p < 0.001).

RESULT

Associations between spontaneous body temperature on hospital admission and in-hospital mortality in patients with coma after cardiac arrest.

	All patients (N = 177)	Survivors (N = 87)	Non-survivors (N = 90)	p value*
Admission BT (°C), overall	34.9 (34–35.8)	35.1 (34.4–35.8)	34.5 (33.7–35.9)	0.04
Admission BT (°C), according to the time of the year of cardiac arrest				
March–May (N = 37)	34.7 (34.1–35.3)	35.2 (34.4–35.9)	34.2 (33.5–34.8)	0.002
June–August (N = 58)	35.5 (34.4–36.3)	35.1 (34.4–36)	36.1 (34.4–36.6)	0.05
September–November (N = 42)	34.8 (33.9–35.7)	35.1 (34.8–35.9)	34.3 (33.1–35.7)	0.01
December–February (N = 40)	34.4 (33.3–35.2)	34.8 (33.7–35.8)	33.7 (32.5–35)	0.08

Data are expressed as median (interquartile range). Body temperature (BT) is given in degrees Celsius.
* p values for comparisons between survivors and non-survivors (Mann–Whitney *U* test).

RESULT

Associations between body temperature variations during induced hypothermia and in-hospital mortality.

	All patients (N = 177)	Survivors (N = 87)	Non-survivors (N = 90)	p value*
Time to target temperature, min	247 (73–371)	270 (158–375)	200 (25–363)	0.03
Cooling rate, °C/h	0.4 (0.2–0.5)	0.4 (0.2–0.5)	0.3 (0.2–0.4)	0.65
Time of passive rewarming, min	530 (393–660)	479 (360–600)	600 (464–744)	0.01
Minimal BT during TH, °C	33.1 (32.1–34)	33.6 (32.2–34)	33 (32–34)	0.19
Mean BT during TH, °C	33.2 (33–33.5)	33.2 (33.1–33.5)	33.3 (33–33.5)	0.81
Maximal BT during NT, °C	38.5 (38.1–38.9)	38.1 (37.8–38.3)	38.1 (37.5–38.3)	0.68
Mean BT during NT, °C	37.7 (37.3–37.9)	37.7 (37.4–37.9)	37.6 (37.3–37.9)	0.30
Rate of fever during NT, % of patients	76%	73%	78%	0.45

Data are expressed as median (interquartile range). Body temperature (BT) is given in degrees Celsius. Fever was defined as BT > 38 °C.
* p values for comparisons between survivors and non-survivors (Mann–Whitney *U* test).

LIMITATION

- This was a single-center study, thus data cannot be generalized and would require further confirmation by others.
- precise information on temperature at the site of CA and whether CA occurred indoor vs. outdoor was not available.
- the duration of transport was not precisely assessed in this study, and could be a confounding factor.
- Rectal temperature was used as a measure admission BT which may influence results since rectal temperature may be higher than central core temperature
- lack of a better understanding of the precise mechanisms implicated in post-CA induced altered thermoregulation
- Measuring heat/energy removal by the Arctic Sun cooling device system would have provided potentially informative data on deranged thermoregulation however these data were not available.

DISCUSSION

- Main findings

1. Spontaneous BT on admission is associated with in-hospital mortality
2. non-survivors had lower admission BT than survivors; except during warmer months (June–August), where admission BT was actually higher in non-survivors,
3. The time to target temperature was shorter in non-survivors, however no associations between outcome and the cooling rate was found;
4. Longer time of passive rewarming was associated with in-hospital mortality.

DISCUSSION

- In major trauma patients, spontaneous hypothermia on admission is associated with increased mortality, independently from injury pattern or severity --- hypothalamic dysfunction with impairment of thermoregulatory pathways is implicated
- The fact that non-survivors seemed to "adjust" to outdoor temperature (i.e. they had colder spontaneous BT in winter time and warmer spontaneous BT in summer time)
- these patients had a state of impaired thermoregulation
  - Global brain ischemia following CA, causing a dysfunction of the central hypothalamic thermostat and the inability to maintain BT contro
  - damage peripheral vasomotor pathways in the skin, involved in temperature-induced processes of vasoconstriction/vasodilatation.

CONCLUSION

- Impaired BT regulation is a marker of poor outcome after CA and TH.
- lower spontaneous admission BT and longer time of passive rewarming were associated with in-hospital mortality.
- no correlation between outcome and the rate of cooling
- impaired thermoregulation is an important pathophysiologic determinant of post-resuscitation disease and CA prognosis.
- Admission body temperature is a marker of post-resuscitation disease severity
- Using the cooling rate rather than the time to target temperature when assessing the potential benefit of early cooling on outcome

DISCUSSION

- comparable rates of cooling between survivors and non-survivors
- cooling rates, rather than time to target temperature, should be used to assess the efficiency and rapidity of cooling induction.
- no significant relationship between the rate of cooling and in-hospital mortality
- Faster cooling might improve outcome after CA is still debated

DISCUSSION

- BT regulation during rewarming is critical and may have important implications. Fast rewarming (>0.5 °C/h) after hypothermic CA or traumatic brain injury may aggravate brain damage.
- There is however no firm recommendation as to whether rewarming after TH should be passive or controlled using new computerized cooling device systems.
- significant association between longer rewarming time and in-hospital mortality.
- no association between in-hospital mortality and mean or minimal BT during TH.
- no relationship between mean or maximal BT during early postrewarming NT.
- Fever during NT was no associated with in-hospital mortality.

QUESTION TIME

- 這篇文章提到特地測量不同季節病人的入院體溫
- 得出一般而言體溫越低 預後越差 但夏天反而是體溫越高 預後越差
- 可見體溫調控出問題的病人預後差(夏天體溫高 冬天體溫低 無法恒溫)
- 但此論文的醫院所在處為瑞士
- 夏天的平均氣溫不到三十度
- 可見就算是夏天 受到氣溫影響下體溫應該還是低的
- 也因此其推論應該是有問題的

QUESTION TIME

- 如何決定paper的樣本數目是否足夠?

THANKS