Review Article

Advances in clinical studies of cardiopulmonary resuscitation

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BACKGROUND: The survival rate of patients after cardiac arrest (CA) remains lower since 2010 International Consensus on Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care (ECC) was published. In clinical trials, the methods and techniques for CPR have been overly described. This article gives an overview of the progress in methods and techniques for CPR in the past years.

DATA SOURCES: Original articles about cardiac arrest and CPR from MEDLINE (PubMed) and relevant journals were searched, and most of them were clinical randomized controlled trials (RCTs).

RESULTS: Forty-two articles on methods and techniques of CPR were reviewed, including chest compression and conventional CPR, chest compression depth and speed, defibrillation strategies and priority, mechanical and manual chest compression, advanced airway management, impedance threshold device (ITD) and active compression-decompression (ACD) CPR, epinephrine use, and therapeutic hypothermia. The results of studies and related issues described in the international guidelines had been testified.

CONCLUSIONS: Although large multicenter studies on CPR are still difficult to carry out, progress has been made in the past 4 years in the methods and techniques of CPR. The results of this review provide evidences for updating the 2015 international guidelines.

KEY WORDS: Resuscitation; Cardiac arrest; Chest compression; Defibrillation; Airway management; Epinephrine; Hypothermia; Clinical Research; Review

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INTRODUCTION

Since 2010 International Consensus on Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care (ECC) Science with Treatment Recommendations, a guideline based on cardiac arrest (CA) and CPR research evidences from 2005 to 2010, was published, the focus of the contents on CPR has changed in recent years. Clinical randomized controlled trials (RCTs) proved that advances in methods and techniques for CPR are still the most important topics. The present review tried to summarize the advances in methods and techniques for CPR in the past four years.

Chest compression CPR versus conventional CPR with rescue breathing

Lots of clinical controlled trials involve effectiveness

of chest compression CPR vs. conventional CPR with rescue breathing. Ogawa et al^[1] compared the outcomes of CPR with chest compression CPR ($n=20\ 707$) and conventional CPR ($n=19\ 328$) in patients with out-hospital cardiac arrest (OHCA) from a nationwide emergency medical service (EMS) system in Japan from January 2005 to December 2007. Conventional CPR was superior to chest compression CPR in both one-month survival (adjusted $OR\ 1.17$; $95\%CI\ 1.06–1.29$) and neurologically favorable one-month survival (1.17 ; $1.01–1.35$). The benefit of conventional CPR was greater in younger non-cardiac cases ($P=0.025$) than in those who received a delayed CPR ($P=0.015$) or in all cases who had combined CPR ($P=0.037$). Kitamura et al^[2] also evaluated the time-dependent effectiveness of CPR for witnessed adult OHCA of cardiac origin in a nationwide

prospective observational study from 1 January 2005 to 31 December 2007 in Japan. Among 55 014 cases, 12 165 (22.1%) received chest compression CPR and 10 851 (19.7%) received conventional CPR with rescue breathing. For a long arrest (>15 minutes), conventional CPR showed a higher rate of survival with favourable neurological outcome than did chest compression CPR (2.0% vs. 1.3%, adjusted *OR* 1.56, 95%*CI* 1.02–2.44). Iwami et al^[3] observed outcomes of patients after OHCA of presumed cardiac origin (*n*=1 376) who were witnessed and received shocks with public-access automated external defibrillation (AED) by bystanders in a nationwide prospective observational study in Japan from 1 January 2005 to 31 December 2009. Compared with patients who had conventional CPR (*n*=870) (40.7% vs. 32.9%, adjusted *OR* 1.33; 95%*CI* 1.03–1.70), those who received chest compression CPR (*n*=506) demonstrated a higher one-month survival rate as well as favorable neurological outcome. A retrospective cohort study^[4] reported two randomized trials comparing the short-term survival of CPR using chest compression alone or chest compression plus rescue breathing. Of 2 496 cases of adult OHCA in that study, 1 243 (50%) were randomly assigned to chest compression alone and 1 253 (50%) to chest compression plus rescue breathing. Follow-up revealed that in these 2 496 cases there were 2 260 deaths and 236 long-term survivors, and that chest compression alone was associated with a lower risk of death in comparison with chest compression plus rescue breathing (adjusted *HR* 0.91, 95%*CI* 0.83–0.99).

Hence, conventional CPR with rescue breathing may benefit patients with OHCA and compression CPR may improve the survival of patients who are subjected to shocks with public AED or require dispatcher instruction strategy.

The depth and speed of chest compressions

Stiell et al^[5] investigated the association between compression depth and outcomes of OHCA in a prospective cohort study of Resuscitation Outcomes Consortium (ROC). In 1 029 adults from the USA and Canada from May 2006 to June 2009, the median compression rate was 106 per minute, median compression fraction 0.65, and median compression depth 37.3 mm, with 52.8% of the cases having depth <38 mm and 91.6% having depth <50 mm. There was an inverse association between depth and compression rate (*P*<0.001). The adjusted *OR* showed a strong tendency toward better outcomes with increased depth for return of spontaneous circulation (ROSC), 1-day survival, and

hospital discharge, but there was no evidence to support or refute the 2010 recommendations of >50 mm in this trial. Stiell et al^[6] further sought to determine the optimal compression depth range in a ROC clinical trial of OHCA in 9 136 adults from nine cities from the USA and Canada. The results showed that each 5-mm increment in compression depth is strongly associated with better survival to hospital discharge, and the maximum survival was at a depth of 45.6 mm (15-mm interval with highest survival between 40.3 and 55.3 mm) with no differences between men and women. Vadeboncoeur et al^[7] assessed the relationship between the depth of chest compression and the survival in a prospective analysis of OHCA of cardiac etiology in 593 adults from two EMS agencies. The mean depth of chest compressions was 49.8±11.0 mm and the rate was 113.9±18.1 per minute. The mean depth was significantly deeper in survivors (53.6 mm, 95%*CI* 50.5–56.7) than in non-survivors (48.8 mm, 95%*CI* 47.6–50.0). Each 5-mm increase in the mean depth significantly increased the odds ratio of survival to hospital discharge (*OR* 1.29, 95%*CI* 1.00–1.65) and survival with favorable functional outcome (*OR* 1.30, 95%*CI* 1.00–1.70). Idris et al^[8] observed the relationship between chest compression rate used by EMS providers participating in ROC and outcome of OHCA in 3 098 adults from December 2005 to May 2007. The mean compression rate was 112±19 per minute. The ROSC rate peaked at a compression rate of 125 per minute and then declined. The chest compression rate was associated with ROSC but not with survival to hospital discharge.

It is now clear that within certain range, deeper and faster chest compression is strongly associated with better survival, just as a guideline target.

Strategies and priority for defibrillation

Stiell et al^[9] compared the strategy of a brief period of CPR (30 seconds to 60 seconds) with early analysis of rhythms with the strategy of a longer period of CPR (180 seconds) by later analysis of rhythms in a ROC PRIMED cluster-randomized trial, involving 9 933 adults with OHCA between June 2007 and November 2009 from 10 cities in the USA and Canada. No difference was found in the outcomes for survival to hospital discharge with satisfactory functional status as compared with later-analysis group (*n*=4 643) and early-analysis group (*n*=2 590) (5.9% vs. 5.9%, *P*=0.59). Weisfeldt et al^[10] assessed the frequencies of ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) and survival to hospital discharge in a ROC prospective cohort study of 12 930 adults with OHCA between 2005 and 2007 in 10 North

American communities. For arrests at home ($n=9\,564$), the incidence of VF or pulseless VT was 25% when witnessed by EMS personnel, 35% when witnessed by a bystander, and 36% when the bystander applied AED. For arrests in public ($n=2\,042$), the corresponding rates were 38%, 60%, and 79%, respectively. The aOR for initial VF or pulseless VT in public versus at home was 2.28 (95%CI 1.96–2.66) for bystander-witnessed arrests and 4.48 (95%CI 2.23–8.97) for bystander-applied AED arrests. The rate of survival to hospital discharge was 34% for arrests in public with AEDs applied by bystanders versus 12% for arrests at home (adjusted OR 2.49, 95%CI 1.03–5.99). Cheskes et al^[11] examined the relationship between perishock pauses and survival to hospital discharge in the ROC Epistry study of OHCA patients between December 2005 and June 2007, and presented with a shockable rhythm (VF or pulseless VT) data for at least 1 shock ($n=815$). The odds of survival were significantly lower for patients with preshock pause ≥ 20 seconds (OR 0.47, 95%CI 0.27–0.82) and peri-shock pause ≥ 40 seconds (OR 0.54, 95%CI 0.31–0.97) than those with pre-shock pause < 10 seconds and peri-shock pause < 20 seconds. Post-shock pause was not independently associated with a significant change in the odds of survival. Survival to hospital discharge was decreased by 18% and 14% for every 5-second increase in both pre-shock and peri-shock pause intervals (up to 40 and 50 seconds, respectively); there was no significant association with changes in post-shock pause interval. Blom et al^[12] performed a cohort study of OHCA due to cardiac causes between 2006 and 2012 in the Netherlands. The survival rate with favorable neurologic outcome after OHCA was increased ($n=6\,133$, 16.2% to 19.7%, $P=0.021$) solely in patients with a shockable initial rhythm ($n=2\,823$, 29.1% to 41.4%, $P<0.001$). The increased rate of AED use during the study period (21.4% to 59.3%; $P<0.001$) decreased the time from emergency call to defibrillation-device connection (median 9.9–8.0 minutes, $P<0.001$). AED use indicated the increased survival rate and favorable neurologic outcome in patients with a shockable initial rhythm. A cohort study in 204 hospitals in the USA showed the association between AED use and the survival rate for patients with in-hospital cardiac arrest (IHCA).^[13] Of 11 695 patients treated between January 1, 2000 and August 26, 2008, 9 616 (82.2%) had nonshockable rhythms [asystole and pulseless electrical activity (PEA)] and 2 079 (17.8%) had shockable rhythms. AED use was associated with a lower survival rate after IHCA compared with no AED use (16.3% vs. 19.3%, adjusted RR 0.85, 95%CI 0.78–0.92). For non-shockable rhythms,

AED use was associated with a lower survival rate (10.4% vs. 15.4%, adjusted RR 0.74, 95%CI 0.65–0.83). For shockable rhythms, AED use was not associated with the survival rate (38.4% vs. 39.8%, adjusted RR 1.00, 95%CI 0.88–1.13).

The time of chest compression CPR before rhythm analysis and defibrillation should not be limited to 2 minutes or 5 cycles. The ratio of arrests to initial VF or pulseless VT is much higher in public settings than at home, and the value of defibrillation involving AED use may be related to the place where arrests occur. For patients with shockable rhythm, shortening peri-shock and pre-shock pauses is beneficial to survival to hospital discharge, and refining AED software and paramedic education to avoid delay may be a significant task. AED use should be recommended for patients with OHCA although it is not associated with improved survival among hospitalized patients.

Mechanical versus manual chest compression CPR

Hock Ong et al^[14] conducted a phased, prospective cohort study in adults with prolonged, non-traumatic CA at emergency departments of two city hospitals. Of 1 011 patients, 459 were in the manual CPR phase (1 January 2004 to 24 August 2007) and 552 in the load-distributing band (LDB) CPR phase (16 August 2007 to 31 December 2009); the mean duration from collapse to arrival at the departments was 34:03 (SD 16:59) and 33:18 minutes (SD 14:57) respectively. The rate of survival to hospital discharge was higher in the LDB-CPR phase than in the manual CPR phase (3.3% vs. 1.3%, adjusted OR 1.42, 95%CI 0.47–4.29). Neurologically intact survivors on discharge were more in the LDB group than in the manual group (12 vs. 1, $P=0.01$). Rubertsson et al^[15] observed LUCAS mechanical chest compressions and simultaneous defibrillation versus manual CPR in a multicenter RCT of 2 589 adults with OHCA between January 2008 and February 2013 in four Swedish, 1 British, and 1 Dutch ambulance services and their referring hospitals, and after a 6-month follow-up no significant difference was observed in survival, survival with good neurological outcome at 4 hours, ICU discharge, hospital discharge, 1 month, and 6 months between the mechanical CPR group ($n=1\,300$) and manual CPR group ($n=1\,289$). Wik et al^[16] compared integrated automated load distributing band CPR (iA-CPR) with manual CPR (M-CPR) in a randomized controlled trial of adult OHCA of presumed cardiac origin at three US and two European sites between

March 5, 2009 and January 11, 2011. Of 4 231 patients, 2 099 (49.6%) received iA-CPR and 2 132 (50.4%) M-CPR. The aOR of survival to hospital discharge for iA-CPR compared with M-CPR was 1.06 (95%CI 0.83–1.37), which was statistically equivalent. Perkins et al^[17] conducted a pragmatic cluster-randomized controlled PARAMEDIC trial including adult patients with non-traumatic OHCA from 91 urban and semi-urban ambulance stations of four UK Ambulance Services between April 15, 2010 and June 10, 2013. The patients were randomly assigned (1:2) to receive LUCAS-2 mechanical chest compression or manual chest compressions according to the first vehicle to arrive on scene. A total of 4 471 eligible patients were enrolled, 1 652 in the LUCAS-2 group, 2 819 in the manual group. The 30-day survival was similar in the LUCAS-2 group (6%) and the manual CPR group (7%) (adjusted *OR* 0.86, 95%CI 0.64–1.15), and no serious adverse events were noted. Smekal et al^[18] reported the incidence of CPR-related injuries by manual chest compression compared with mechanical chest compression with LUCAS in non-survivors after OHCA in a prospective multicentre trial in Sweden. In 222 patients included, 75.9% in the manual CPR group (*n*=83) and 91.4% in the mechanical CPR group (*n*=139) (*P*=0.002) suffered CPR-related injuries. Sternal fractures accounted for 54.2% of the manual CPR group and 58.3% of the mechanical CPR group (*P*=0.56), whereas rib fractures were seen in 64.6% of the manual CPR group versus in 78.8% of the mechanical CPR group (*P*=0.02). The median number of rib fractures was 7 in the manual CPR group and 6 in the mechanical CPR group. CPR-related injury was not the cause of death.

In short, mechanical chest compression CPR and manual chest compression CPR have similar outcomes of survival. But recent reports showed that mechanical compression CPR for OHCA was not more effective than manual compression CPR. The mechanical compression CPR may be advantageous in special conditions like simultaneous defibrillation, transportation, diagnostic imaging, or catheter intervention.^[15,19,20]

Advanced airway management

Studnek et al^[21] retrospectively investigated the association of pre-hospital endotracheal intubation (ETI) with survival in 1 142 patients with OHCA from July 2006 to December 2008 in North Carolina, and found that patients with no ETI attempted were 2.33 and 5.46 (95%CI 1.63–3.33 and 3.36–8.90, respectively) times more likely to have ROSC and their survival to hospital discharge was compared with those with one successful

ETI. Egly et al^[22] also analyzed retrospectively non-traumatic OHCA cases brought to a large suburban tertiary care emergency department by paramedic services between 1995 and 2006 in the USA. Of 1 414 patients, 86.2% were intubated, and univariate analysis showed no difference in survival between the intubated and non-intubated groups (6.5% vs. 10.0%, *OR* 0.63, 95%CI 0.37–1.08). For patients initially in VT/VF, their survival to discharge decreased in the intubation group shown by a multivariate analysis (adjusted *OR* 0.52, 95%CI 0.27–0.998). Intubated non-VF patients were more likely to survive to admission (adjusted *OR* 2.96, 1.04–8.43), but not to discharge (1.8% vs. 1.0%, *P*=1.0). Kajino et al^[23] assessed the association between ETI/SGA and neurological outcome in a prospective cohort study of witnessed non-traumatic OHCA from January 1, 2005 to December 31, 2008 in Osaka. Of 7 517 patients, 5 377 were treated with advanced airways, including 1 679 patients with ETI and 3 698 with SGA. One-month survival with favorable neurological outcome was similar between ETI and SGA (3.6% vs. 3.6%, *P*=0.95). The time interval from collapse to ETI was significantly longer than that from collapse to SGA (17.2 min vs. 15.8 minutes, *P*<0.001). Early placement of an advanced airway was significantly associated with better neurological outcome (adjusted *OR* for 1-minute delay 0.91, 95%CI 0.88–0.95). Wang et al^[24] compared the outcomes of patients receiving ETI with those receiving supraglottic airway (SGA) after OHCA in a secondary analysis of data from a multicenter ROC PRIMED trial. Of 10 455 adult patients with non-traumatic OHCA, 8 487 (81.2%) received ETI and 1 968 (18.8%) received SGA. The survival to hospital discharge with satisfactory functional status was 4.7% in patients with ETI and 3.9% in patients with SGA. Compared with SGA, ETI was associated with increased survival to hospital discharge (adjusted *OR* 1.40, 95%CI 1.04–1.89), ROSC (1.78, 1.54–2.04) and 24-hour survival (1.74, 1.49–2.04). ETI was more associated with improved outcomes than SGA after OHCA. In a prospective nationwide study in Japan from January 2005 to December 2010, Hasegawa et al^[25] analyzed the relationship between pre-hospital advanced airway management and outcomes in patients with OHCA. Of the eligible 649 359 patients, 367 837 (57%) underwent bag-valve-mask ventilation and 281 522 (43%) advanced airway management, including 41 972 (6%) with ETI and 239 550 (37%) with SGA. In the full cohort, the advanced airway incurred a lower rate of favorable neurological outcome compared with the bag-valve-mask (1.1% vs. 2.9%, *OR* 0.38, 95%CI 0.36–0.39). The

odds ratios of neurologically favorable survival were lower for both ETI (adjusted *OR* 0.41, 95%*CI* 0.37–0.45) and SGA (adjusted *OR* 0.38, 95%*CI* 0.36–0.40). In a propensity score-matched cohort, the adjusted odds ratios of neurologically favorable survival were lower for both ETI (adjusted *OR* 0.45, 95%*CI* 0.37–0.55) and SGA (adjusted *OR* 0.36, 95%*CI* 0.33–0.39). McMullan et al^[26] compared outcomes between ETI versus SGA, and no advanced airway versus ETI or SGA in adult OHCA in the Cardiac Arrest Registry to Enhance Survival (CARES) trial. Of 10 630 patients included, 5 591 received ETI, 3 110 received SGA, and 1 929 had no advanced airway, and among them unadjusted neurologically-intact survivals to hospital discharge were 5.4%, 5.2% and 18.6%, respectively. Compared with SGA, ETI had higher ROSC (*OR* 1.35, 95%*CI* 1.19–1.54), survival to hospital admission (1.36, 1.19–1.55), hospital survival (1.41, 1.14–1.76), and hospital discharge with good neurologic outcome (1.44; 1.10–1.88). Compared with ETI or SGA, patients receiving no advanced airway had higher survival to hospital admission (1.31, 1.16–1.49), hospital survival (2.96, 2.50–3.51) and hospital discharge with good neurologic outcome (4.24, 3.46–5.20).

This indicated that OHCA survival tends to be higher in patients without advanced airway than those with advanced airway, and in patients with ETI than those with SGA, or that there are similar outcomes between ETI and SGA. Advanced airway management may be associated with improved outcomes only when it is used skillfully and quickly.

Impedance threshold device and active compression-decompression

Aufderheide et al^[27] compared the use of impedance threshold device (ITD) with sham ITD in a ROC trial of OHCA patients who underwent standard CPR at 10 sites in the USA and Canada. Of 8 718 patients included, 4 345 were randomly assigned to treatment with a sham ITD and 4 373 with ITD. A total of 260 patients (6.0%) in the sham-ITD group and 254 patients (5.8%) in the active-ITD group survived to hospital discharge with satisfactory function (RD adjusted for sequential monitoring, -0.1% ; 95%*CI* -1.1 to 0.8 ; $P=0.71$). There were also no significant differences in ROSC on arrival at the emergency department, survival to hospital admission, and survival to hospital discharge. Aufderheide et al^[28] assessed outcomes of patients to receive standard CPR (control group, $n=813$) or active

compression-decompression CPR with impedance threshold device (ACD+ITD) (intervention group, $n=840$) in a randomized trial of adult non-traumatic OHCA of presumed cardiac cause in 46 EMS agencies of the USA. Compared with controls, survival to hospital discharge with favourable neurological function was higher in the intervention group (9% vs. 6%, *OR* 1.58, 95%*CI* 1.07–2.36), survival to 1 year was higher in the intervention group (9% vs. 6%, $P=0.03$) with equivalent cognitive skills, disability ratings, and emotional-psychological statuses, and the major adverse event rate was similar in both groups but more pulmonary edema was seen in the intervention group (11% vs. 7%, $P=0.015$). Frascone et al^[29] further examined the effectiveness of treatment with ACD+ITD or standard CPR for adult OHCA of non-traumatic origin in a secondary analysis of data from a randomized prospective multicenter trial in the USA between October 2005 and July 2009. In 2 738 patients enrolled, 1 335 were treated with S-CPR and 1 403 with ACD+ITD. Survival to hospital discharge with favorable neurologic function was higher in patients treated with ACD+ITD than those treated with S-CPR (7.9% vs. 5.7%, *OR* 1.42, 95%*CI* 1.04–1.95). The 1-year survival was also higher in patients treated with ACD+ITD (7.9% vs. 5.7%, *OR* 1.43, 95%*CI* 1.04–1.96). The rates of major adverse events were similar between the two groups.

Consequently, active compression-decompression cardiopulmonary resuscitation (CPR) with decreased intrathoracic pressure by an impedance threshold device in the decompression phase can improve hemodynamics and long-term survival after OHCA compared with standard CPR. An increased survival rate may be achieved in non-traumatic patients treated with ACD+ITD, regardless of the etiology of cardiac arrest.

Epinephrine use

Jacobs et al^[30] conducted a double-blind randomized placebo-controlled trial to determine the effect of epinephrine (adrenaline) on survival to hospital discharge, ROSC and neurological outcome of OHCA in Australia. They analyzed 534 patients, 262 in a placebo group and 272 in an epinephrine group. ROSC occurred in 22 (8.4%) and 64 (23.5%) (*OR* 3.4, 95%*CI* 2.0–5.6), and survival to hospital discharge occurred in 5 (1.9%) and 11 (4.0%) (*OR*=2.2, 95%*CI* 0.7–6.3) patients receiving placebo or epinephrine respectively. All but 2 patients (both in the epinephrine group) had good neurological function. Olasveengen et al^[31] compared

outcomes of OHCA patients receiving epinephrine with those of patients not receiving epinephrine from a RCT performed May 2003 to April 2008 in Norway. OR for being admitted to hospital, survival to hospital discharge and survival with favorable neurological outcome for the epinephrine group ($n=367$) versus the no-epinephrine group ($n=481$) was 2.5 (95%CI 1.9–3.4), 0.5 (95%CI 0.3–0.8) and 0.4 (95%CI 0.2–0.7), respectively. OR for survival for epinephrine versus no-epinephrine adjusted for confounders was 0.52 (95%CI 0.29–0.92). Hagihara et al^[32] evaluated the association between epinephrine use before hospital arrival and mortality of adult OHCA in a prospective, nonrandomized, observational propensity analysis of data in 2005–2008 in Japan. Of 417 188 patients, 15 030 were treated with epinephrine and 402 158 without epinephrine. ROSC before arrival at the hospital accounted for 18.5% of patients treated with epinephrine and 5.7% of those treated without epinephrine ($P<0.001$), with the corresponding rates of 18.3% and 10.5% in 13 401 propensity-matched patients ($P<0.001$). The 1-month survival rate and the survival rate with favorable neurological function were 5.4% and 1.4% respectively in patients treated with epinephrine and 4.7% and 2.2% in patients treated without epinephrine (all $P<0.001$), and the corresponding rates were 5.1% and 1.3% in propensity-matched patients treated with epinephrine and 7.0% and 3.1% in those treated without epinephrine (all $P<0.001$). Goto et al^[33] analyzed whether prehospital epinephrine administration would improve the survival rate in OHCA patients ($n=209\ 577$ who were divided into the initial shockable rhythm ($n=15\ 492$) and initial non-shockable rhythm ($n=194\ 085$) cohorts collected from a nationwide database between 2009 and 2010 in Japan. For shockable rhythm, prehospital ROSC, one-month survival, and one-month favorable neurological outcomes in the non-epinephrine group were higher than those in the epinephrine group (27.7% vs. 22.8%, 27.0% vs. 15.4%, and 18.6% vs. 7.0%, respectively; all $P<0.001$). For non-shockable rhythm, prehospital ROSC and 1-month survival in the epinephrine group were higher than those in the non-epinephrine group (18.7% vs. 3.0% and 3.9% vs. 2.2%, respectively; all $P<0.001$); but there was no significant difference between epinephrine and non-epinephrine groups for one-month favorable neurological outcomes ($P=0.62$). Epinephrine administration for patients with non-shockable rhythms was independently associated with prehospital ROSC (adjusted OR 8.83, 6.18, 4.32; 95%CI 8.01–9.73, 5.82–6.56, 3.98–4.69; for epinephrine administration times ≤ 9 minutes, 10–19

minutes, and ≥ 20 minutes, respectively), with improved one-month survival (adjusted OR 1.78, 1.29; 95%CI 1.50–2.10, 1.17–1.43; for epinephrine administration times ≤ 9 minutes and 10–19 minutes, respectively), and with deteriorated 1-month favorable neurological outcomes (adjusted OR 0.63, 0.49; 95%CI 0.48–0.80, 0.32–0.71; for epinephrine administration times 10–19 minutes and ≥ 20 minutes, respectively). Donnino et al^[34] conducted a post hoc analysis of prospectively collected data in Get With The Guidelines-Resuscitation (GWTGR) from 570 American hospitals from January 1, 2000 to November 19, 2009. The included 25 095 adult patients had a cardiac arrest in hospital (IHCA) with initial non-shockable rhythm (asystole or PEA). There was a stepwise decrease in survival to hospital discharge with an increasing time to epinephrine for 1–3 minutes (adjusted OR 1.0, reference group), for 4–6 minutes (0.91, 95%CI 0.82–1.00), 7–9 minutes (0.74, 95%CI 0.63–0.88), and >9 minutes (0.63, 95%CI 0.52–0.76). A similar stepwise effect was observed on ROSC, 24-hour survival, and survival with favorable neurologic status at hospital discharge. Mentzelopoulos et al^[35] performed a randomized, double-blind, placebo-controlled, parallel-group trial from September 1, 2008 to October 1, 2010 in 3 Greek tertiary care centers. Altogether 268 consecutive patients with IHCA requiring epinephrine received treatment with either vasopressin (20 IU/CPR cycle) plus epinephrine (1 mg/CPR cycle; cycle duration approximately 3 minutes) in the vasopressin+steroids+epinephrine (VSE) group ($n=130$) or saline placebo plus epinephrine (1 mg/CPR cycle; cycle duration approximately 3 minutes) in the control group ($n=138$), for the first 5 CPR cycles after randomization, followed by additional epinephrine if needed. During the first CPR cycle, patients were treated with methylprednisolone (40 mg) in the VSE group or saline placebo in the control group. Postresuscitation shock was treated with stress-dose hydrocortisone (300 mg daily for 7 days maximum and gradual taper) (VSE group, $n=76$) or saline placebo (control group, $n=73$). Patients in the VSE group versus patients in the control group had a higher probability for ROSC of 20 minutes or longer (83.9% vs. 65.9%; OR 2.98; 95%CI 1.39–6.40) and survival to hospital discharge with favorable neurological status (13.9% vs. 5.1%, OR 3.28, 95%CI 1.17–9.20). Patients with postresuscitation shock in the VSE group versus corresponding patients in the control group had a higher probability for survival to hospital discharge with favorable neurological status (21.1% vs. 8.2%, OR 3.74, 95%CI 1.20–11.62), improved hemodynamics

and central venous oxygen saturation, and less organ dysfunction. Adverse event rates were similar in the two groups.

Obviously, epinephrine may be related to improved short-term survival but decreased long-term outcome in OHCA, and it is also related to improved one-month survival of OHCA patients with initial non-shockable rhythms when the time of epinephrine administration was <20 minutes. Earlier administration of epinephrine is also associated with a higher probability of ROSC, survival in hospital, and neurologically intact survival to hospital discharge in IHCA with initial non-shockable rhythms. For IHCA requiring epinephrine, VSE combined treatment may improve survival to hospital discharge with favorable neurological status.

Therapeutic hypothermia

Dumas et al^[36] assessed the prognostic value of therapeutic hypothermia for neurological outcome at hospital discharge of 1 145 OHCA patients treated between January 2000 and December 2009. Hypothermia was induced in 457/708 patients (65%) in VF/VT and in 261/437 patients (60%) in PEA/asystole. The rate for favorable neurological status at hospital discharge was higher in the VF/VT patients than in the PEA/asystole patients (39% vs. 16%, $P<0.001$). Hypothermia was associated with increased odds of good neurological outcome (adjusted OR 1.90, 95% CI 1.18–3.06) in the VF/VT patients, and was not significantly associated with this outcome (adjusted OR 0.71, 95% CI 0.37–1.36) in the PEA/asystole patients. Bernard et al^[37] evaluated the effects on pre-hospital rapid therapeutic hypothermia (32–34 °C) for OHCA patients with initial rhythm of asystole or PEA in a prospective, randomized, controlled clinical trial in Australia. Included 163 patients were assigned to pre-hospital cooling (82 patients) or cooling after hospital admission (81). No difference in outcomes at hospital discharge with favorable neurological outcome was observed in the pre-hospital cooling patients compared with those cooling after hospital admission (12% vs. 9%, $P=0.50$). For patients with cardiac cause, the rate of favorable outcome at hospital discharge was 17% in the pre-hospital cooling patients versus 7% in those cooling after hospital admission ($P=0.146$). Kim et al^[38] assessed the effect of pre-hospital cooling on outcomes of adult OHCA in a randomized clinical trial in the USA between December 15, 2007 and December 7, 2012, with a follow-up to May 1, 2013. A total of 1359 patients (583 with VF and 776 without

VF) were assigned to standard care with or without pre-hospital cooling, while infusion of up to 2 liter of 4 °C normal saline as soon as possible after ROSC. Nearly all of the patients who had been resuscitated from VF and admitted to the hospital received hospital cooling regardless of their randomization. Survival to hospital discharge was similar in patients with VF (62.7% vs. 64.3%, $P=0.69$) and those without VF (19.2% vs. 16.3%, $P=0.30$), respectively. The intervention was also not associated with improved neurological status at discharge in either patients with VF (57.5% vs. 61.9%, $P=0.69$) or those without VF (14.4% vs. 13.4%, $P=0.30$). The pre-hospital cooling patients experienced re-arrest more than the controls (26% vs. 21%, $P=0.008$), in addition to increased diuretic use and pulmonary edema. Debaty et al^[39] reported the effect of intra-arrest therapeutic hypothermia on neurological injury and clinical outcomes after OHCA in a 1:1 randomized, multicenter study in three pre-hospital EMS and four critical care units in France. Of the 245 patients included in this study, 123 received TH during cardiac arrest and 122 received TH after hospital admission. The rate of the patients admitted alive to hospital was not different between the two groups (33% vs. 30%, $P=0.51$). The levels of NSE and inflammatory biomarkers were not different between the groups ($P=0.64$). No difference in survival and cerebral performance was found at one month. Lopez-de-Sa et al^[40] assessed the effect of different levels of hypothermia in patients with witnessed OHCA from March 2008 to August 2011 in Spain. Of the 36 patients enrolled (26 with shockable rhythm and 10 asystole), 18 were assigned to 34 °C and 18 to 32 °C. Eight (44.4%) of the 18 patients in the 32 °C group survived free from severe dependence (Barthel Index score ≥ 60 points) at 6 months compared with 2 of the 18 (11.1%) patients in the 34 °C group (Log-rank $P=0.12$). All patients with initial asystole rhythm died before 6 months in both groups. Eight of 13 (61.5%) patients with initial shockable rhythm assigned to 32 °C were alive free from severe dependence at 6 months compared with 2 of 13 (15.4%) assigned to 34 °C (Log-rank test, $P=0.029$). The incidence of complications was similar in both groups except for the incidence of lower seizures (1 vs. 11, $P=0.0002$), higher bradycardia (7 vs. 2, $P=0.054$) in patients assigned to 32 °C compared with 34 °C. Nielsen et al^[41] analyzed effectiveness of different levels of hypothermia in an international multicenter Targeted Temperature Management Trial (TTM Trail). Altogether 950 unconscious adults after OHCA of presumed cardiac cause were randomly assigned to targeted temperature

at either 33 °C or 36 °C. Of 939 patients included in the primary analysis at the end of the trial, 50% in the 33 °C group died in contrast to 48% in the 36 °C group (HR 1.06, 95%CI 0.89–1.28, $P=0.51$). A 180-day follow-up demonstrated that 54% of the patients in the 33 °C group died or had poor neurologic function compared with 52% in the 36 °C group (RR 1.02, 95%CI 0.88–1.16, $P=0.78$). The results of analyses adjusted for known prognostic factors were similar. Bro-Jeppesen et al^[42] reported the effect on systemic vascular resistance and myocardial function at 33 °C vs. 36 °C in the single-center sub-study of 171 OHCA patients included in the TTM Trial. Systemic vascular resistance index (SVRI) was increased in the 33 °C group compared with the 36 °C group ($P<0.0001$), and lactate levels ($P=0.0008$) after 24 hours of cooling were associated with decreased cardiac index ($P<0.0001$), heart rate ($P=0.01$), and stroke volume index ($P=0.004$), as compared with the 36 °C group.

Obviously, therapeutic hypothermia may provide more survival benefit for OHCA patients with initial shockable rhythm (VF/VT) or with cardiac cause. Intra-arrest or pre-hospital cooling is not beneficial to survival or neurological status after OHCA as hospital cooling. The optimal targeted temperature of cooling is still indefinite and awaits further investigation, yet larger trials showed that a targeted temperature of 33 °C could not benefit patients after OHCA of presumed cardiac cause as compared with 36 °C.

In conclusion, although a large multicenter study on CPR may be still difficult, progress has been made in the past years in the methods and techniques of CPR. The progress will be the striking evidence to update the guidelines for CPR in 2015.

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