Journal Meeting

Reporter: R1 許哲彰
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The role of hypothermia in post-cardiac arrest patients with return of spontaneous circulation:
A systematic review

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Background

- Mild hypothermia (32–34 ◦C for12–24h)

➔ improve neurological outcome in initially comatose survivors of cardiac arrest.

- update the systematic review that provided evidence for the treatment recommendation on therapeutic hypothermia

Methods

- Follow ILCOR (International Liaison Committee on Resuscitation)
- PICO (Patient/population, Intervention, Comparator, Outcome) question
- Search strategy:
  PubMed, EMBASE database,
  AHA Resuscitation End Note library,
  Cochrane database
- Evidence appraisal： LOE & quality
- Data presentation:
  Parametric data ➔ mean (standard deviation)
  non-parametric ➔ median (interquartile range)

Table 1
ILCOR level of evidence for therapeutic interventions.

LOE 1: Randomized controlled trials (or meta-analyses of RCTs)
LOE 2: Studies using concurrent controls without true randomization (e.g. "pseudo"-randomized) or meta-analyses of such studies)
LOE 3: Studies using retrospective controls
LOE 4: Studies without a control group (e.g. cases series)
LOE 5: Studies not directly related to the specific patient/population (e.g. different patient/population, animal models, mechanical models etc.)

Table 2
Quality factors for studies of each level of evidence.

Meta-analysis (of LOE 1 or LOE 2 studies)	Randomised controlled Trials (LOE 1)	Studies using controls without randomisation (concurrent LOE 2, or retrospective LOE 3)	Studies without controls (LOE 4)	Studies not directly related to the specific patient/population (LOE5)
• Were specific objectives of the review stated (based on specific clinical question in which patient, intervention, operator, comparator, outcome (PICO) were identified)?	• Was the assignment of patients to treatment randomised?	• Were comparison groups clearly defined?	• Were outcomes measured in an objective way?	Studies not related to the specific patient/population (e.g. different patient/population, animal models, mechanical models etc.) should have their methodological quality allocated to the type of study, i.e.
• Was study design defined?	• Was the randomisation list concealed?	• Were outcomes measured in the same (preferably blinded) objective way in both groups?	• Were known confounders identified and appropriately controlled for?	• RCT = good
• Were selection criteria stated for studies to be included (using appropriately crafted search strategies)?	• Were all patients who entered the trial accounted for in its conclusions?	• Were known confounders identified and appropriately controlled for?	• Was follow-up of patients sufficiently long and complete?	• Studies without randomised controls = fair
• Were characteristics and methodological quality of each trial identified?	• Were the patients analysed in the groups to which they were randomised?	• Was follow-up of patients sufficiently long and complete?		• Studies without controls = poor
	• Were patients and clinicians "blinded to which treatment was being received?			Animal studies should also be designated using italics
	• Aside from the experimental treatment, were the groups treated equally?			
	• Were the groups similar at the start of the trial?			

Good studies = have most (all of the relevant quality items. Fair studies = have some of the relevant quality items. Poor studies = have few of the relevant quality items (but sufficient value to include for further review).

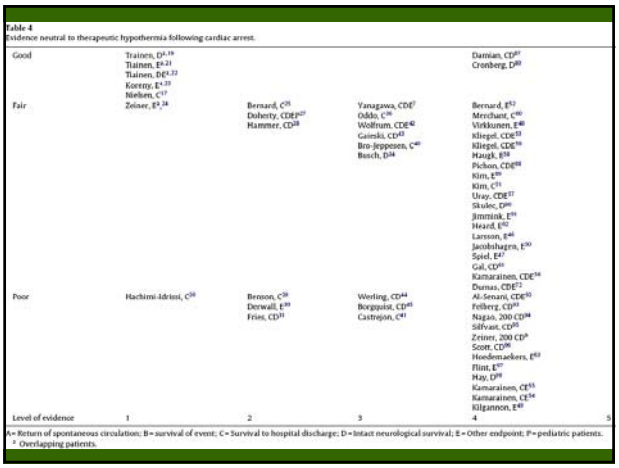

Table 4
Evidence neutral to therapeutic hypothermia following cardiac arrest.

Good	Trainen, D[1,19] Tiainen, E[4-21] Tiainen, D[4,22] Koremy, L[4,23] Nielsen, C[17]			Damian, CD[37] Cronberg, D[40]
Fair	Zeiner, E[5,24]	Bernard, C[25] Doherty, CDE[27] Hammer, CD[28]	Yanagawa, CDE[7] Oddo, C[36] Wolfrum, CDE[42] Gaieski, CD[43] Bro-Jeppesen, C[40] Busch, D[34]	Bernard, E[52] Merchant, C[46] Virkkunen, E[48] Kliegel, CDE[53] Kliegel, CDE[56] Haugk, E[54] Pichon, CDE[58] Kim, E[59] Kim, C[31] Uray, CDE[17] Skulec, D[60] Jimmink, E[61] Heard, E[62] Larsson, E[64] Jacobshagen, E[30] Spiel, E[47] Gal, CD[49] Kamarainen, CDE[16] Dumas, CDE[72] Al-Senani, CDE[50] Fellberg, CD[63] Nagao, 200 CD[34] Silfvast, CD[65] Zeiner, 200 CD[8] Soret, CD[66] Hoedemaekers, E[67] Flint, E[67] Hay, D[68] Kamarainen, CE[55] Kamarainen, CE[54] Kilgannon, E[69]
Poor	Hachimi-Idrissi, C[26]	Benson, C[29] Derwall, E[33] Fries, CD[35]	Werling, CD[44] Borgquist, CD[45] Castrejon, C[41]	Felbrig, CD[63] Nagao, 200 CD[34] Silfvast, CD[65] Zeiner, 200 CD[8] Soret, CD[66] Hoedemaekers, E[67] Flint, E[67] Hay, D[68] Kamarainen, CE[55] Kamarainen, CE[54] Kilgannon, E[69]
Level of evidence	1	2	3	4

A = Return of spontaneous circulation; B = survival of event; C = Survival to hospital discharge; D = Intact neurological survival; E = Other endpoint; P = pediatric patients.
[a] Overlapping patients.

Results

- 4 LOE1 (meta-analyses)
- 7 LOE1 (R C T), but 6 from the same group
- 9 LOE2 (non-randomized, concurrent controls)
- 15 LOE 3 (retrospective controls)
- 40 LOE4 (no controls)
- 1 LOE 5 (extrapolated from non-cardiac arrest group)

Results

- **Who to cool?**

1. Witnessed cardiac arrest, VF or non perfusing VT & presumed cardiac origin of the arrest. (more complications in the hypothermia group. Ex: sepsis, bleeding, pneumonia)
2. ROSC following a VF cardiac arrest.
3. STEMI following ROSC after a VF cardiac arrest who underwent PCI
4. Comatose survivors of VF cardiac arrest.
   - Neurological outcome improved
   - Mortality improved

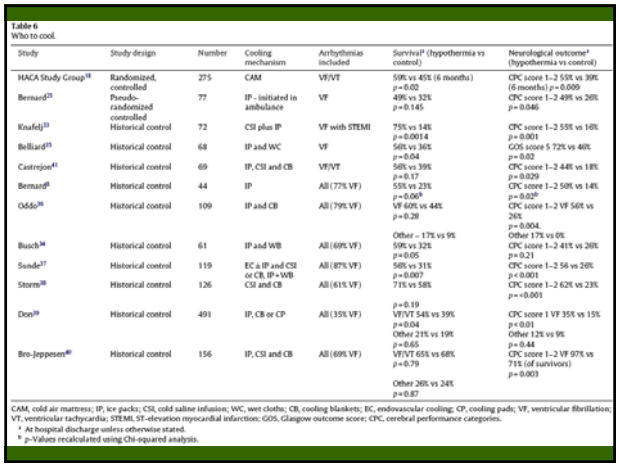

Table 6
Who to cool.

Study	Study design	Number	Cooling mechanism	Arrhythmias included	Survival[a] (hypothermia vs control)	Neurological outcome[a] (hypothermia vs control)
HACA Study Group[18]	Randomized, controlled	275	CAM	VF/VT	50% vs 45% (6 months) $p = 0.02$	CPC score 1–2 55% vs 39% (6 months) $p = 0.009$
Bernard[25]	Pseudo-randomized controlled	77	IP - initiated in ambulance	VF	49% vs 32% $p = 0.145$	CPC score 1–2 49% vs 26% $p = 0.046$
Knafelj[33]	Historical control	72	CSI plus IP	VF with STEMI	75% vs 14% $p = 0.0014$	CPC score 1–2 55% vs 16% $p = 0.001$
Belliard[35]	Historical control	68	IP and WC	VF	58% vs 36% $p = 0.04$	GOS score 5 72% vs 46% $p = 0.02$
Castrejon[41]	Historical control	69	IP, CSI and CB	VF/VT	58% vs 39% $p = 0.17$	CPC score 1–2 44% vs 18% $p = 0.029$
Bernard[8]	Historical control	44	IP	All (77% VF)	55% vs 23% $p = 0.06$[b]	CPC score 1–2 50% vs 14% $p = 0.02$[b]
Oddo[36]	Historical control	109	IP and CB	All (79% VF)	VF 60% vs 44% $p = 0.28$ Other – 17% vs 9%	CPC score 1–2 VF 58% vs 26% $p = 0.004$. Other 17% vs 0%
Busch[34]	Historical control	61	IP and WB	All (69% VF)	59% vs 32% $p = 0.05$	CPC score 1–2 41% vs 26% $p = 0.21$
Sunde[37]	Historical control	119	EC à IP and CSI or CB, IP + WB	All (87% VF)	56% vs 31% $p = 0.007$	CPC score 1–2 56 vs 26% $p < 0.001$
Storm[38]	Historical control	126	CSI and CB	All (61% VF)	71% vs 58% $p = 0.19$	CPC score 1–2 62% vs 23% $p = <0.001$
Don[39]	Historical control	491	IP, CB or CP	All (35% VF)	VF/VT 54% vs 39% $p = 0.04$ Other 21% vs 19% $p = 0.65$	CPC score 1 VF 35% vs 15% $p < 0.01$ Other 12% vs 9% $p = 0.44$
Bro-Jeppesen[40]	Historical control	156	IP, CSI and CB	All (69% VF)	VF/VT 65% vs 68% $p = 0.79$ Other 26% vs 24% $p = 0.87$	CPC score 1–2 VF 97% vs 71% (of survivors) $p = 0.003$

CAM, cold air mattress; IP, ice packs; CSI, cold saline infusion; WC, wet cloths; CB, cooling blankets; EC, endovascular cooling; CP, cooling pads; VF, ventricular fibrillation; VT, ventricular tachycardia; STEMI, ST-elevation myocardial infarction; GOS, Glasgow outcome score; CPC, cerebral performance categories.
[a] At hospital discharge unless otherwise stated.
[b] p-Values recalculated using Chi-squared analysis.

Results

- **How to cool?**

1. IV of ice-cold fluids (30ml/kg of 4 ◦C N/S or Ringer's)
   ➔ ↑MAP , ↑ PH, renal function improve.
2. Ice packs over groins, arm pits and around the head and neck.
3. Combine internal and surface cooling device (air or water circulating, gel-coated, intravascular…..)

- Typical external cooling devices:

cooling blankets or pads with water filled circulating systems.

Results

- **How to cool?**

- Overcooling: ice bag > IV
- IV is more reliable: IV was out of range for 3.2±4.8%; others out of range 40~80% ($p < 0.05$).

- Transnasal delivery of perflurocarbon nebulised with oxygen was excluded due to started during cardiac arrest.
- Optimal rate of warming : not known ; currently about 0.25–0.5 ◦C/hr

Results

- **When to cool?**
- ROSC after VF; 2L of ice-cold Ringer
  pre-hospital V.S. on arrival
  neurological outcome: no difference

Limit : initial BT differ on arrival
after 30min ➔ similar

Results

- **When to cool?**
- In one case series, IV cooling p't
➔ time to coldest BT is a predictor of good neurological outcome.

- In one registry-based case series
➔ time to initiate cooling (median:90min, interquartile:60~165min), not associated with good neurological outcome

Results

- **Safe with PCI?**
- 3 historical controls & 3 case series
➔ feasible in cardiac arrest by AMI

Results

- **Harm from cooling?**
- Large prospective, observational, registry based study of OHCA p't showed increased complication, but….

Associated with increased mortality:

1. Sustained hyperglycemia
2. Seizures treated with anticonvulsant

Results

- **Harm from cooling?**
- PN, bleeding, e- & metabolic disorder, sepsis ↑ in all IV device (IABP, cooling…) group.
- IL-6, PN, catecholamine use, bacteria colonization, DVT, arrhythmia: ↑
- Shivering: ↑ metabolic rate, O2 demand, and MI.
- Insulin sensitivity & secretion: ↓

Discussion

- Therapeutic hypothermia following cardiac arrest in comatose patients with ROSC improves mortality and neurological outcome.
- Just one LOE I study, others use the same data from the study.

- Have benefit even if delayed.
- 32~34C for 24 hr, optimal strategy: unknown
- Time to initiate cooling.
- Length, speed, technique of cooling & Rate of re-warming

Authors conclusion and recommendation

- VF/VT out-of-hospital cardiac arrest : effective ! reasonable evidence
- Cardiac arrest from non-shockable rhythms or in-hospital arrest: only observational data
- Can do T.H. in pre- and in-hospital setting.
- Can be done in conjunction with other interventions such as PCI.
- Whilst devices with temperature feedback appear to provide BT control.

My conclusion

- T.H. is useful especially in shockable p't
- Initiate T.H. ASAP
- More complications but improved outcome
- Need more evidence

- Thank you for your attention!