Original Article
doi: 10.6515/ACS.201907_35(4).20190113A

Emergency & Intensive Care

Usefulness of Therapeutic Hypothermia to Improve Survival in Out-of-Hospital Cardiac Arrest

Po-Yen Ko,[1,2,3] Ling-Ling Wang,[1,2] Yi-Jiun Chou,[1,2] Jeffrey, J. P. Tsai,[3] Su-Hua Huang,[4] Chih-Ping Chang,[1,2] Yi-Tzone Shiao[5] and Jen-Jyh Lin[1,2]

Background: In recent years, therapeutic hypothermia (TH) has been used to improve outcomes in patients with out-of-hospital cardiac arrest (OHCA). Despite these recommendations, many centers are still hesitant to implement such hypothermia protocols. In this study, we assessed the effects of TH for OHCA patients.

Methods: A total of 58 OHCA patients who had return of spontaneous circulation after OHCA presumed to be due to cardiac causes were enrolled. Twenty-three patients underwent TH, which was performed using a large volume of ice crystalloid fluid infusions in the emergency room and conventional cooling blankets in the ICU to maintain a body temperature of 32-34 °C for 24 hours using a tympanic thermometer. Patients in the control group received standard supportive care without TH. Hospital survival and neurologic outcomes were compared.

Results: There were no significant differences between the groups in patient characteristics, underlying etiologies and disease severity. In the 23 patients who received TH, 17 were alive at hospital discharge. In the 35 patients who received supportive care, only 11 were alive at hospital discharge (73.91% vs. 31.43%, $p = 0.0015$). Approximately 52% of the patients in the TH group had good neurologic outcomes (12 of 23) compared with the 20% (7 of 35) of the patients in the supportive group ($p = 0.01$).

Conclusions: TH can improve the outcomes of OHCA patients. Further large-scale studies are needed to verify our results.

Key Words: Out-of-hospital cardiac arrest • Percutaneous coronary intervention • Therapeutic hypothermia

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is one of the most serious healthcare challenges in industrialized countries.[1] Only 23.8% of individuals experiencing OHCA survive to hospital admission, and only 7.6% survive to discharge.[2]

Because the brain is particularly sensitive to insufficient perfusion, death and disability secondary to anoxic brain damage remain the major problems in OHCA patients. Therapeutic hypothermia (TH) is widely regarded to be the only known therapy to protect the neurological system in post-cardiac arrest patients with anoxic injury resulting in coma after the return of spontaneous circulation (ROSC).

Landmark studies have documented that TH has a beneficial effect on survival and neurologic outcomes in comatose patients after an OHCA with an initial shockable rhythm of ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT).[3,4] Based on these results, the advanced life support task force of the International Liaison Committee on Resuscitation (ILCOR) recommend TH in unconscious patients who have been resuscitated from OHCA when the presenting rhythm is VF.[5] Guidelines issued by the American Heart Association (AHA)

Received: February 10, 2018 Accepted: January 13, 2019
[1]Division of Cardiology, Department of Medicine, China Medical University Hospital; [2]China Medical University; [3]Department of Bioinformatics and Medical Engineering; [4]Department of Biotechnology, Asia University; [5]Asia University, Taichung, Taiwan.
Corresponding author: Dr. Jen-Jyh Lin, Division of Cardiology, Department of Medicine, China Medical University Hospital, No. 2, Yuh-Der Road, Taichung 40447, Taiwan. Tel: 886-4-2205-2121 ext. 2027; Fax: 886-4-2360-2467; E-mail: kpy0907@hotmail.com

and the European Resuscitation Council recommend considering TH for patients with ROSC after OHCA regarding the presenting heart rhythm.[6,7] However, this recommendation has seldom been incorporated for a variety of reasons, including insufficient data and the technique being too technically difficult to use.[8] In the present study, we assessed the effect of TH for OHCA patients using a simple method.

METHODS

This was a retrospective cohort study of the use of TH in patients with ROSC after OHCA. Using our medical record database, all consecutive OHCA patients between September 2012 and August 2014 who were resuscitated in the emergency department (ED) with a Glasgow coma scale (GCS) score of less than 8 and who remained alive to intensive care unit (ICU) admission were included. Patients who had sepsis, surgical, neurological or gynecologic/obstetric diagnoses were excluded. Fifty-eight patients were included for analysis. Data relating to factors at resuscitation, age, sex and various diagnostic and therapeutic procedures including hypothermia were gathered from both ambulance and hospital records. Data relating to factors at resuscitation were collected prospectively, whereas data relating to post-resuscitation care were collected retrospectively.

Fifty-eight patients were included, with 23 assigned to the TH group and 35 to the non-TH group. Patients in the non-TH group received standard supportive care but no active measures were taken to cool the patients. Our TH protocol included a cold crystalloid intravenous infusion for immediate induction in the ED with cold (4 °C) 0.9% sodium chloride through a peripheral or central vein at a dose of 30 mL/kg of body weight. We also ceased using the extracorporeal membrane oxygenation (ECMO) warmer in ECMO patients. The patient then underwent coronary angiography and a percutaneous coronary intervention if myocardial infarction was suspected. After admission to the ICU, a cooling blanket was placed below the patient and was connected to a cooling machine. The initial machine setting was turned to “manual mode” and “targeted to 4 °C” until the core temperature reached 33 °C, and then the machine was switched to “auto mode” and kept at 33 °C for 24 hours followed by the application of cooling blankets. We used a noncontact tympanic thermometer to monitor the core body temperature, and the body temperature was kept at 32-34 °C for 24 hours. After 24 hours from the start of treatment, the temperature was rewarmed to 37 °C at a rate of 0.25 °C per hour. All patients received muscle relaxant medication immediately after receiving TH, and the Richmond Agitation-Sedation Scale (RASS) was kept at -4 to -5. When performing TH, the stability of temperature control is important. Therefore, we checked the body temperature and adjusted the blanket temperature every hour during the maintenance phase and every 4 hours during the rewarming phase to decrease fluctuations in temperature.

The primary outcome was survival to hospital discharge with a favorable neurological outcome. Neurological status at hospital discharge was evaluated using cerebral performance category (CPC) with the following levels: (1) normal mental performance, (2) mild disability, (3) severe disability, (4) vegetative state, and (5) brain death, as previously described.[9] A “good” neurologic outcome was defined as 1 to 2 points on a 5-point Glasgow-Pittsburgh cerebral performance category (GP-CPC) scale, with 3 to 5 points defined as a “poor outcome.”

Statistical analysis was performed using SAS software version 9.3 (SAS Institute, Cary, NC). Continuous data were presented as the mean ± standard deviation and analyzed using the Student’s *t*-test or Wilcoxon rank-sum test in two independent groups, as appropriate. Categorical data were presented using numbers with percentages. Between-group comparisons of categorical variables and outcome variables were performed using the chi-square test or Fisher’s exact test. Univariate and multivariate logistic regression models were used to identify the independent factors for survival. All statistical tests were two-tailed, and the level of significance was set at 0.05.

RESULTS

There were no significant differences in age, sex, and underlying diseases between the patients who received TH and standard supportive care (non-TH group) (Table 1). There was also no significant difference in the distribution of initial rhythm between the two groups.

Table 1. Baseline characteristics

	NON-TH (n = 35)	TH (n = 23)	p
Age, mean ± SD	62.71 ± 18.28	54.74 ± 15.13	
Age, median (IQR)	61 (28)	60 (18)	0.1414*
Sex			
Male, n (%)	25 (71.43%)	20 (86.96%)	0.1654#
Female, n (%)	10 (28.57%)	3 (13.04%)	
Previous disease status			
CHF, n (%)	5 (14.29%)	5 (21.74%)	0.4963†
Old CVA, n (%)	2 (5.71%)	3 (13.04%)	0.3758†
DM, n (%)	16 (45.71%)	9 (39.13%)	0.6204#
CAD, n (%)	8 (22.86%)	5 (21.74%)	0.9204#
HTN, n (%)	16 (45.71%)	13 (56.52%)	0.4207#
COPD/asthma, n (%)	1 (2.86%)	0 (0%)	1†
ESRD on H/D, n (%)	5 (14.29%)	2 (8.7%)	0.6916†

* Wilcoxon rank-sum test; # Chi-square test; † Fisher's exact test.
CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA, cerebral vascular accident; DM, diabetes mellitus; ESRD on H/D, end stage renal disease on hemodialysis; HTN, hypertension; TH, therapeutic hypothermia.

Most patients in both groups were diagnosed with acute myocardial infarction, and there was no significant difference in treatment method, including percutaneous coronary intervention (PCI), intra-aortic balloon pumps (IABPs), and ECMO. The mean temperature during the maintenance phase was 35.16 °C in the TH group, compared to 36.5 °C in the non-TH group ($p = 0.004$) (Table 2). The hospital survival rate was 73.91% (17/23) in the TH group, compared to 31.43% (11/35) in the non-TH group ($p = 0.0015$). The TH group also had better neurological outcomes compared to the non-TH group (52.17% vs. 20%, $p = 0.0107$). The duration of hospital stay (including all patients) was longer in the TH group than in the non-TH group (12 days vs. 5 days, $p = 0.0126$; Table 3). When adjusting for key pre-hospital and post-resuscitative factors (Tables 4, 5), negative predictors of survival included ECMO usage. The TH regimen was a significant independent predictor of survival (odds ratio 5.89, 95% confidence interval 1.55-22.34, $p < 0.01$) and

Table 2. Disease severity

	NON-TH (n = 35)	TH (n = 23)	p
Initial rhythm			
PEA/asystole, n (%)	16 (45.71%)	6 (26.09%)	0.1318#
VT/VF, n (%)	19 (54.29%)	17 (73.91%)	0.1318#
CPR time (minutes) mean ± SD	21.35 ± 16.43	18.61 ± 19.50	
CPR time , median (IQR)	16.5 (22)	10 (23)	0.2160*
IABP	13 (37.14%)	6 (26.09%)	0.3802#
ECMO	10 (28.57%)	5 (21.74%)	0.561#
AMI	28 (80%)	20 (86.96%)	0.7245†
PCI	16 (45.71%)	16 (69.57%)	0.074#
STEMI	9 (27.27%)	7 (30.43%)	0.7966#
NSTEMI	19 (54.29%)	13 (56.52%)	0.8670#
D2B (rule out ECMO) mean ± SD	228 ± 151.09	51 ± 11.58	
D2B, median (IQR)	200 (248)	53 (8)	0.0200*
Target lesion			
LM	0 (0%)	0 (0%)	-
LAD	10 (52.63%)	10 (47.62%)	0.7515#
LCX	2 (10.53%)	2 (9.52%)	1†
RCA	6 (31.58%)	7 (33.33%)	0.9058#
Qualified rate of hypothermia	-	19 (82.61%)	-
DTC time (hours) mean ± SD	-	18.81 ± 28.04	-
DTC time (hours) median (IQR)	-	10 (11)	-
Mean temperature, mean ± SD	36.40 ± 1.26	35.09 ± 1.19	
Mean temperature, median (IQR)	36.5 (1.7)	35.16 (1.67)	0.004*

* Wilcoxon rank-sum test; # Chi-square test; † Fisher's exact test.
AMI, acute myocardial infarction; CPR, cardiopulmonary resuscitation; D2B, door to balloon time; DTC, door to cool time; ECMO, extra-corporeal membrane oxygenation; IABP, intra-aortic balloon pump; IQR, interquartile range; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LM, left main coronary artery; NSTEMI, non ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PEA, pulseless electrical activity; RCA, right coronary artery; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; TH, therapeutic hypothermia; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 3. Outcome

	NON-TH (n = 35)	TH (n = 23)	p
Hospital days, mean ± SD	13.57 ± 18.53	27.74 ± 31.73	
Hospital days, median (IQR)	5 (18)	12 (41)	0.0126*
Survival	11 (31.43%)	17 (73.91%)	0.0015#
Good neurologic results	7 (20%)	12 (52.17%)	0.0107#

* Wilcoxon rank-sum test; # Chi-square test.
IQR, interquartile range; SD, standard deviation; TH, therapeutic hypothermia.

Table 4. Univariate and multivariate predictors of survival

	Univariate		Multivariate	
	OR (95% CI)	p value	OR (95% CI)	p value
Hypothermia	6.18 (1.913-19.974)	0.0023	5.89 (1.55-22.34)	0.0092
Age	0.97 (0.939-1.002)	0.0636	0.97 (0.93-1.01)	0.104
Sex (male)	2.57 (0.69-9.578)	0.1595	1.32 (0.28-6.21)	0.7263
Previous disease status				
CHF	0.39 (0.091-1.709)	0.2137		
Old CVA	1.68 (0.259-10.886)	0.5864		
DM	0.98 (0.347-2.775)	0.9708		
CAD	0.9 (0.26-3.088)	0.8622		
HTN	1.32 (0.47-3.703)	0.5995		
ESRD	1.5 (0.304-7.391)	0.6183		
Initial rhythm				
PEA/asystole	0.33 (0.109-1.017)	0.0536		
VT/VF	3 (0.983-9.149)	0.0536		
CPR time	0.99 (0.955-1.017)	0.355		
IABP	0.5 (0.162-1.54)	0.2271		
ECMO	0.18 (0.044-0.732)	0.0166	8.92 (1.72-46.45)	0.0093
PCI	2.76 (0.944-8.069)	0.0635		
STEMI	0.78 (0.242-2.496)	0.6727		
NSTEMI	1.54 (0.545-4.385)	0.4132		

CAD, coronary artery disease; CHF, congestive heart failure; CPR, cardiopulmonary resuscitation; CVA, cerebral vascular accident; DM, diabetes mellitus; ECMO, extra-corporeal membrane oxygenation; ESRD, end stage renal disease; HTN, hypertension; IABP, intra-aortic balloon pump; NSTEMI, non ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PEA, pulseless electrical activity; STEMI, ST-segment elevation myocardial infarction; VF, ventricular fibrillation; VT, ventricular tachycardia.

good neurological outcome (odds ratio 3.75, 95% confidence interval 1.08-13.08, p = 0.038). The multivariate analysis showed that PCI had a trend to improve survival and neurological outcomes, but the difference did not reach statistical significance. An initial VT/VF rhythm was associated with a trend of good neurological results, but again the difference did not reach statistical significance.

DISCUSSION

OHCA is a major cause of unexpected deaths in developed countries. Summary data from 37 communities in Europe indicated that the annual incidence of emergency medical services-treated OHCA for all rhythms is 38 per 100,000 population. Based on these data, the survival rate to hospital discharge is 10.7% for all-rhythm and 21.2% for VF cardiac arrest.[10] Recent data from 10 North American sites had similar findings. in that the median survival rate to hospital discharge was 8.4% from any rhythm and 22.0% after VF.[1] There is some evidence that long-term survival rates after cardiac arrest are increasing.[11] In patients initially resuscitated, anoxic neurologic injury is an important cause of morbidity and

Table 5. Univariate and multivariate predictors of good neurologic outcome

	Univariate		Multivariate	
	OR (95% CI)	p value	OR (95% CI)	p value
Hypothermia	4.36 (1.362-13.978)	0.0131	3.75 (1.08-13.08)	0.038
Age	0.97 (0.94-1.006)	0.1084	0.98 (0.94-1.03)	0.4668
Sex (male)	1.13 (0.297-4.258)	0.8623	0.55 (0.11-2.84)	0.4779
Previous disease status				
CHF	0.19 (0.022-1.585)	0.1237		
Old CVA	1.41 (0.215-9.251)	0.7192		
DM	0.68 (0.221-2.096)	0.5025		
CAD	0.89 (0.235-3.364)	0.8623		
HTN	0.86 (0.285-2.563)	0.7797		
ESRD	0.31 (0.034-2.74)	0.2895		
Initial rhythm				
PEA/asystole	0.2 (0.049-0.788)	0.0215		
VT/VF	5.07 (1.27-20.211)	0.0215	3.85 (0.87-17.04)	0.0753
CPR time	0.95 (0.902-0.996)	0.0356		
IABP	0.27 (0.067-1.08)	0.0642		
AMI	0.68 (0.167-2.778)	0.593		
PCI	2.28 (0.72-7.226)	0.1611		
STEMI	0.56 (0.151-2.039)	0.3758		
NSTEMI	1.17 (0.383-3.571)	0.7844		

AMI, acute myocardial infarction; CAD, coronary artery disease; CHF, congestive heart failure; CPR, cardiopulmonary resuscitation; CVA, cerebral vascular accident; DM, diabetes mellitus; ESRD, end stage renal disease; HTN, hypertension; IABP, intra-aortic balloon pump; NSTEMI, non ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PEA, pulseless electrical activity; STEMI, ST-segment elevation myocardial infarction; VF, ventricular fibrillation; VT, ventricular tachycardia.

mortality.[12] In one report, OHCA in the U.S. had a mortality rate greater than 90% resulting in more than 300,000 deaths per year, and only 3% of the patients were discharged with good neurological outcomes.[13] Those who survive the devastating event often retain a hypoxic brain injury and a permanently incapacitating neurologic defect.[14]

The "chain of survival" concept was developed to overcome this low survival rate and was incorporated into the ILCOR and AHA guidelines in the 1990s, including early access to emergency medical care, early cardiopulmonary resuscitation, early defibrillation, and early advanced cardiac life support.[15,16] However, the 2010 AHA guidelines introduced a fifth link into the chain, namely postcardiac arrest care to improve patient outcomes.[17] The two main aspects of postcardiac arrest care are the use of TH[3,4] and percutaneous coronary intervention,[18,19] in addition to other advanced interventions.[20-22]

Despite these recommendations, many centers are still hesitant to implement hypothermia protocols.[9,23-27] Recent data on the use of TH showed a wide variation in the proportion of treated patients.[25,28,29] A recent Italian study showed that only 16% of ICUs routinely used TH for patients post-cardiac arrest,[30] and surveys in Germany in 2006 and 2007 showed that only 23.5% and 38.5%[26,31] of units were routinely using it. However, the vast majority (85.6%) of UK ICUs are now using TH following cardiac arrests in accordance with the ILCOR guidelines.[28] A major reason cited for the lack of TH use is the belief that using TH is too technically difficult and that it is slow to administer.[8]

Body temperature measurement is clinically important. However, inserting a temperature probe into a patient's esophagus or inferior vena cava to monitor the core body temperature is too invasive and expensive for patients with relatively poor outcomes, and this standard method means that this therapy is not generally used in most countries. Although core temperature is the gold standard, a less invasive, cheaper and simple method has become important in these patients to monitor body temperature. More and more evidence has shown that a tympanic thermometry can provide accurate measurements of core temperatures and can be recommended for this purpose.[32,33] Although we did not have core temperature data in this study to compare with tympanic thermometer data, the TH group had good outcome results with the use of a noncontact tympanic thermometer.

In this study, although 82% of our TH patients achieved the target temperature, the mean "door-to-cool" (DTC) (ED arrival to a temperature of 34 °C) was up to 10 hours. We also found that 17% of the patients did not achieve the target temperature, mainly because the team members lacked experience in the beginning and were unable to adjust the blanket temperature rapidly according to the body temperature. Therefore, we introduced a protocol for first-line members and arranged education courses for them. Another reason for the long DTC time may be due to delayed neuromuscular blockade (NMB) infusion in some patients, in whom shivering attacks may have increased oxygen demand and generated heat. In addition, we noted a high rate of ECMO usage (21%) and up to 70% of the TH patients received a PCI. Therefore, the time taken to arrive at the ICU was delayed owing to a longer transfer time and procedure time; however, patients not achieving DTC goals were not associated with worse outcomes in another study.[34] Moreover, mortality has been reported to be significantly higher when TH was started within 2 hours of cardiac arrest than when it was started later.[35] Therefore, a shorter DTC time does not appear to be crucial in these patients, and correcting the underlying disease and maintaining hemodynamic status is more important.

Our study is a small non-randomized single center observation with several important limitations. Although the study was performed in the same hospital, both patient selection and treatment selection bias between the two groups might have influenced the outcomes. Patient selection was generally made according to the doctor's decision, and this was mainly made according to disease severity, underlying disease or family willingness. In addition, it is possible that the patients who died earlier might not have received or were less likely to receive TH treatment. Moreover, the rate of rewarming was 0.25 °C/hour, however, the body temperature was monitored and blanket temperature was adjusted every 4 hours during the rewarming phase. Nevertheless, it is not easy to monitor fluctuations and accuracy in the rewarming phase with a rate of 0.25 °C/hour. Subsequently, we also noted that ECMO usage was a negative predictor of survival because the doctors used ECMO in patients with more severe disease. It is important to emphasize that although the differences were not statistically significant, they may have been clinically relevant. The impressive benefits of TH on survival and improved neurological outcomes might therefore be overestimated even though our data were consistent with other large randomized trials. Indeed, because of these very important trials, the randomization to "no-TH" may not be ethical. The main value of our study is to demonstrate the effect of TH in patients after ROSC with presumed cardiac causes, and our findings may improve the usage rate of TH in other countries.

CONCLUSIONS

The purpose of this study was to describe our experience using TH in patients with OHCA of presumed cardiac causes. Even though our cooling method and temperature monitoring were relatively simplistic, success was still noted in a significant number of patients. Our results suggest that TH can be used to achieve good outcomes even without the use of modern machines. Combining PCI and TH provided a significant improvement in hospital survival and favorable neurologic outcomes in cardiac post-resuscitation OHCA patients without significant bleeding complications. Future studies are needed to confirm our findings.

DECLARATION OF CONFLICT OF INTEREST

All the authors declare no conflict of interest.

REFERENCES

1. Nichol G, Thomas E, Callaway CW, et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. *JAMA* 2008; 300:1423-31.
2. Sasson C, Rogers MAM, Dahl J, Kellermann AL. Predictors of survival from out-of-hospital cardiac arrest a systematic review and meta-analysis. *Circ Cardiovasc Qual* 2010;3:63-U111.
3. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypo-

thermia. *N Engl J Med* 2002;346:557-63.

4. Holzer M, Cerchiari E, Martens P, et al. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002;346:549-56.
5. Nolan JP, Morley PT, Hoek TLV, 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.
6. Callaway CW, Donnino MW, Fink EL, et al. Part 8: post-cardiac arrest care: 2015 American Heart Association Guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2015;132:S465-82.
7. Nolan JP, Soar J, Zideman DA, et al. European Resuscitation Council Guidelines for resuscitation 2010 section 1 executive summary. *Resuscitation* 2010;81:1219-76.
8. Merchant RM, Soar J, Skrifvars MB, et al. Therapeutic hypothermia utilization among physicians after resuscitation from cardiac arrest. *Crit Care Med* 2006;34:1935-40.
9. Cummins RO, Chamberlain DA, Abramson NS, et al. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein Style. A Statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. *Circulation* 1991;84:960-75.
10. Atwood C, Eisenberg MS, Herlitz J, Rea TD. Incidence of EMS-treated out-of-hospital cardiac arrest in Europe. *Resuscitation* 2005;67:75-80.
11. Hollenberg J, Herlitz J, Lindqvist J, et al. Improved survival after out-of-hospital cardiac arrest is associated with an increase in proportion of emergency crew-witnessed cases and bystander cardiopulmonary resuscitation. *Circulation* 2008;118:389-96.
12. Edgren E, Hedstrand U, Kelsey S, et al. Assessment of neurological prognosis in comatose survivors of cardiac-arrest. *Lancet* 1994;343:1055-9.
13. Eisenberg MS, Mengert TJ. Primary care: cardiac resuscitation. *N Engl J Med* 2001;344:1304-13.
14. Bunch TJ, White RD, Smith GE, et al. Long-term subjective memory function in ventricular fibrillation out-of-hospital cardiac arrest survivors resuscitated by early defibrillation. *Resuscitation* 2004;60:189-95.
15. Assoc AH, Resuscitatio ILC. Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care - an international consensus on science. Part 3: adult basic life support. *Circulation* 2000;102:I22-59.
16. Ecc Committee S, Task Forces of the American Heart A. Subcommittees and Task Forces of the American Heart Association: 2005 American Heart Association Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2005;112(24 Suppl):IV1-203.
17. Peberdy MA, Callaway CW, Neumar RW, et al. Part 9: post-cardiac arrest care: 2010 American Heart Association Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2010;122:S768-86.
18. Spaulding CM, Joly LM, Rosenberg A, et al. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. *N Engl J Med* 1997;336:1629-33.
19. Zanuttini D, Armellini I, Nucifora G, et al. Impact of emergency coronary angiography on in-hospital outcome of unconscious survivors after out-of-hospital cardiac arrest. *Am J Cardiol* 2012;110:1723-8.
20. Maekawa K, Tanno K, Hase M, et al. Extracorporeal cardiopulmonary resuscitation for patients with out-of-hospital cardiac arrest of cardiac origin: a propensity-matched study and predictor analysis. *Crit Care Med* 2013;41:1186-96.
21. Sakamoto T, Morimura N, Nagao K, et al. Extracorporeal cardiopulmonary resuscitation versus conventional cardiopulmonary resuscitation in adults with out-of-hospital cardiac arrest: a prospective observational study. *Resuscitation* 2014;85:762-8.
22. Grasner JT, Meybohm P, Caliebe A, 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.
23. Abella BS, Rhee JW, Huang KN, et al. Induced hypothermia is underused after resuscitation from cardiac arrest: a current practice survey. *Resuscitation* 2005;64:181-6.
24. Kennedy J, Green RS, Stenstrom R, Comm CCC. The use of induced hypothermia after cardiac arrest: a survey of Canadian emergency physicians. *CJEM* 2008;10:125-30.
25. Oksanen T, Pettilae V, Hynynen M, Varpula T. Therapeutic hypothermia after cardiac arrest: implementation and outcome in Finnish intensive care units. *Acta Anaesth Scand* 2007;51:866-71.
26. Wolfrum S, Radke PW, Pischon T, et al. Mild therapeutic hypothermia after cardiac arrest - a nationwide survey on the implementation of the ILCOR guidelines in German intensive care units. *Resuscitation* 2007;72:207-13.
27. 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.
28. Binks AC, Murphy RE, Prout RE, et al. Therapeutic hypothermia after cardiac arrest - implementation in UK intensive care units. *Anaesthesia* 2010;65:260-5.
29. Skulec R, Truhlar A, Knor J, et al. Broad implementation of therapeutic hypothermia after cardiac arrest-mission possible. *Resuscitation* 2010;81:779-80.
30. Bianchin A, Pellizzato N, Martano L, Castioni CA. Therapeutic hypothermia in Italian intensive care units: a national survey. *Minerva Anestesiol* 2009;75:357-62.
31. Sander M, von Heymann C, Spies C. Implementing the International Liaison Committee on resuscitation guidelines on hypothermia after cardiac arrest. The German experience: still a long way to go? *Crit Care* 2006;10.
32. Yamagishi A, Toyama Y, Tobise F, et al. Usefulness of a noncontact continuous tympanic thermometer in patients undergoing cardiac surgery using an artificial heart-lung machine. *Masui* 2012;

61:896-900.

33. Jefferies S, Weatherall M, Young P, Beasley R. A systematic review of the accuracy of peripheral thermometry in estimating core temperatures among febrile critically ill patients. *Crit Care Resusc* 2011;13:194-9.
34. Pearson DA, Mayer K, Wares CM. Therapeutic hypothermia and temperature management. *Ther Hypothermia Temp Manag* 2017; 7:81-7.
35. The Italian Cooling Experience (ICE) Study Groupa. Early- versus late-initiation of therapeutic hypothermia after cardiac arrest: preliminary observations from the experience of 17 Italian intensive care units. *Resuscitation* 2012;83:823-8.