Journal Meeting

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#1 Clinical paper

Severe QTc prolongation under mild hypothermia treatment and incidence of arrhythmias after cardiac arrest — A prospective study in 34 survivors with continuous Holter ECG

Article data

- Clinical paper
- Journal : *Resuscitation* 2011, article in press
- Authors : Christian Storm et al.
- From : Campus Virchow-Klinikum, Charité Universitätsmedizin Berlin, Berlin, Germany

背景

- 低體溫治療在新的guideline出來後，已經成爲一些心肺功能停止經復甦後的標準療法 (ILCOR & ERC)
- 32~34℃的低體溫治療可以改善病人神經學的預後
- 先前的研究指出低體溫可能造成一些心律不整 (transient bradycardia, QTc prolongation)

Arryhthmias

- 惡性的心律不整(malignant arrhthmias)可能導致嚴重的後果，例如VT, Vf, Torsade de pointes，讓人不得不小心
- QTc prolongation 又特別容易導致惡性的心律不整
- How about monitor it by *Holter EKG* ?

Methods

- Prospective , single center study
- Period : April 2009 ~ December 2009
- Case : 34 were enrolled
- 不論initial rhythm，所有人在經過ACLS guideline復甦之後，都接受低體溫治療
- 住院後隨即開始低體溫治療同時裝上Holter EKG

Cooling method

- IV cold saline insusion (4℃,1000-1500 cc bolus)
- Followed by surface cooling (ArcticSun2000®)
- Target BT : 33℃, maintain for 24 hr
- Iv sedation and anagesia to prevent shivering : midazolam, fentanyl, and pancuronium
- Monitor K+

Monitor the EKG

- Start Holter EKG monitor just after ROSC
- Monitor 48 hrs
- Bazett formula: $QTc = QT/\sqrt{RR}$
- Arrhythmias
  - Salve 3–5 beats
  - non- sustained >5 beats ≤29 s
  - Sustained VT ≥ 30 s

Clinical outcome

- Assessed at the time discharged from ICU
- Pittsburgh Cerebral Performance Category (CPC)
- CPC 1-2 : favorable outcome
- CPC 3-5 : unfavorable outcome

Results

Table 1
Baseline characteristics given as number/total number and % or median and interquartile range (IQR; 25–75).

Variable	Patients (n = 34)
Baseline characteristics	
Age (years)	61.5 (52.0–77.5)
Female sex-no./total no.(%)	12 (35.3)
APACHE score	31.5 (24.5–37.0)
Location of cardiac arrest	
Out-of-hospital no./total-no. (%)	28 (82.3)
In-hospital no./total-no. (%)	6 (17.6)
Cause of cardiac arrest	
AMI-no./total no. (%)	10 (29.4)
Primary arrhythmia-no./total-no. (%)	14 (41.2)
Respiratory no./total-no. (%)	8 (23.5)
Other no./total no.(%)	2 (5.9)
Initial rhythm	
Asystole no./total-no (%)	12 (35.3)
PEA no./total-no (%)	7 (20.6)
VF no./total-no (%)	15 (44.1)
PCI-no/total no (%)	17 (50)
Time to ROSC (min)	12 (8.5–17)
Length of ICU stay (days)	14.5 (5.5–27.5)
Time on ventilator (h)	236 (116.5–418.0)

DC Shock: 2 (1,26~4.0)

Continuous Holter EKG

- Median HR : 85.50
- VT occurred during hypothermia:3 (8.8%) non-sustained and without treatment
- Torsade de pointes : 0

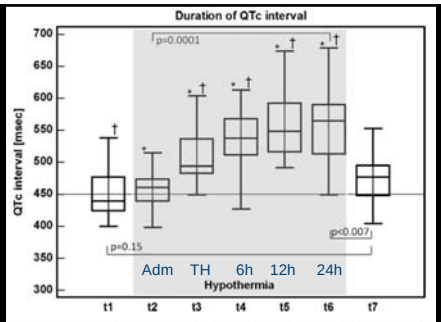

Fig. 1. Duration of QTc interval [ms] at different time points of measurement, horizontal line at 450 ms indicates upper level of normal range of QTc interval. Time points t1: out-of-hospital ECG ($n = 17$), t2: admission to hospital ($n = 34$), t3: start of MTH ($n = 34$) and Holter monitoring, t4: after 6 h at 33 °C, t5: after 12 h at 33 °C, t6: end of MTH after 24 h at 33 °C, t7: end of Holter monitoring after 48 h > 36 °C. Changes in QTc interval are tested between different time points: t2–t6 ($p = 0.0001$), t1–t7 ($p = 0.15$), t6–t7 ($p < 0.007$); * indicates testing between t2 and t3, t4, t5, t6 (all $p = 0.0001$); † indicates testing between t1–t3 ($p = 0.008$) and t1–t4, t5, t6 (all $p < 0.0001$).

The QTc

- Serum potassium were within normal limit
  - 3.5-5.5 mmol/L
- Hypothermia induce an off-on-off phenomenon
- Singnificant in t 3~6 (hypothermia stage)
- Max QTc :673.52 ms after 12h of 33℃

Drugs effecting QTc

- Amiodarone use
  - During resuscitation : 32.4 %
  - ICU admission : 8.8 %
- Antibiotics
  - 44.1 % (cepha, quinolone, ampi, …)
  - No detail discussion about it

Neurological outcome

- CPC 1-2 : 17 p't (50%)
- CPC 3-5 : 17 p't (50%)
- Overall mortality :13 p't (38.2%)

Discussion

- QTc prolongation during mild therapeutic hypothermia without a severe incidence of life-threatening arrhythmias
- No Torsade de pointes, only low incidence of VT

Physiology

- BT ↓ :
  - HR ↓
  - Spontaneous depolarization of pace-maker cells ↓
  - Myocardial impulse conduction ↓
  - Action potential ↑
- EKG change :
  - Prolonged PR interval
  - Expanded QRS
  - QT interval ↑

Hypothermia and arrhythmia

- Stablization of cell membrane during hypothermia in swine model
- Mild therapeutic hypothermia lower the incidence of arrhythmias
- < 30 ℃ will increase the risk
- Closely monitor BT and avoid over cooling
- Monitor serum potassium level

Amiodarone

- Recommended in refractory VF or pulseless VT
- Acting at potassium channel
- Lengthening the action potential
- Amiodarone increase no risk of arrythmias during MTH treatment

Limitations

- In post cardiac arrest patient, QTc prolongation is generally possible for multiple reasons
- Due to the ethical reason, it's not possible to perform RCT and control study
- No 12-lead EKG for OHCA patients
  → interpretation bias

Conclusion

- During mild therapeutic hypothermia treatment, QTc and EKG should be closely monitored to prevent malignant arrhythmias
- Beware of anti-arrythmic drug and Abx that may affect the QTc interval
- Routine and frequent EKG record should become a standard protocol during hypothermia treatment

#2 Case report

Reversible brain death after cardiopulmonary arrest and induced hypothermia

Article data

- Case Report
- Journal : *Crit Care Med* 2011 Vol. 39, No. 6
- Authors : Adam C. Webb, MD et al.
- From : Departments of Neurology and Neurosurgery, Neuroscience Critical Care, Emory University School of Medicine, Atlanta, USA

Case

- A 55-year-old male present to ER due to respiratory failure with SpO2 60 %
- He stated that he "cannot breathe"
- Lethargic and develop 2nd heart block
- Past history : asthma without relief from bronchodilators

Then…

- ABG
  - pH : 6.96
  - PCO_2 : 97 mmHg
  - HCO_3 : 22 mEq/L
- Intubation → PEA
- Start CPR and ROSC after 20 mins
- Transfer to ICU at hour 1

Therapeutic hypothermia

- Start at hr 16
- Achieve 33 ℃ at hr 48
- Rewarming began at hr 50
- Consult neurologist for prognosis at hr 56

Table 3. Serum creatinine and transaminase levels

Hours	Creatinine, mg/dL	AST, U/L	ALT, U/L
0	1.83	55	40
22	1.41	142	64
49	1.17	277	89
68	1.35	285	94
92	1.64	262	110
116	2.56	100	82

AST, aspartate aminotransferase; ALT, alanine transaminase.

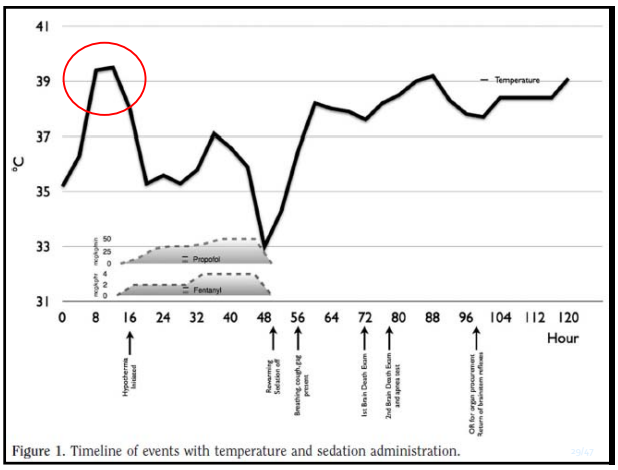

Figure 1. Timeline of events with temperature and sedation administration.

Table 1. Timing and description of important events

Hours		
0		Return of spontaneous circulation
2	CT	Initial examination in intensive care unit: no eye opening, no response to pain, pupils 3 mm nonreactive, multifocal myoclonus
7		Head computed tomography scan suggests diffuse cerebral edema consistent with global hypoxic–ischemic injury
16[a]		Therapeutic hypothermia initiated with surface cooling and cold saline infusion
50[a]		Rewarming initiated and propofol and fentanyl infusion stopped

Table 2. Timing and details of neurologic examinations

Hours	Eye Opening	Motor Responses	Pupillary Responses	Corneal Reflex	Cough/Gag	Spontaneous Respirations	Myoclonic Movements
2	–	–	2 mm NR	–	–	–	+
56	–	+	2 mm, sluggish	–	+	+	+

EEG

- A 16-channel continuous EEG was performed at hour 56
- No discernible cerebral electrical activity at < 10 μV
- The tracing was somewhat obscured by muscle artifact from frequent myoclonic activity

Downhill at hour 72

- Absent of dolls eye sign, cold caloric responses
- Meet the criteria of brain death based on American Academy of Neurology (AAN) guidelines

Table 2. Timing and details of neurologic examinations

Hours	Eye Opening	Motor Responses	Pupillary Responses	Corneal Reflex	Cough/Gag	Spontaneous Respirations	Myoclonic Movements
2	–	–	2 mm NR	–	–	–	+
56	–	+	2 mm, sluggish	–	+	+	+
72	–	–	4 mm NR	–	–	–	–
78	–	–	4 mm NR	–	–	–	–

Hour 78

- Re-examination for brain death after 6 hrs
- 10-min apnea test
  - ABG pCO_2 from 41 → 108 mmHg under O_2 mask 6L/min
- Family preferred organ donation
- Organ Procurement Organization added 1 gm of methylprednisolone as donor protocol

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7	Head computed tomography scan suggests diffuse cerebral edema consistent with global hypoxic–ischemic injury
16[a]	Therapeutic hypothermia initiated with surface cooling and cold saline infusion
50[a]	Rewarming initiated and propofol and fentanyl infusion stopped
56[a]	Examination: no eye opening, no response to pain, sluggishly reactive 2-mm pupils, no corneal reflexes, intact cough reflex and gag reflex, spontaneous respirations present
72[a]	First clinical examination consistent with brain death
78[a]	Second clinical examination consistent with brain death
78[a]	10-min apnea test with rise in pCO_2 from 41 to 108 mm Hg

Hour 98, at OR

- Anethesiologist noticed that patient was coughing
- Corneal reflex (+), spontaneous breathing (+)
- GCS : E1VtM1
- DC organ donation
- Inform family and send patient back to ICU

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56	–	+	2 mm, sluggish	–	+	+	+
72	–	–	4 mm NR	–	–	–	–
78	–	–	4 mm NR	–	–	–	–
98	–	–	4 mm NR	+	+	+	–
120	–	–	4 mm NR	+	+	+	–

Afterward…

- Still poor neurological prognosis
- Keep full supportive treatment
- Repeat EEG at hour 106
  - No discernible cerebral electrical activity at > 2 μV for over 30 mins
- Hour 145 : reflex and spontaneous breathing (-)
- Repeat CT : diffuse cerebral edema and transtentorial and cerebellar tonsillar herniation

Table 2. Timing and details of neurologic examinations

Hours	Eye Opening	Motor Responses	Pupillary Responses	Corneal Reflex	Cough/Gag	Spontaneous Respirations	Myoclonic Movements
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56	–	+	2 mm, sluggish	–	+	+	+
72	–	–	4 mm NR	–	–	–	–
78	–	–	4 mm NR	–	–	–	–
98	–	–	4 mm NR	+	+	+	–
120	–	–	4 mm NR	+	+	+	–
145	–	–	4 mm NR	–	–	–	–
168	–	–	4 mm NR	–	–	–	–
192	–	–	4 mm NR	–	–	–	–

NR, nonreactive.

78[a]	10-min apnea test with rise in pCO_2 from 41 to 108 mm Hg
98[a]	Patient taken to operating room for organ procurement: noted cough, bilateral corneal reflex, and respirations
106	Repeat electroencephalogram shows no discernible cerebral electrical activity
145	Loss of remaining brainstem function, clinical examination again consistent with brain death
171	Somatosensory-evoked potential shows absence of P17 and N20 responses
194	Magnetic resonance image shows diffuse cerebral and cerebellar edema, transtentorial and cerebellar herniation
200	Nuclear cerebral blood flow study confirms absence of cerebral blood flow
202	Termination of mechanical ventilation, patient pronounced dead by cardiopulmonary criteria

[a]Designates events marked on timeline in Figure 1.

Finally…

- Termination the ventilator and declare death by cardiopulmonary criteria on hour 202
- The medical team did not mention the donation to the family because of such circumstances

Discussion

- This is the first case report of reversible findings of brain death
- The limitation of EEG
  - Only measures cerebral cortical function
  - Not brainstem function

The outcome

- It did not affect the overall neurological outcome
- But affect the eligibility of organ donation rule
- Much effect on the trust of family to the medical team

AAN brain death guidelines

- 5 questions related to variability in brain death determination
  1. Are there patients who fulfill the clinical criteria for brain death who later recover brain function ?
  2. Are there available evidence in the literature for an adequate observation period to ensure that cessation of neurologic function is permanent ?
     - Previous AAN guideline : 6 hrs between clinical exam

Another case report

- 10-month-old boy with reversible findings of brain death after cardiac arrest and under therapeutic hypothermia
- Clinical based guidelines may be insufficient to determine irreversibility of brain death
- Maybe the hypothermia is the key factor

The possible explanation

1. Brainstem ischemic shock
   - Initially ischemic shock and recover and then be finally injured again by a cascade of cellular injury
2. Hypothermia
   - Longer induction and shorter duration in our case. It may alter the timeline of progression to brain death.

The possible explanation

3. The effect of corticosteroids
   - 2 doses of methylprednilolone was administered
   - The possibility of steroid-related reversible brain death is unlikely and unprecedented
- To determine brain death
  - More caution in the first 24 hr post cardiac arrest
  - Now… plus the factor of therapeutic hypothermia

Conclusion

- Cautious approach when determining brain death after cardiac arrest when hypothermia is used
- No current guidelines of a minimum acceptable waiting period or ancillary testing
- A single clinical brain death examination in conjunction with an apnea test may be insufficient