Therapeutic hypothermia after cardiac arrest: A survey of practice in the intensive care units (ICU) in Hong Kong

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Abstract

***Background*: Previous studies showed that therapeutic hypothermia after out-of-hospital ventricular fibrillation arrest significantly improved neurological outcome and survival. This retrospective case series aims to examine the practice of therapeutic hypothermia in resuscitated post cardiac arrest patients in Hong Kong.**

***Methods*: Post cardiac arrest patients with therapeutic hypothermia in six local ICUs from January 2007 to June 2012 were identified. Baseline demographic characteristics, clinical data on the cardiac arrest, cooling profile and patient outcomes were recorded. Statistical analyses were performed to identify factors associated with good neurological outcome at hospital discharge.**

***Results*: 117 patients underwent therapeutic hypothermia within the aforementioned time period. Majority was out-of-hospital arrest (75.2%) and male (70.1%). The median age was 59. The initial presenting cardiac rhythm was shockable in 59.0%. Thirty-two point two percents of the patients enjoyed good neurological outcome. The hospital mortality was 49.6%. The median cooling rate and time from regain of spontaneous circulation (ROSC) to target temperature were 0.50°C/hour and 6.5 hours respectively. Multivariate logistic regression analysis revealed that an older age, a longer downtime and a higher blood glucose range during therapeutic hypothermia had a reduced odds ratio for good neurological outcome while a shockable presenting rhythm was the strongest independent predictor for good neurological outcome (OR 34.25, 95% CI 5.30-221.22, p<0.001).**

***Conclusions*: Therapeutic hypothermia is probably underutilized in Hong Kong. It is most beneficial for patients with an initial shockable rhythm. In future practice, more attention should be paid in attaining rapid cooling, maintaining tight temperature and glucose control.**

Introduction

According to a survey in 1997, the incidence of sudden cardiac deaths was 1.8 per 100,000 populations in Hong Kong.(1) Many initially resuscitated patients either succumb during subsequent hospitalization or suffer permanent neurological damage, caused not only by hypoxia but also by reperfusion injury.

Two independent multicenter prospective randomized trials showed that rapid induction and maintenance of mild hypothermia to 32-34 °C for 12-24 hours after out-of-hospital ventricular fibrillation (VF) cardiac arrest significantly improved neurological outcome and long term survival. (2,3) The International Liaison Committee on Resuscitation (ILCOR) recommended since late 2002 that therapeutic hypothermia (TH) should be offered to those unconscious adult patients who are resuscitated from out-of-hospital cardiac arrest with an initial rhythm of ventricular

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fibrillation and such cooling should also be considered for other rhythms or in-hospital cardiac arrest.(4)

This is a retrospective case series, which aims to examine the practice of therapeutic hypothermia in resuscitated post cardiac arrest patients in local intensive care units (ICU) in Hong Kong.

Methods

Patients who had undergone therapeutic hypothermia were identified by the Clinical Data Analysis and Reporting System using ICD-9 diagnosis code, 427.5, "cardiac arrest" and ICD-9 procedure code, 99.81, "hypothermia (central) (local)" and by personal registries in six local ICUs. These ICUs include Alice Ho Miu Ling Nethersole Hospital, Caritas Medical Centre, Pamela Youde Nethersole Eastern Hospital, Ruttonjee Hospital, Queen Elizabeth Hospital and Queen Mary Hospital. Data from January 2007 to June 2012 were included. Electronic medical notes as recorded in the clinical information system and paper records were reviewed. The study protocol was approved by the Clinical Research Ethics Committees of the respective clusters to which the hospitals belong.

Baseline demographic, clinical, and laboratory data of each subject were collected retrospectively. Temperature measurements and medications dosing were retrieved. Discharge location and Pittsburgh cerebral performance category (CPC) were recorded. Neurological outcome was categorized at hospital discharge as good (CPC 1-2, minimal to moderate disability), or poor (CPC 3-5, severe disability, vegetative state or dead). Acute Physiology and Chronic Health Evaluation (APACHE) IV scores were retrieved from the Hospital Authority ICU APACHE score data registry.

Statistics

Data were analyzed using the Statistical Package for Social Sciences, version 15.1. Continuous data were expressed as medians with interquartile ranges (IQR) and proportions as percentages because of non-normal distributions. Continuous and categorical data were compared using Wilcoxon Mann-Whitney tests and Fisher's exact tests as appropriate. A logistic regression model with backward elimination was used to identify independent factors that were associated with good neurological outcome (defined as CPC categories 1 or 2). Co-linearity between variables was excluded prior to modeling. Two-tailed tests of significance were adopted and $p<0.05$ was considered statistically significant.

Results

From January 2007 to June 2012, a total of 117 post cardiac arrest patients were given therapeutic hypothermia in the six ICUs mentioned above. The baseline demographic data and profile of cardiac arrest were showed in **Table 1**. The median age was 59 and 70.1% were male. Seventy-five point two percents were out-of-hospital arrests, 34.1% of which had cardiopulmonary resuscitation by bystanders. Seventy point one percents were considered cardiac causes of arrest, the most common of which was acute coronary syndrome (ACS, 62.2%), followed by idiopathic ventricular fibrillation (22.0%). The most frequent initial cardiac rhythm was ventricular fibrillation or ventricular tachycardia (VT) (59.0%). The median time from arrest to ROSC (downtime) was 17.3 minutes. The median APACHE IV score was 119.0 with a predicted mortality rate of 80%. The median durations of ICU stay and hospital stay were 7 and 12 days respectively.

Table 2 summarized the details of the cooling profile in our series. Ninety-four point nine percents cases initiated TH in ICU. Only 6 cases initiated at the Accident and Emergency Department (5.1%). The median time from ROSC to initiation of cooling was 129.5 minutes. The cooling rate was 0.50 °C/hour and the median time from ROSC to target temperature (32-34°C) were 6.5 hours. Six cases failed to achieve target temperature. Most institutions utilized a combination of cooling methods for initiation and maintenance of TH. Cold intravenous fluid (53.0%) was most frequently used, followed by cold water blankets (47.9%) and surface ice packs (42.7%). No center used endovascular catheter but extracorporeal circulation (6 cases of continuous venovenous hemofiltration and 2 cases of extracorporeal membrane oxygenation) was employed for maintenance of TH in 8 cases (6.8%). The actual duration of hypothermia, defined as the duration when core temperature was less than 34°C, ranged from 0 to 39 hours with a median of 16.0 hours. For monitoring of core body temperature, nasal and rectal temperature probes were most commonly used, accounting for 36.8% and 50.4% respectively. Tympanic

membrane temperature was also measured in 86.3% for accessory purpose. For rewarming, only 25.5% cases were rewarmed in a controlled manner. Others were rewarmed passively. The median rewarming rate was 0.50°C/hour.

The most frequent adverse event (**Table 3**) encountered during TH was sustained hyperglycemia (defined as two consecutive hemoglucostix values more than 8mmol/L for longer than 4 hours), which occurred in 81.9%, followed by shivering in 60.2%. Muscle relaxants were given in 65.0% of the cases.

Overcooling with a core body temperature below 32°C was encountered in 44.4% patients. The lowest temperature was 28.1°C. Overcooling was not significantly associated with hospital mortality, poor neurological outcomes or complications like sepsis, bleeding or arrhythmia by univariate analyses.

Hypokalemia, defined as serum potassium level less than 3mmol/L during TH, occurred in 25.9% and was significantly associated with the occurrence of arrhythmia (p=0.04).

Sepsis occurred in 52.6% in our series. The most common site of infection was pneumonia (77.0%), followed by bloodstream infections (14.8%). Bleeding complications occurred in 28.2%. Most were minor. Only 5.1% were major bleeding complications that required transfusion.

Arrhythmic complications were categorized into atrial arrhythmia or ventricular arrhythmia within 72 hours of TH. Such complications occurred in 15.4% and 9.4% of patients respectively, and were associated with hypokalemia (p=0.04) but not overcooling (p=0.35).

Post-rewarming hyperthermia, defined as core body temperature more than 38°C within 72 hours after cessation of TH, occurred in 69.2% in our series.

Hypoglycemia episodes with hemoglucostix value less than 4mmol/L was found in 15.4% patients during TH.

The hospital mortality of the whole series was 49.6%. Thirty-two point two percents of the patients enjoyed good neurological outcome at hospital discharge.

Univariate analyses (**Table 4**) revealed that a younger age, an initial shockable rhythm, cardiac causes of arrest, out-of-hospital arrest, a shorter downtime, lower APACHE IV score were significantly associated with good neurological outcome, whereas sustained hyperglycemia, a higher blood glucose range during TH were associated with poor neurological outcome at hospital discharge.

The results of the multivariate logistic regression analysis were shown in **Table 5**. Older age, longer downtime and higher blood glucose range during TH had a reduced odds ratio while a shockable initial rhythm is a strong independent predictor for good neurological outcome (OR 34.25, 95% CI 5.30-221.22, p<0.001).

Discussion

Therapeutic hypothermia had been proven to be beneficial for patients who are resuscitated from out-of-hospital VT/VF arrest.(2,3) Proposed mechanisms include reduction of excitatory neurotransmitters, decreased apoptotic neuronal death, decreased production of inflammatory cytokines, decreased oxygen free radicals and suppression of epileptogenic electrical activity, etc.(5)

Few studies have investigated post-resuscitation care in Hong Kong. This study describes the practice of TH after cardiac arrest in 6 local ICUs 10 years after the publication of the two landmark trials and international guidelines. Given the number of resuscitated cardiac arrests, it is shown that TH is still not a routine and common practice for these eligible patients locally.

The most common way of cooling in local ICUs are a combination of cold intravenous fluid and surface cooling (>50%), possibly due to the simplicity and low cost. Provided an adequate body surface area are covered, surface cooling were effective and safe for rapid induction of therapeutic hypothermia. Cooling associated skin injury albeit uncommon, should be watched out for especially for those who are on high dose vasopressor and with impaired left ventricular ejection fraction.(6) While surface cooling is convenient, it needs extreme nursing vigilance and experience to maintain the target temperature. This may explain why the median actual duration of hypothermia was 16.0 hours only, which was well below the targeted 24 hours. Besides, unintentional overcooling may occur because it takes time for peripheral and core thermal compartments

to equilibrate. In our series, overcooling occurred in 44.4% of the patients, which is less frequent than that reported by Merchant et al, who reported a frequency up to 63%.(7)

Many cooling devices are available commercially. There is little published evidence as to which one is the safest and most effective. The most frequently used commercial surface cooling devices in our centers were Blanketrol® and Criticool®. They are compatible with cardiac intervention because of the radiolucency. However, their routine uses have been limited by the high cost of the disposable cooling pads. No center in our series utilized intravascular catheter for TH, probably because of its cost and the invasive nature.

To maximize the neuroprotective effect of therapeutic hypothermia, it might be necessary to induce hypothermia as soon as possible after ROSC. Animal model showed that delay in therapeutic hypothermia might negate the benefit. (8) Whether this applies to human remains controversial as spontaneous hypothermia before initiation of therapeutic cooling may actually reflect loss of cerebral thermoregulatory ability and more global cerebral injury, which is a poor prognostic sign itself.(9-12)

In our study, cooling was initiated at the Accident and Emergency Department in only 6 cases. Such practice was associated significantly shorter time from ROSC to initiation of TH (p=0.03), but not cooling rate (p=0.30) or time to target temperature (p=0.74). Whether this practice improves better neurological outcome warrants more studies.

Rectal or nasal probes were employed in most centers to monitor core body temperature during TH. Tympanic membrane temperature, despite being measured in 86.3%, is generally believed to inaccurate in reflecting core temperature changes. While rectal temperature is accurate during state of thermal balance, its reading may lag during induction phase. (13) The continual instillation of iced cold saline during induction may therefore result in overcooling. Central intravascular monitoring is considered the most accurate and responsive temperature measurement technique, but is more invasive and associated with complications of central venous cannulation.

Up till now, the optimal duration of TH remains unknown. The centers in our series targeted therapeutic hypothermia for 24 hours. Nevertheless, the median actual duration of hypothermia was 16.0 hours only due to difficulty in tight temperature control.

Most patients were rewarmed passively. Only 25.5% were rewarmed in a controlled manner. The latter group tended to have a more consistent rewarming time. Previous studies suggested that "post-resuscitation" syndrome, which is characterized by raised inflammatory cytokines, vasodilatation and hypotension, can be exacerbated by rapid decooling. (14) Slow and gradual rewarming in a controlled manner theoretically should be more preferable although definite clinical evidence is still lacking. The suggested rewarming rate is 0.2°C to 0.5°C/hour.(15)

Post-rewarming hyperthermia occurred in 69.2% of the patients in our series. Seventeen point three percents were not actively dealt with. Although our studies did not demonstrate a statistical significant relationship between post-rewarming hyperthermia and poor neurological outcome (p=0.327), previous studies have shown that hyperthermia within 48 to 72 hours of cardiac arrest may worsen neurological outcome. (16,17) Hence, prevention and more proactive management of post-rewarming hyperthermia should be considered.

Several groups were not associated with appreciable benefits from TH. We found that TH was more beneficial for those with out-of-hospital arrest. Thirty-eight point six percents of these patients enjoyed good neurological outcome versus only 10.3% of those resuscitated in-hospital arrests. This was not surprising as in-hospital arrests were more often associated with non-cardiac causes of arrest like uncontrolled sepsis, cancer. This finding is also consistent with previous studies.(18,19) Nevertheless, such association between location of cardiac arrest and good neurological outcome was not confirmed after multivariate logistic regression. This may be due to a high negative correlation between in-hospital arrests and a shockable rhythm ($R=-0.45$, $p<0.001$). The hospital mortality for this group of patients was 79.3%, which was remarkably similar to the 77.8% reported by Yap in her review of in-hospital cardiac arrests in a local teaching hospital.(20)

Patients presenting with PEA or asystole had a gloomy prognosis even with TH. The hospital mortality for this group was up to 85.0% and only 5.0% enjoyed good neurological outcome versus 50.7% in those with VF/VT

despite similar downtime. Whether TH confers any benefits to patients with non-shockable rhythms remains debatable. A systemic review and meta-analysis concluded that TH is associated with reduced in-hospital mortality.(21) However, the authors also commented that most studies they included in their analysis had substantial risks of bias and quality of evidence was very low. On the other hand, analysis of a large registry of 1145 cardiac arrests showed that TH was not associated with good neurological outcome for patients presenting with PEA or asystole.(22)

Out of 51 cases of ACS related cardiac arrests, only 4 received primary percutaneous coronary intervention (PCI) in our series. Another 11 patients had subsequent PCI after awakening from coma. This is in contrast with the recommendation from Advanced Cardiovascular Life Support algorithm where PCI is included together with TH in the post resuscitation bundle of care. Multiple studies have shown that TH, routine coronary angiography and primary PCI for patients after out-of-hospital cardiac arrest of presumed cardiac origin can be incorporated together, which may be associated with improved survival and neurological outcome.(23-25) Even in those with no ST elevation on ECGs, Dumas et al. reported that routine coronary angiography disclosed coronary artery disease in 58% in their series of out-of-hospital cardiac arrest and PCI appeared to be protective.(26)

Shivering was the second most frequent adverse event reported, occurring in 60.2% of the patients. This should have been underestimated because of lack of standardization of the way and frequency of clinical assessment in this retrospective series. Therefore it remains a subjective, intermittent and observer-dependent assessment.

Hypokalemia occurred in 25.9%. Mirzoyev et al. found that hypokalemia of less than 3.0mmol/L and the associated increased QTc were significantly associated with development of polymorphic VT, while rebound hyperkalemia did not reach concerning levels.(27) Hence, it was advised that close monitoring of serum potassium and ECG, maintenance of serum potassium level above 3.0mmol/L, and if possible, avoid drugs that may prolong QTc, are important especially during the cooling phase.

Bleeding complications occurred in 28.2% in our series. Most were minor gastrointestinal bleeding like coffee ground aspirate from nasogastric feeding tubes. Major bleeding complications requiring transfusion occurred in only 5.1% patients. This is consistent with most reports of TH-treated OHCA patients. (2,28)

Sepsis occurred in 52.6% in our series. The most common site of infection was pneumonia (77.0%). Other series of post cardiac arrest patients also demonstrated a high incidence of sepsis from 46% to 67% and similarly, pneumonia was the most common infection.(29,30) Several theories explain why hypothermia increases infectious complications. Firstly, hypothermia impairs secretion of proinflammatory cytokines and suppresses leukocyte migration and phagocytosis. Hypothermia induced insulin resistance and hyperglycemia may further increase the infection risks. Hypothermia may also delay the diagnosis as it modifies parameters and scores like modified clinical pulmonary infection scores artificially. Despite the fact that pneumonia increased length of mechanical ventilation and ICU stay, it did not worsen neurologic outcome or ICU mortality.(29,31) Nielsen et al. even found an inverse relationship between infection and mortality, which might be related to the greater risk of infection during a longer hospital stay.(28)

Blood glucose homeostasis is altered during TH. Proposed mechanisms include reduced glucose utilization, decreased endogenous insulin secretion and increased resistance to exogenous insulin.(32) Cueni-Villoz et al. found that mean blood glucose, blood glucose variability and insulin dose were higher during hypothermia when compared with periods of normothermia.(32) Increased blood glucose variability was even found to be an independent risk factor of hospital mortality after adjusting for markers of disease severity like downtime, initial arrest rhythm and cardiac arrest etiology. Our findings also confirmed this. A higher range of blood glucose during TH had a reduced odds ratio of 0.82 for good neurological outcome (**Table 5**). We also found an alarmingly high rate of sustained hyperglycemia (81.9%).

Table 6 tabulates the comparison between our performance with that from the European Resuscitation Council Hypothermia After Cardiac Arrest Registry Study Group. (33) Compared with Europeans, we attained slower cooling rate and were less meticulous in the temperature control, which was evidenced by the shorter actual duration of hypothermia.

Given the number of resuscitated cardiac arrests, TH was probably underutilized in Hong Kong. We did not look into the reasons for non-use but previous surveys conducted in other countries revealed that major reasons behind were unawareness of the scientific data, lack of protocol, technical constraints, resource and logistical issues.(34,35)

Our study has several limitations. Firstly, this survey reflects the practice of TH in the 6 local ICUs aforementioned. It may not mirror the practice in other ICUs in Hong Kong. Secondly, inadequate coding in the electronic medical records may have resulted in missing data or selection bias. Besides, the study was retrospective and some of pre-hospital data may be missing or inaccurate. Last but not least,this study was not designed to investigate the timing for neuroprognostication. Some of the patients who had died may be due to withholding or active withdrawal of life-sustaining therapies because of the in-charge physicians' perception of a minute chance of neurological recovery, thereby adding to a higher percentage of patients with poor outcome. In fact, data from the National Registry of Cardiopulmonary Resuscitation in the United States (NRCPR) showed that 63% of the patients who were resuscitated from a cardiac arrest were given a "Do Not Resuscitate" status and 43% had care actively withdrawn. (36) Nevertheless, we believe that this phenomenon of "self-fulfilling prophecy" was minimal in our study as the median length of stay in our group of patients with hospital mortality was 12 days, which was much longer than the average 1.5 days in the NRCPR series.

Conclusions

This study reviewed the performance of TH in Hong Kong ICUs. The results showed that TH is most beneficial for an initial shockable rhythm. In future practice,more attention should be paid in attaining rapid cooling, maintaining tight temperature and glucose control.

Table 1. Baseline demographic data and profile of cardiac arrest

	Frequency	Median (IQR)
Male	70.1%	
Age		59 (46-72)
Cardiac causes	70.1%	
Initial VT/VF	59.0%	
Out-of-hospital arrest	75.2%	
Downtime (minutes)		17.3 (10.0-28.3)
APACHE IV score		119.0 (100.3-134.5)
Predicted mortality		0.80 (0.64-0.88)
ICU stay (days)		7 (4-11)
Hospital stay (days)		12 (7-24)

Legend: IQR=interquartile range; APACHE=Acute Physiology and Chronic Health Evaluation; VT=ventricular tachycardia; VF=ventricular fibrillation; ICU=intensive care unit.

Table 2. Cooling profile

	Median (IQR)
Initial temperature (°C)	35.9 (35.1-36.7)
Cooling rate (°C/hour)	0.50 (0.29-0.97)
Time from ROSC to initiation of TH (minutes)	129.5 (69.5-202.5)
Time from ROSC to target temperature (hours)	6.5 (3.0-11.7)
Actual duration of TH with core temperature <34°C (hours)	16.0 (8.5-23.0)
Rewarming rate (°C/hour)	0.50 (0.32-0.69)

Legend: IQR=interquartile range; ROSC=regain of spontaneous circulation; TH=therapeutic hypothermia.

Table 3. Adverse events

	Frequency
Sustained hyperglycemia	81.9%
Shivering	60.2%
Sepsis	52.6%
Overcooling	44.4%
Hypophosphatemia	28.0%
Arrhythmia	26.5%
Hypokalemia	25.9%
Hypoglycemia	15.4%
Bleeding complications requiring transfusion	5.1%

Table 4. Univariate analyses comparing good (CPC 1-2) and poor neurological outcomes (CPC 3-5)

Variable	Neurological outcome	Value	p value
Age	Good	54.0	
	Poor	61.0	0.001
Initial shockable rhythm (%)	Good	94.6	
	Poor	42.3	<0.001
Cardiac causes of arrest (%)	Good	97.3	
	Poor	57.7	<0.001
Out-of-hospital arrest (%)	Good	91.9	
	Poor	67.9	0.005
Downtime (min)	Good	14.0	
	Poor	20.5	0.002
Initial temperature (°C)	Good	36.2	
	Poor	35.7	0.069
Cooling rate (°C/hour)	Good	0.48	
	Poor	0.50	0.194
Actual TH duration (hours)	Good	15.0	
	Poor	18.0	0.247
Rewarming rate (°C/hour)	Good	0.61	
	Poor	0.42	0.065
APACHE IV score	Good	98	
	Poor	124	<0.001
Hypokalemia (%)	Good	27.0	
	Poor	26.0	0.905
Overcooling (%)	Good	51.4	
	Poor	41.0	0.298
Shivering (%)	Good	74.3	
	Poor	53.9	0.062
Arrhythmia (%)	Good	32.4	
	Poor	24.4	0.362
Sepsis (%)	Good	48.6	
	Poor	55.8	0.471
Bleeding (%)	Good	18.9	
	Poor	33.3	0.110
Hypoglycemia (%)	Good	8.1	
	Poor	19.2	0.125
Sustained hyperglycemia (%)	Good	62.2	
	Poor	90.9	<0.001
Blood glucose range (mmol/L)	Good	4.0	
	Poor	6.5	0.001
Post-rewarming hyperthermia (%)	Good	75.7	
	Poor	66.7	0.327

Legend: CPC=Pittsburgh cerebral performance category; TH=therapeutic hypothermia; APACHE=Acute Physiology and Chronic Health Evaluation.

Table 5. Multivariate logistic regression analysis with good neurological outcome (CPC 1 or 2) at hospital discharge as dependent factor

Variable	Odds ratio for good neurological outcome	95% CI	p value
Age	0.96	0.93-0.99	0.022
Shockable rhythm	34.25	5.30-221.22	<0.001
Downtime	0.92	0.87-0.98	0.005
Blood glucose range	0.82	0.69-0.98	0.028

Legend: CPC=Pittsburgh cerebral performance category; CI=confidence interval.

Table 6. Cooling profile compared with the data from Europe (33)

	Local series		The European data	
	Median	IQR	Median	IQR
Time from ROSC to initiation of cooling (min)	129.5	69.5-202.5	131.0	75.0-118.0
Initial temperature (°C)	35.9	35.1-36.7	35.5	34.8-36.2
Cooling rate (°C/hour)	0.50	0.29-0.97	1.1	0.5-1.8
Actual duration of hypothermia (hours)	16.0	8.5-23.0	24.3	23.7-26
Duration of rewarming (hours)	7.0	4.0-10.0	9.0	6.8-12.0

Legend: IQR=interquartile range; ROSC=regain of spontaneous circulation.

References

1. Kwok KM, Lee KL,Lau CP,Tse HF. Sudden cardiac death: prevention and treatment. Hong Kong Med J 2003;9:357-62.
2. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl JMed 2002;346:549-56.
3. Bernard SA,Gray TW,Buist MD,Jones BM,Silvester W,Gutteridge G, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346:557-63.
4. Nolan JP, Morley PT, Vanden Hoek TL, Hickey RW, Kloeck WG, Billi J,et al. Therapeutic hypothermia after cardiac arrest: an advisory statement by the advanced life support task force of the International Liaison Committee on Resuscitation. Circulation 2003;108:118-21.
5. González-Ibarra FP, Varon J,López-Meza EG. Therapeutic hypothermia: critical review of the molecular mechanisms of action. FrontNeurol 2011;2:4.
6. Jarrah S, Dziodzio J, Lord C, Fraser GL, Lucas L, Riker RR, et al. Surface cooling after cardiac arrest: effectiveness, skin safety, and adverse events in routine clinical practice. Neurocrit Care 2011;14:382-8.
7. Merchant RM, Abella BS, Peberdy MA, Soar J, Ong ME, Schmidt GA, et al. Therapeutic hypothermia after cardiac arrest: unintentional overcooling is common using ice packs and conventional cooling blankets. Crit Care Med 2006;34:S490-4.
8. Kuboyama K, Safar P, Radovsky A, Tisherman SA, Stezoski SW, Alexander H. Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: a prospective, randomized study. Crit Care Med 1993;21:1348-58.
9. den Hartog AW, de Pont AC, Robillard LB, Binnekade JM, Schultz MJ, Horn J. Spontaneous hypothermia on intensive care unit admission is a predictor of unfavorable neurological outcome in patients after resuscitation: an observational cohort study. Crit Care 2010;14:R121.
10. Nielsen N, Hovdenes J, Nilsson F, Rubertsson S, Stammet P, Sunde K, et al. Outcome, timing and adverse events in therapeutic hypothermia after out-of-hospital cardiac arrest. Acta Anaesthesiol Scand 2009;53:926-34.
11. Wolff B, Machill K, Schumacher D, Schulzki I, Werner D. Early achievement of mild therapeutic hypothermia and the neurologic outcome after cardiac arrest. Int J Cardiol 2009;133:223-8.
12. Wörner J, Oddo M. Too cold may not be so cool: spontaneous hypothermia as a marker of poor outcome after cardiac arrest. Crit Care 2010;14:1002.
13. Weingart S, Mayer S, Polderman K. Rectal probe temperature lag during rapid saline induction of hypothermia after resuscitation from cardiac arrest. Resuscitation 2009;80:837-8.
14. Seder DB, Van der Kloot TE. Methods of

cooling: practical aspects of therapeutic temperature management. Crit Care Med 2009;37:S211-22.
15. Polderman KH, Herold I. Therapeutic hypothermia and controlled normothermia in the intensive care unit: practical considerations, side effects, and cooling methods. Crit Care Med 2009;37:1101-20.
16. Zeiner A, Holzer M, Sterz F, Schorkhuber W, Eisenburger P, Havel C, et al. Hyperthermia after cardiac arrest is associated with an unfavorable neurologic outcome. Arch Intern Med 2001;161:2007-12.
17. Takasu A, Saitoh D, Kaneko N, Sakamoto T, Okada Y. Hyperthermia: is it an ominous sign after cardiac arrest? Resuscitation 2001;49:273-7.
18. Rittenberger JC, Guyette FX, Tisherman SA, DeVita MA, Alvarez RJ, Callaway CW. Outcomes of a hospital-wide plan to improve care of comatose survivors of cardiac arrest. Resuscitation 2008;79:198-204.
19. Kory P, Fukunaga M, Mathew JP, Singh B, Szainwald L, Mosak J, et al. Outcomes of Mild Therapeutic Hypothermia After In-Hospital Cardiac Arrest. Neurocrit Care 2012;16:406-12.
20. Yap HY, Li TS, Tan KS, Cheung YS, Chui PT, Lam PK, et al. Characteristics, management process, and outcome of patients suffering in-hospital cardiopulmonary arrests in a teaching hospital in Hong Kong. Hong Kong Med J 2007;13:258-65.
21. Kim YM, Yim HW, Jeong SH, Klem ML, Callaway CW. Does therapeutic hypothermia benefit adult cardiac arrest patients presenting with non-shockable initial rhythms?: A systematic review and meta-analysis of randomized and non-randomized studies. Resuscitation 2012;83:188-96.
22. Dumas F, Grimaldi D, Zuber B, Fichet J, Charpentier J, Pène F, et al. Is hypothermia after cardiac arrest effective in both shockable and nonshockable patients?: insights from a large registry. Circulation 2011;123:877-86.
23. Hovdenes J, Laake JH, Aaberge L, Haugaa H, Bugge JF. Therapeutic hypothermia after out-of-hospital cardiac arrest: experiences with patients treated with percutaneous coronary intervention and cardiogenic shock. Acta Anaesthesiol Scand 2007;51:137-42.
24. Gräsner JT, Meybohm P, Caliebe A, Böttiger BW, Wnent J, Messelken M, et al. Postresuscitation care with mild therapeutic hypothermia and coronary intervention after out-of-hospital cardiopulmonary resuscitation: a prospective registry analysis. Crit Care 2011;15:R61.
25. Cronier P, Vignon P, Bouferrache K, Aegerter P, Charron C, Templier F, et al. Impact of routine percutaneous coronary intervention after out-of-hospital cardiac arrest due to ventricular fibrillation. Crit Care 2011;15:R122.
26. Dumas F, Cariou A, Manzo-Silberman S, Grimaldi D, Vivien B, Rosencher J, et al. Immediate percutaneous coronary intervention is associated with better survival after out-of-hospital cardiac arrest: insights from the PROCAT (Parisian Region Out of hospital Cardiac ArresT) registry. Circ Cardiovasc Interv 2010;3:200-7.
27. Mirzoyev SA, McLeod CJ, Bunch TJ, Bell MR, White RD. Hypokalemia during the cooling phase of therapeutic hypothermia and its impact on arrhythmogenesis. Resuscitation 2010;81:1632-6.
28. Nielsen N, Sunde K, Hovdenes J, Riker RR, Rubertsson S, Stammet P, et al. Adverse events and their relation to mortality in out-of-hospital cardiac arrest patients treated with therapeutic hypothermia. Crit Care Med 2011;39:57-64.
29. Mongardon N, Perbet S, Lemiale V, Dumas F, Poupet H, Charpentier J, et al. Infectious complications in out-of-hospital cardiac arrest patients in the therapeutic hypothermia era. Crit Care Med 2011;39:1359-64.
30. Gajic O, Festic E, Afessa B. Infectious complications in survivors of cardiac arrest admitted to the medical intensive care unit. Resuscitation 2004;60:65-9.
31. Perbet S, Mongardon N, Dumas F, Bruel C, Lemiale V, Mourvillier B, et al. Early-onset pneumonia after cardiac arrest: characteristics, risk factors and influence on prognosis. Am J Respir Crit Care Med 2011;184:1048-54.
32. Cueni-Villoz N, Devigili A, Delodder F, Cianferoni S, Feihl F, Rossetti AO, et al. Increased blood glucose variability during therapeutic hypothermia and outcome after cardiac arrest. Crit Care Med 2011;39:2225-31.
33. Arrich J, European Resuscitation Council Hypothermia After Cardiac Arrest Registry Study Group. Clinical application of mild therapeutic hypothermia after cardiac arrest. Crit Care Med 2007;35:1041-7.
34. Abella BS, Rhee JW, Huang KN, Vanden Hoek TL, Becker LB. Induced hypothermia is underused after resuscitation from cardiac arrest: a current practice survey. Resuscitation 2005;64:181-6.
35. Laver SR, Padkin A, Atalla A, Nolan JP. Therapeutic hypothermia after cardiac arrest: a survey of practice in intensive care units in the United Kingdom. Anaesthesia 2006;61:873-7.
36. Peberdy MA, Kaye W, Ornato JP, Larkin GL, Nadkarni V, Mancini ME, et al. Cardiopulmonary resuscitation of adults in the hospital: a report of 14720 cardiac arrests from the National Registry of Cardiopulmonary Resuscitation. Resuscitation 2003;58:297-308.