

CLINICAL PRACTICE GUIDELINES

Advances in the Clinical Management of Cardiac Arrest

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cardiopulmonary resuscitation;
epinephrine*

ABBREVIATIONS

AED = automated external defibrillators
ALS = advanced life support
BLS = basic life support
COCPR = chest compression only CPR
CPP = coronary perfusion pressure
CPR = cardiopulmonary resuscitation
ICU = intensive care unit
ITD = impedance threshold device
NO = nitric oxide
OHCA = out-of-hospital arrest
ROSC = return of spontaneous
circulation
VF = ventricular fibrillation
VSE = vasopressin-steroids epinephrine
VT = ventricular tachycardia

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ABSTRACT

Cardiac arrest constitutes an extremely life-threatening condition that inevitably and promptly results in death if left untreated. Cardiac arrest outcomes still remain very poor, especially when the presenting cardiac rhythm is nonshockable. Important, recent, clinical research has focused on the quality of cardiopulmonary resuscitation (CPR), the mechanical augmentation of the circulation during CPR, CPR drugs, and therapeutic hypothermia. Chest compression depth of at least 51 mm increases the probability of neurologically favorable survival. Despite initially promising results, a large effectiveness study failed to confirm the efficacy of the mechanical augmentation of the circulation. Epinephrine has finally been shown to slightly improve functional outcome after out-of-hospital cardiac arrest, especially when given early. In a recent, in-hospital study of 268 patients, the addition of vasopressin and methylprednisolone during CPR and the administration of hydrocortisone in postresuscitation shock improved functional outcome after vasopressor-requiring cardiac arrest; however, corticosteroid efficacy still needs to be separately confirmed in a large, international trial. Lastly, preliminary human data may support the conduct of high quality trials evaluating the efficacy of beta adrenergic antagonists in shockable cardiac arrest, and nitrates may warrant evaluation in the clinical setting. The purpose of this paper is to review these potentially important advances in the management of cardiac arrest.

INTRODUCTION

New out-of-hospital and in-hospital cardiac arrest statistics sourced from the Resuscitation Outcomes Consortium Cardiac Registry and Get With The Guidelines®-Resuscitation data show that the incidence of cardiac arrest with any initial rhythm is not decreasing,¹ despite recent advances in preventive medicine and interventional therapeutic strategies. As for in-hospital cardiac arrest, a study published in 2011, concluded that its incidence may actually be increasing.² This is important for understanding the burden of in-hospital cardiac arrest and developing strategies to improve care for hospitalized patients.

A large registry study in the United States showed no significant change in survival to discharge among elderly, hospitalized patients treated with cardiopulmonary resuscitation (CPR) for cardiac arrest from 1992 to 2005.³ However, a more recent registry study indicates that both survival to hospital discharge and neurological outcome im-

**CIRCULATORY SUPPORT - CHEST
COMPRESSIONS - FIRST PRIORITY**

proved substantially within 2000-2009.⁴ Still, rates of survival to hospital discharge with favorable neurological outcome remain low, i.e. approximately 16% in 2009; pooled data from vasopressor-requiring and non-vasopressor-requiring cardiac arrest.⁴ Thus, further research aimed at improving survival and neurological recovery of cardiac arrest patients is considered as imperative.

Cardiac arrest etiology encompasses a variety of cardiac and noncardiac underlying pathologies. Also, cardiac arrest can occur under different circumstances (e.g. in the presence or absence of witnesses), and settings (e.g. out-of-hospital or in-hospital). This heterogeneity suggests that a single approach to resuscitation may be unrealistic; however, a core bundle of actions results in a universal strategy for achieving successful resuscitation. These actions are termed as the links in the “Chain of Survival”.

The purpose of the current article is to review recent, clinical evidence-based advances in treating patients with cardiac arrest from practices of basic life support (BLS) and advanced life support (ALS) to the post-resuscitation phase in the intensive care unit.

**KEY CHANGES AND CONTINUED
POINTS OF EMPHASIS FROM THE 2005
BLS GUIDELINES**

Prompt recognition of cardiac arrest and action by the rescuer continue to be priorities for the *2010 American Heart Association (AHA) Guidelines for CPR and emergency cardiovascular care*.⁵ Rescuers should start CPR immediately if the adult victim is unresponsive and not breathing or only gasping. The “look, listen, and feel” for breathing is no longer recommended. Authors emphasize on uninterrupted (interruptions of less than 10 seconds) and efficient chest compressions. Compressions take priority over airway and breathing, due to the fact that the majority of cardiac arrests in adults result from a primary cardiac cause and thus the major problem is that oxygen delivery to the heart and brain is limited by blood flow rather than by arterial oxygen content.^{6,7} CPR sequence has now changed to Circulation-Airway-Breathing. Guideline experts advise on pushing hard (at least 50 mm) and fast (rate: 100/min), while still allowing full recoil of the chest during decompression. Moreover, experts advise against “excessive ventilation”. The compression to ventilation ratio is 30:2, and when an artificial airway is established, 1-second-lasting breaths (rate: 8-10/min), and asynchronous with compressions are considered as adequate. While positive-pressure ventilation has been a mainstay of CPR, it has recently come under scrutiny because of the potential for the increased intrathoracic pressure’s impeding of the venous return to the heart.

The “Hands-Only CPR” campaign is now being led by AHA across the United States. There are multiple reasons “chest compression only CPR” (COCPR) might have advantages over conventional CPR. These include the rapid deterioration of forward blood flow that occurs during an even brief interruption of chest compressions,^{8,9} the long ramp-up time to return to adequate blood flow after resuming chest compressions,^{8,9} the reduction in cardiac venous return during positive pressure ventilation,¹⁰ the complexity of conventional CPR,^{11,12} the significant time required to administer the artificial breaths,¹²⁻¹⁴ and the critical importance of cerebral and coronary circulation during cardiac arrest.^{8,9,15,16}

An increase in the rate of bystanders’ willingness to perform COCPR has been observed. A recent study has evaluated the rate of bystander CPR, as well as survival to hospital discharge, when COCPR has been performed.¹⁷ This prospective, observational, cohort analysis included 4415 patients who experienced out of hospital cardiac arrest of presumed cardiac etiology. There was a significant difference in good neurological recovery (cerebral performance category score of 1 or 2) between the COCPR group (62/814; 7.6%; 95% confidence interval -CI, 5.8%-9.4%) and the conventional CPR group (34/651; 5.2%; 95% CI, 3.5%-6.9%) ($P < 0.001$).¹⁷ Furthermore, the largest of the COCPR vs conventional CPR studies,¹⁸ also found a statistically significant increase in neurologically intact survival with COCPR (18.9% vs. 13.5%, $P = 0.03$). COCPR should not be preferred in victims of asphyxial cardiac arrest (e.g. in the setting of drowning), as in such cases, the prompt reversal of the hypoxemia through ventilation is critical for the restoration of spontaneous circulation (ROSC) and the achievement of a favorable functional outcome.^{19,20}

A coronary perfusion pressure (CPP) of at least 15 mmHg is required to achieve ROSC.⁵ Several authors suggest that chest compressions of 38–51 mm are not deep enough for ROSC.²¹⁻²⁴ Finally, several reports demonstrate that chest compressions deeper than 51 mm are associated with improved short term outcomes.²⁵⁻²⁸ This chest compression depth is also recommended by the current Guidelines.^{29,30}

In a recent analysis,³¹ the authors evaluated whether the depth of chest compressions provided by prehospital rescuers is independently associated with survival and favorable functional outcome. This study included 593 adults with out-of-hospital arrest (OHCA) of presumed cardiac etiology. Chest compression quality was measured during resuscitation, including minute-by-minute rate and depth data. Interruptions in compressions were assessed using the chest compression fraction, i.e. the percentage of time compressions were performed throughout the entire resuscitation procedure. Chest compression rate was similar for survivors 113.5 (95% CI 108.5–118.6) and non-survivors 112.7 (95% CI 110.9–114.4).

Chest compression depth was significantly greater in survivors (53.6 mm; 95% CI 50.5–56.7) than in non-survivors (48.8 mm; 95% CI 47.6–50.0). Notably, the median percentage of chest compressions of at least 51 mm was 64.0% (95% CI 47.0–81.0) for survivors and 45.0% (95% CI 39.6–50.4) for non-survivors.

The odds of survival increased by 29% for every 5 mm increase in mean chest compression depth (adjusted odds ratio - OR = 1.29; 95% CI 1.00–1.65). Likewise, a favorable functional outcome had 30% better odds for each 5 mm increase in chest compression depth (adjusted OR = 1.30; 95% CI 1.00–1.70). Furthermore, the odds of survival to hospital discharge and favorable functional outcome increased by 21% for each 10% increment of chest compressions of at least 51 mm. In addition, survivors were more likely to have been treated with mean chest compression depth of at least 51 mm as compared with non-survivors (64% vs. 45%). However, while deeper chest compressions were positively associated with improved outcomes, the optimal chest compression depth remains unknown.

DEFIBRILLATION

Defibrillation is the application of a preset electrical current across the myocardium to cause synchronous depolarization of the cardiac muscle. In ventricular fibrillation (VF)/ventricular tachycardia (VT) cardiac arrest, the goal of defibrillation is to restore an organized cardiac rhythm (ideally normal sinus rhythm) that will result in ROSC. Defibrillators work as capacitors discharging their stored energy through a circuit that includes the patient's heart. Optimal, monophasic and biphasic defibrillator current (I) ranges within 30-40 A and 15-20 A, respectively.³² Current duration (t) ranges within 10-20 ms, and the adult patient transthoracic impedance (R) usually ranges within 70-80 Ω.³² The energy delivered to the patient is proportional to the stored charge (Q) and the capacitor voltage (V):

$$\text{Energy} = \frac{1}{2} \cdot Q \cdot V = \frac{1}{2} \cdot (I \cdot t) \cdot (I \cdot R) = \frac{1}{2} \cdot I^2 \cdot R \cdot t.$$

For monophasic defibrillators, the recommended energy level is 360 J. For biphasic defibrillators, the initial energy level should be at least 150 J.³² The sum of the defibrillator's electrode areas should be at least 150 cm²,³³ and a force of 8 kg should be applied on them, in order to minimize R and thus maximize current flow through the heart.³²

The use of automated external defibrillators (AEDs) has revolutionized the capability of timely delivery of defibrillation to VF/VT victims. The availability of AEDs is currently recommended for both public, out-of-hospital and non-monitored, in-hospital settings.³² The safety and effectiveness of AEDs with respect to prompt defibrillation and survival is supported by a considerable amount of previously published data.³⁴ Nevertheless, in a recent retrospective analysis of OHCA the use of AEDs by bystanders was quite infrequent, i.e. an AED

was retrieved and used successfully before ambulance arrival in less than 2% of 1035 OHCA cases.³⁵

Whenever the first shock is preceded by CPR, the delay between chest compression interruption and shock delivery (pre-shock pause) should be kept to less than 5 s, and chest compressions should be resumed immediately after the shock.³² There is currently insufficient data to support or refute a pre-specified period of 2-3 min of pre-shock CPR in the out-of-hospital setting.³² However, regarding in-hospital VF/VT, defibrillation should be administered as soon as possible. Defibrillation in the (early) electrical phase (i.e. within 1-3 min of VF/VT onset) has a high probability of success that may exceed 90%, especially when a biphasic waveform is used.³² Patients experiencing VF/VT in the cardiac catheterization laboratory or following cardiac surgery may be treated with three quick successive (stacked) shocks.³² In all other cases of in-hospital or out-of-hospital VF/VT, shocks should be interspersed with 2-min periods of chest compressions and vasopressors and antiarrhythmics should be given after the third shock.³²

The optimal energy for defibrillation is that which achieves VF/VT termination and ROSC whilst causing the minimum of myocardial damage.^{32,36} Biphasic vs monophasic waveforms are more effective at terminating ventricular arrhythmias at lower energy levels, and have greater first shock efficacy.^{32,37-39} However, the potential superiority of biphasic waveforms with respect to neurologically favourable survival still remains to be demonstrated.³²

Multiple clinical studies suggest that it is possible to predict the success of defibrillation from VF waveform analysis with varying reliability.⁴⁰ However, a recent, multicenter study comparing a VF waveform analysis algorithm for identification of VF unlikely to respond to immediate defibrillation with a standard shock-first protocol failed to show any waveform analysis-associated improvement in survival to hospital discharge.⁴¹ Consequently, the value of VF waveform analysis remains uncertain.⁴⁰

MECHANICAL AUGMENTATION OF CIRCULATION

Over the past 25 years, a variety of alternatives to conventional, manual CPR have been developed in an effort to enhance perfusion during attempted resuscitation from cardiac arrest and to improve survival. In the 2010 AHA guidelines,⁴² the authors warn that usage of such devices may delay or interrupt CPR. They claim that these devices typically require more personnel, training, and equipment, or they apply to a specific setting. In recent bibliography, there is a lot of debate about active compression-decompression (ACD-CPR) CPR, applied in conjunction with the impedance threshold device (ITD).

ACD-CPR is performed with a device that includes a suction cup to actively lift the anterior chest during decompression

(Fig. 1). The application of external negative suction during the decompression phase of CPR creates negative intrathoracic pressure, thus potentially enhancing venous return to the heart.

The ITD is a pressure-sensitive valve that is attached to an endotracheal tube, supraglottic airway, or face mask (Fig. 2). The ITD limits air entry into the lungs during the decompression phase of CPR, creating negative intrathoracic pressure and improving venous return to the heart and cardiac output during CPR.⁴³⁻⁴⁶ It does so without impeding positive pressure ventilation or passive exhalation. Studies of the mechanisms involved in animals and humans provide the physiological underpinnings for “the other side of breathing”: to increase circulation to the heart and brain. A review article⁴⁷ on the effects of the respiratory pump to improve vital organ perfusion by ITD, described studies that focused on the fundamental relationship between the generation of negative intrathoracic pressure during inspiration through a low-level of resistance created by an ITD and the physiologic effects of a respiratory pump. A decrease in intrathoracic pressure during inspiration through a fixed resistance resulting in an intrathoracic pressure of -7 cmH₂O has multiple physiological benefits, including enhanced venous return, cardiac stroke volume and aortic blood pressure, lower intracranial pressure; resetting of the cardiac baroreflex, elevated cerebral blood flow oscillations, and an increased tissue blood flow/pressure gradient.

Already in the early 2000s, some studies reported that the combination of ACD-CPR and ITD, when performed correctly, results in an increase of more than 50% in coronary perfusion pressure, and an improved 24-hour survival

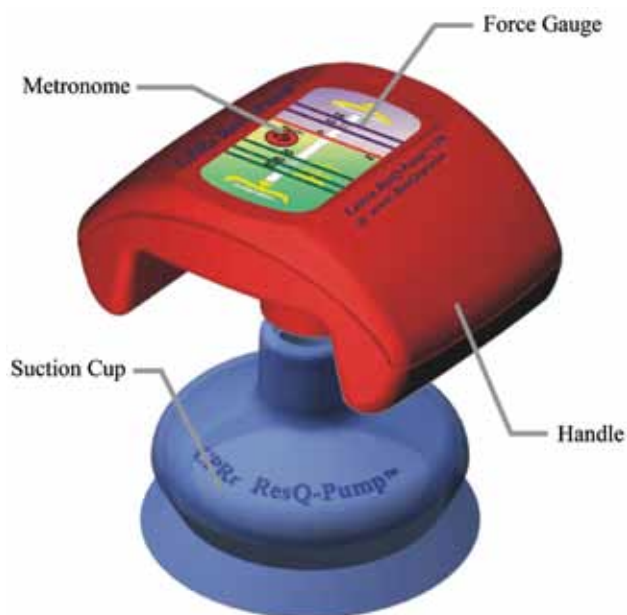


FIGURE 1. The active compression-decompression device.

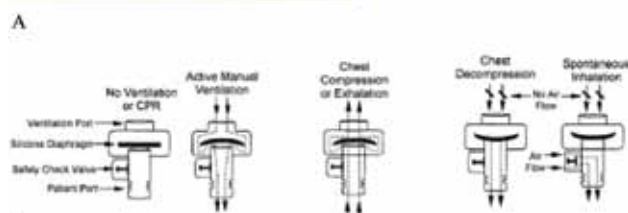


FIGURE 2. The impedance threshold device (A) and its working principle (B; reproduced with permission from Lurie KG et al *Respir Care* 2003;48(1):52-57).

and neurological function in cardiac arrest patients.^{48,49} The results of a presumed cardiac-cause OHCA, multicenter, randomized, unblinded trial, demonstrated a relative increase of 53% in survival to hospital discharge with favorable neurological outcome, when a combination of ACD-CPR and ITD was applied compared with standard CPR.⁵⁰ One year after OHCA, survival was still higher (by more than 50%) in the intervention group and there were similar proportions of restoration of neurologic function in both groups. There was no significant difference in the overall major adverse event rates between groups. However, pulmonary edema was more common in the intervention group. The aforementioned study further demonstrated that it is practicable to teach and implement ACD-CPR and ITD skills in urban, suburban, and rural Emergency Service environments.

Opposed to this study is a large effectiveness trial, which did not confirm a survival advantage with the use of an ITD during standard CPR in patients with nontraumatic OHCA.⁵¹ The authors suggested that the neutral results could have been due to the fact that the ITD may not generate or its use by the Emergency Service systems couldn't recreate the proposed physiological benefits. Another possible explanation was that the ITD did generate the physiological effects seen in experimental studies but couldn't change clinical outcomes.

EPINEPHRINE

The primary goal of pharmacologic therapy during cardiac arrest is to facilitate restoration and maintenance of a perfusing, spontaneous rhythm. Toward this goal, ALS drug therapy during CPR is often associated with increased rates of ROSC and survival to hospital admission but not increased rates of long-term survival with good neurological outcome.

One study randomized patients to intravenous or no intravenous medications during OHCA.⁵² The study demonstrated higher rates of ROSC in the intravenous vs the no intravenous group (40% vs 25%; OR 1.99; 95% CI 1.48 to 2.67), but there was no significant difference in the survival to hospital discharge (10.5% vs. 9.2%; OR 1.16; 95% CI 0.74 to 1.82), or the survival to hospital discharge with favorable neurological outcome (9.8% vs. 8.1%; OR 1.24; 95% CI 0.77 to 1.98). Among patients randomized to intravenous access, 79% received epinephrine, 46% atropine and 17% amiodarone, and it was not possible to determine the efficacy of these drugs (either individually or in combination) with respect to the reported outcomes. Furthermore, as the intervention could not be blinded, the potential for paramedics to respond differently, particularly when knowing that patients randomized to the no intravenous access group would have drug therapy withheld, may have introduced a bias. While the investigators identified no difference in a number of CPR quality measures across both study arms in the 75% of events assessed, the potential bias inherent with non-blinding could not be ruled out.

Accordingly, the first randomized, double-blind, placebo-controlled trial of epinephrine in OHCA reported that epinephrine increases ROSC but not survival to hospital discharge.⁵³ A recent review of epinephrine in OHCA⁵⁴ included another four prospective cohort studies,⁵⁵⁻⁵⁸ one retrospective cohort study,⁵⁹ one survival analysis,⁶⁰ and one case control study.⁶¹ The authors of the review reported on the paucity of supporting evidence for the use of epinephrine in OHCA. Several experts have recently suggested that new, large, randomized, controlled trials may be needed to reliably establish the effect of epinephrine on the survival to hospital discharge and neurological outcome.

A recent, retrospective analysis of prospectively collected, population-based data (n=49165 adults with witnessed OHCA of cardiac origin) showed that epinephrine administration within 10 min of collapse was associated with improved survival to hospital discharge (OR 1.73; 95% CI 1.46 to 2.04) and good neurological outcome (OR 1.39, 95% CI 1.08 to 1.78).⁶² Epinephrine effectiveness has been now reconfirmed by a large propensity analysis showing a slightly improved, neurologically favorable survival with epinephrine use vs. no use (0.7% vs. 0.4%; OR 1.57 95% CI 1.04 to 2.37) in 9058 pairs of patients with nonshockable OHCA.⁶³ Another recent review of 20909 in-hospital cardiac arrest events showed that increasing the

epinephrine dosing interval from the guideline-recommended of 3-5 min to 6-10 min was associated with improved survival to hospital discharge (adjusted ORs 1.30-2.17; 95% CIs 1.02-1.62 to 1.65-2.92).⁶⁴ Consequently, future trials should also determine the optimal timing of epinephrine administration (initial and dosing interval) as well.

VASOPRESSIN AND STEROIDS

In a previous, single-center, randomized, controlled study,⁶⁵ combined vasopressin-epinephrine during CPR and corticosteroid supplementation during and after CPR vs. epinephrine alone during CPR and no steroids resulted in improved overall survival to hospital discharge. Patients in the vasopressin-steroids epinephrine (VSE) group had more frequent ROSC, and attenuated postresuscitation systemic inflammatory response^{65,66} and organ dysfunction.⁶⁵ This preliminary study could not reliably assess VSE efficacy with respect to neurologically favorable survival to hospital discharge. The current authors addressed this question with a 3-center study of vasopressor-requiring, in-hospital cardiac arrest,⁶⁷ the study protocol was identical to that of the preliminary study.⁶⁵ This randomized, controlled trial included 268 consecutive patients with cardiac arrest requiring epinephrine according to resuscitation guidelines (from 364 patients assessed for eligibility). Patients received either vasopressin (20 IU/CPR cycle) plus epinephrine (1 mg/CPR cycle; cycle duration approximately 3 min) (VSE group, n = 130) or saline placebo plus epinephrine (1 mg/CPR cycle; cycle duration approximately 3 min) (control group, n = 138) for the first 5 CPR cycles after randomization, followed by additional epinephrine if needed. During the first CPR cycle after randomization, patients in the VSE group received 40 mg of methylprednisolone and patients in the control group received saline placebo. Shock after resuscitation was treated with stress-dose hydrocortisone (VSE group) or saline placebo (control group; see below).

Patients in the VSE group vs. patients in the control group had higher probability for ROSC for 20 minutes or longer (83.9% vs 65.9%; OR 2.98; 95% CI 1.39 to 6.40) and survival to hospital discharge with good neurological outcome (13.9% vs 5.1%; OR 3.28; 95% CI 1.17 to 9.20). Results on the postresuscitation shock subgroup were also favorable for the VSE combination (see below). **Table 1** displays important peri-arrest characteristics and variables of the pooled study population;^{65,67} these data are presented mainly to enable readers to independently assess the baseline status of the 2 pooled groups. **Figure 3** displays the pooled outcome data from the total of the 368 studied patients.

Both VSE studies exhibit limitations: results refer only to in-hospital cardiac arrest, there was no assessment of CPR quality, the VSE protocol did not allow a precise determination of the relative contribution of vasopressin and steroids to

TABLE 1. Important baseline and peri-arrest characteristics of the pooled study populations of references 65 and 67.

Baseline Characteristic or Per-arrest Variable	Control group (n = 190)	VSE Group (n = 178)	P value^a
Age - years	64.6 ± 18.5	63.8 ± 17.6	
Male gender - no. (%)	117 (61.6)	125 (70.2)	
Hypertension - no. (%)	110 (57.9)	95 (53.4)	
Coronary disease - no. (%)	62 (32.6)	65 (36.5)	
Diabetes - no. (%)	45 (23.7)	48 (27.0)	
Hypotension ^b	70 (36.8)	84 (47.2)	
Respiratory ^c	71 (37.4)	52 (29.2)	
Myocardial ischemia ^c	36 (19.0)	42 (23.6)	
Metabolic	27 (14.2)	13 (7.3)	
Lethal Arrhythmia	14 (7.4)	10 (5.6)	
Other	2 (1.1)	6 (3.4)	
VF/pulseless VT – no. (%)	30 (15.8)	29 (16.3)	>0.99
Asystole – no. (%)	128 (67.4)	113 (63.5)	0.45
PEA – no. (%) ^c	32 (16.8)	36 (20.2)	0.42
Witnessed arrest - no. (%)	169 (89.0)	159 (89.3)	>0.99
Location of cardiac arrest			
Hospital ward - no. (%)	83 (43.7)	78 (43.8)	0.98
Intensive care area - no. (%)	67 (35.3)	65 (36.5)	
Emergency department - no. (%)	31 (16.3)	29 (16.3)	
Operating room - no. (%)	9 (4.7)	6 (3.4)	
ALS duration, median (IQR) - min	20 (10-30)	14 (7-24)	0.01
Time to ALS initiation from emergency call - median (IQR; range) - min	1 (1-2; 0-4) ^d	1 (1-2; 0-4) ^c	0.16
Epinephrine dose, median (IQR) - mg	5 (3-9)	4 (2-6)	0.01
Rate of ROSC ≥20 min, after second vasopressor dose - no. (%)	33 (17.4)	50 (28.1)	0.02
Overall rate of ROSC – no (%)	118 (62.1)	148 (83.1)	<0.001

VSE = vasopressin-steroids-epinephrine; VF = ventricular fibrillation; VT = ventricular tachycardia; PEA = pulseless electrical activity; ALS = advanced life support; IQR = interquartile range; ROSC = return of spontaneous circulation.

^a, Baseline characteristics were not compared between the 2 groups.

^b, Imbalance potentially favoring control group outcomes⁶⁸.

^c, Imbalance potentially favoring VSE group outcomes⁶⁸.

^d, Data available from 171 patients.

^e, Data available from 159 patients.

the positive VSE group outcomes, there were some baseline imbalances with respect to cardiac arrest etiology and presenting rhythm potentially favoring the VSE group (Table 1, footnote),^{68,69} and there was no pre-specified determination of 1-year outcomes. Also, in the second VSE study,⁶⁷ attending physicians frequently prescribed open label, stress-dose hydrocortisone, especially to patients with high vasopressor requirements in the postresuscitation period; this caused cancellation of any further hydrocortisone or saline placebo administration according to patient randomization.⁶⁷ Thus, although these results are considerably encouraging, they may require confirmation by a larger, international trial before potential incorporation into the CPR guidelines.⁷⁰ Additional

CPR drug regimens supported by animal data and potentially warranting further clinical evaluation may include combined epinephrine, vasopressin, and nitroglycerin,⁷¹ epinephrine and atenolol,⁷² epinephrine and nitroglycerin,⁷³ and epinephrine and levosimendan.⁷⁴

THE POSTRESUSCITATION PHASE

The high mortality rate of patients who initially achieve ROSC after cardiac arrest can be attributed to a pathophysiological process that involves multiple organs. Although prolonged, whole-body ischemia initially causes global tissue and

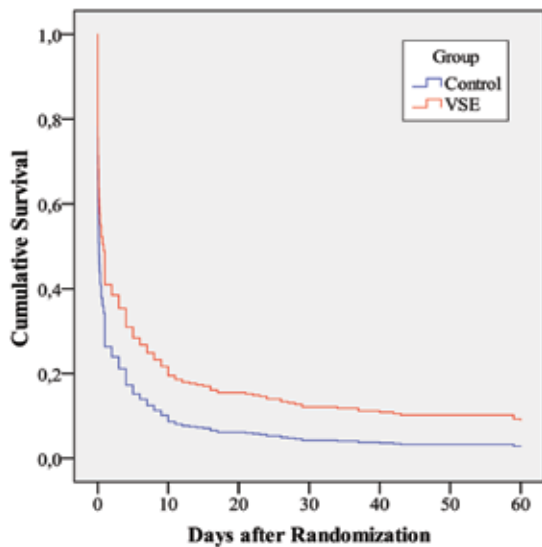


FIGURE 3. Cox regression analysis results on survival to hospital discharge with favorable neurological recovery [i.e. cerebral performance category (CPC) score of 1 or 2] in the pooled study population of references 65 and 67; Vasopressin-steroids-epinephrine (VSE) group: 26/178 (14.6%); Control group: 9/190 (4.7%). Randomization to the VSE group was associated with a lower probability for poor outcome [i.e. death during follow-up, or survival to hospital discharge with a CPC score of 3 (severe cerebral disability) or 4 (vegetative state)]: Hazard ratio 0.67; 95% confidence interval 0.53 to 0.84; $P < 0.001$. This original, pooled analysis has been adjusted for initial cardiac arrest rhythm (i.e., shockable vs. non-shockable), resuscitation-associated bicarbonate dose, time of cardiac arrest occurrence (i.e. night vs. morning-to-late evening hours or holiday vs. working day), and resuscitation-associated dose of epinephrine.

organ injury, while additional damage occurs during and after reperfusion.^{72,76} The unique features of post-cardiac arrest pathophysiology are often superimposed on the disease or injury that caused the cardiac arrest, as well as the underlying comorbidities. Therapies that focus on individual organs may compromise other injured organ systems. The four key components of post-cardiac arrest syndrome are 1) post-cardiac arrest brain injury, 2) post-cardiac arrest myocardial dysfunction, 3) ischemia/reperfusion-triggered, systemic inflammatory response, and 4) persistent underlying pathology.⁷⁷

The recognition of the importance of post resuscitation care on long term survival and favorable neurological outcome led to the addition of a fifth ring to the chain of survival, termed “post-resuscitation care”.

2010 AHA GUIDELINES FOR POST-RESUSCITATION CARE – OVERVIEW

There is paucity of data reported from the post-arrest,

in-hospital phase, and no generally accepted, evidence-based protocol exists, other than brain protection-oriented intensive care.

The AHA 2010 guidelines suggest a multiple system approach:⁷⁸

Although 100% oxygen may have been used during initial resuscitation, providers should titrate inspired oxygen fraction (FiO_2) as soon as possible to the lowest level required, ensuring an adequate arterial oxygen content and avoiding oxygen toxicity. The optimal FiO_2 is under debate. Animal data suggest that ventilation with 100% oxygen (generating a PaO_2 of more than 350 mm Hg at 15 to 60 minutes after ROSC) increases brain lipid peroxidation, neuronal metabolic dysfunction and degeneration, and worsens short-term functional outcome when compared with ventilation with room air or an FiO_2 titrated to a pulse oximeter reading of 94% to 96%.⁷⁹⁻⁸⁴ Physicians should try to achieve an arterial oxygen saturation of at least 94%, for all patients after ROSC. Hyperventilation should be avoided for its adverse hemodynamic effects, as well as for the potential vasoconstriction that low $PaCO_2$ can cause in the cerebral circulation. Minute ventilation should be titrated targeting an end-tidal CO_2 of 35 to 40 mmHg or a $PaCO_2$ of 40 to 45 mmHg. Although human studies have not established ideal targets for blood pressure or blood oxygenation,^{85,86} a mean arterial pressure of at least 65 mmHg and a central-venous oxygen saturation of at least 70% are generally considered as reasonable goals. Vasoactive drug infusions may be considered in order to achieve this goal.

Hyperglycemia⁸⁷⁻⁹¹ or hypoglycemia^{92,93} can have detrimental effects on survival and neurological recovery. The optimum blood glucose concentration and interventional strategy to manage blood glucose in the post-cardiac arrest period is unknown. Moderate glycemic control (144 to 180 mg/dL) seems reasonable in adult patients with ROSC after cardiac arrest.

THERAPEUTIC HYPOTHERMIA

For protection of the brain and other organs, hypothermia is a helpful therapeutic approach in patients who remain comatose (usually defined as a lack of meaningful response to verbal commands) after ROSC.⁷⁸ Questions remain about specific indications and populations, timing and duration of therapy, and methods for induction, maintenance, and subsequent reversal of hypothermia.

The recommended temperature of 32°C to 34°C has been extrapolated from experiments in animals;^{94,95} however, similar results have been observed with milder cooling.⁹⁶ Although a Cochrane review supported these guidelines,⁹⁷ some investigators have suggested a need for additional trials to confirm or refute this treatment strategy.⁹⁸⁻¹⁰⁰

The use of therapeutic hypothermia is supported by the results of 2 prior, randomized, controlled trials of OHCA

with a shockable rhythm that showed improved neurological outcomes in hypothermia-treated patients.^{101,102} In both trials, there were no pre-specified temperature control measures for control patients. Mild hypothermia (32-34°C) for 12 to 24 hours improved neurological recovery and survival, despite delays of 4 to 8 hours in achieving goal temperatures.^{101,102}

Neutral results on hypothermia were reported by the investigators of a recent, international, multicenter, randomized, controlled trial.¹⁰³ This trial compared a target body temperature of 33°C with one of 36°C in patients resuscitated from OHCA of presumed cardiac cause.¹⁰³ Hypothermia was induced as rapidly as possible with the use of ice-cold fluids, ice packs, and intravascular or surface temperature-management devices at the discretion of the attending physician. The time interval between ROSC and induction of hypothermia was 20 to 240 min. There were no significant differences between the two groups in overall mortality at the end of the trial or in the composite outcome of poor neurological function or death at 180 days.¹⁰³

A difference between the recent trial¹⁰³ and the earlier trials,^{101,102} is that the natural trajectory of temperature evolution was not allowed in either group. Indeed, temperature was actively controlled during the intervention period in both groups and fever was prevented during the first 3 days after cardiac arrest.¹⁰³ As in the earlier trials,^{101,102} the investigators did enroll patients with OHCA of presumed cardiac cause, but the sample was larger and approximately 20% of participants had nonshockable rhythms.¹⁰³

Other published studies involving patients with cardiac arrest who were admitted to the ICU¹⁰⁴⁻¹⁰⁸ have shown baseline characteristics and mortality that are in keeping with the findings of the recent, large trial.¹⁰³ The mortality in both groups of this trial was lower than that in the control group of the Hypothermia after Cardiac Arrest trial.¹⁰² This can be attributed to the fact that both prehospital and critical care have improved during the past decade.^{106,109} Fever frequently develops after ROSC because of a systemic inflammatory response. Nevertheless, it is important to acknowledge that there may be a clinically relevant benefit of controlling the body temperature at 36°C, instead of allowing fever to develop in patients who have been resuscitated after cardiac arrest.¹¹⁰

Bernard et al. conducted an investigation in 2010 inducing hypothermia in the field or after hospital admission in patients resuscitated from out of hospital arrest presenting with a shockable rhythm. No benefit was observed.¹¹¹ The recent, large randomized trial by Kim et al found that prehospital, rapid infusion of up to 2 L of cold (4°C) normal saline did induce mild hypothermia, approximately 60 min faster than standard care, but did not improve survival or neurological status at discharge after resuscitation from prehospital, shockable (VF) or nonshockable (non VF) cardiac arrest.¹¹² The intervention was associated with a significantly increased incidence of early re-arrest, and pulmonary edema/diuretic

use (in the Emergency Department).

CORTICOSTEROIDS

Corticosteroids are a class of chemicals involved in a wide range of physiological processes, including stress response, immune response and regulation of inflammation, carbohydrate metabolism, protein catabolism, blood electrolyte levels, and behavior.

Preceding retrospective studies with inherent methodological limitations did not support the use of low-dose corticosteroids during and after CPR.^{113,114} However, more recent laboratory data and clinical results are consistent with a possible, low-dose corticosteroid-associated, benefit in cardiac arrest, especially in patients with postresuscitation shock. Such potential benefit can be explained mainly by the hemodynamic and anti-inflammatory properties of hydrocortisone.¹¹⁵

Cardioprotective effects of glucocorticoids in the acute setting of myocardial ischemia/reperfusion have been shown experimentally with regard to structural and functional myocardial damage.¹¹⁶⁻¹²³ Also, a meta-analysis of human data from 11 controlled trials suggested a possible mortality benefit for corticosteroid treatment of myocardial infarction.¹²⁴

Glucocorticoids attenuate leukocyte/endothelium interactions,¹²⁵⁻¹²⁸ as well as the generation and release of inflammatory cytokines and mediators.¹²⁹⁻¹³² The *Surviving Sepsis Campaign guidelines 2012 for the management of severe sepsis and septic shock* suggest stress-dose hydrocortisone therapy (daily dose: 200 mg) only for patients who are poorly responsive to fluid and vasopressor therapy.¹³³ Likewise, in cardiac arrest patients, treatment-refractory shock is a common post-ROSC complication.^{65,67} Furthermore, postresuscitation shock is frequently partly due to a post-arrest adrenal insufficiency or dysfunction,^{66,134-136} which in turn constitutes an independent predictor of mortality at one week after resuscitation.¹³⁶

The mechanisms underlying the post-cardiac arrest syndrome involve a whole body ischemia and reperfusion that triggers a systemic inflammatory response.^{65,66,77,78,134} Altogether, the high levels of circulating cytokines, the presence of endotoxin in plasma, and the dysregulated production of cytokines found in cardiac arrest patients resemble the immunological profile found in patients with sepsis.^{66,77,78,134}

A recent, observational OHCA study found a 38% incidence of bacteremia upon presentation to the Emergency Department.¹³⁷ A similar incidence of cardiac arrest-associated bacteremia has been previously reported by others as well.¹³⁸ Consequently, actual septic insults may frequently contribute to the development and the severity of the postresuscitation hemodynamic instability. This fact, in conjunction with the lower absolute serum cortisol levels previously documented in patients with poor CPR/postresuscitation outcomes,^{135,139} the previously reported, strong, negative correlation between

cortisol levels and “no-flow” time,¹³⁹ and the frequently severe postresuscitation, hemodynamic instability that does not adequately respond to fluid and vasopressor therapy,^{65,67} provides a robust framework for the rationale of glucocorticoid supplementation in the peri-arrest and postresuscitation period.^{65,67,133}

In our recent in-hospital cardiac arrest studies,^{65,67} we administered 40 mg of methylprednisolone during CPR (in combination with vasopressin / epinephrine – see also above), and stress dose hydrocortisone (300 mg/day for a maximum of 7 days followed by gradual taper) to patients fulfilling a clearly defined criterion for postresuscitation shock. Patients with evidence of myocardial infarction received a 3-day course of stress dose hydrocortisone (followed by gradual taper), in order to prevent any potential retardation of infarct healing.^{65,67} Compared to control, the postresuscitation shock subgroups of the VSE groups had improved post-arrest hemodynamics and central venous oxygen saturation,^{65,67} post-arrest cytokine levels⁶⁵ and organ/system function,^{65,67} and survival to hospital discharge with favorable neurological recovery.^{65,67} Accordingly, pooled subgroup results show more VSE patients (23/103, 22.3%) than control patients (6/88, 6.8%) with good functional outcome (hazard ratio for death during follow-up or severe cerebral disability / vegetative state: 0.64; 95% confidence interval 0.46 to 0.88; P=0.006).^{65,67}

As already mentioned above, due to the VSE combination, we could not separately assess glucocorticoid efficacy.^{65,67,78} Therefore, a large, multicenter, randomized, placebo-controlled evaluation of stress-dose glucocorticoid supplementation in cardiac arrest is still needed.^{65,115} Such a study should provide definitive results on the efficacy, and appropriate dosage and timing of steroid administration. Lastly, although there is no published data suggestive of a glucocorticoid-associated neuroprotection,^{65,67,77,78,115} recent laboratory results suggest that the biosynthetically related estrogens may actually mitigate the effects of global cerebral ischemia.¹⁴⁰

BETA ADRENERGIC ANTAGONISTS

Two small, clinical, prospective human studies tested the effects of beta blockade against regular therapy in patients presenting with electrical storm. In the intervention group of the first study,¹⁴¹ sympathetic blockade resulted in a decline in the mean number of VF episodes from over 20 to 2.6 ± 1.7 per day (P < 0.01). In contrast, 91% of patients in the control group continued to have VF episodes. At the end of the first year of follow-up, 18/27 patients in the beta blockade group were still alive, compared with 1/22 in the control group. In the other human trial,¹⁴² 42 consecutive patients with electrical storm refractory to regular ALS therapy received intravenous landiolol in increasing doses (starting at 2.5 µg/kg/min; maximum dose was 80 µg/kg/min), subsequently titrated to the minimum infusion rate required for arrhythmia control. The

study protocol was ineffective in 9 patients (21%), who died of arrhythmia. From the 33 responders, 21 received carvedilol and 12 were started on bisoprolol, with oral beta-blocker administration immediately after stabilization. Eight of these 33 patients (19%) died afterwards from multiple organ failure or infection, and 25 (60%) survived to hospital discharge.

A recently published review on the use of beta-blockers in cardiac arrest with shockable rhythms concluded that available human studies may point toward a beneficial effect of beta-blockade in patients, which is in accordance with the results from the majority of relevant clinical case reports and animal experimental studies.¹⁴³ However, high quality human trials are warranted, in order to reliably evaluate the potential usefulness of the beta-blockers in cardiac arrest. Indeed, beta-blockers may counteract the potentially deleterious beta-adrenergic effects of epinephrine, which may contribute to the postresuscitation myocardial dysfunction and the recurrence of life-threatening arrhythmias.

OTHER ANTIARRHYTHMIC DRUGS

Amiodarone affects sodium, potassium, and calcium channels and has alpha and beta adrenergic blocking properties.⁴⁰ It can be given as an initial IV bolus of 300 mg to patients with refractory VF/VT cardiac arrest not responsive to CPR, defibrillation (i.e. 3 shocks), and vasopressors. If VF/VT persists after the 4th shock, an additional amiodarone IV bolus of 150 mg may be considered.⁴⁰ Amiodarone effectiveness with respect to improved survival to hospital admission of OHCA patients is supported by the results of 2 blinded, randomized, controlled trials.^{144,145} If amiodarone is not available, the sodium channel blocker lidocaine may be given with an initial IV bolus of 1-1.5 mg/kg, followed by additional IV boluses of 0.5-0.75 mg/kg every 5-10 min and up to a total dose of 3 mg/kg.⁴⁰ Lastly, IV magnesium sulfate can be given exclusively for the treatment of irregular/polymorphic VT associated with prolonged QT interval.^{40,146,147}

NITRATES

The greatest proportion of in-hospital, post-resuscitation mortality is caused by global ischemic brain injury, whereas both myocardial dysfunction and systemic inflammation predispose to poor neurological outcome.¹⁴⁸ Mechanisms of post-resuscitation brain injury include excitotoxicity, free radical formation, pathological activation of proteases, and cell death signalling.^{77,149} The injurious pathways include disruption of the blood-brain barrier, neuro-inflammation, and delayed neuro-degeneration.^{148,150}

Nitrite therapy limits cellular injury and apoptosis after ischemia and reperfusion (I/R).¹⁵¹ It has been proven to be

cytoprotective in numerous animal models of focal I/R injury, including rodent heart, brain, liver and kidney, canine heart, and primate brain.¹⁵¹⁻¹⁵⁵ Systemic nitrite reduction by ceruloplasmin knockout or dietary nitrate/nitrite elimination increased infarction volume in the liver and heart after experimental ischemia.^{156,157} These studies indicate that physiological systemic nitrite levels modulate host resilience to ischemia. The established safety of human and animal nitrite dosing¹⁵⁸ and its potent effects in limiting major organ injury suggest that nitrite represents an ideal candidate for the treatment of cardiac arrest.

Nitric oxide (NO) is produced from NO synthases (NOS, i.e. NOS1, NOS2, and NOS3). NO exerts a number of effects that would be expected to be beneficial during I/R injury.¹⁵⁹ NO is a potent vasodilator which inhibits platelet and leukocyte activation and adhesion, inhibits reactive oxygen species (ROS)-producing enzymes, and directly scavenges ROS.¹⁶⁰ Studies using NOS3 knockout mice showed that NOS3 deficiency aggravates I/R injury in the brain and heart,^{161,162} whereas cardiomyocyte-specific overexpression of NOS3 attenuated postresuscitation myocardial and neurological dysfunction in NOS3-deficient mice.¹⁶³

Several recent studies are also consistent with a nitrite treatment/NO associated benefit in experimental cardiac arrest.^{71,73,164-169} Likely mechanisms of brain protection may involve the primary intra-cellular target of NO, i.e. soluble guanylate cyclase,¹⁶⁷ or increased levels of neuronal nitrite and S-nitrosothiols.¹⁶⁸ The neuroprotective effects of hypothermia seem to be at least partly mediated through enhanced NOS3 signalling.¹⁶⁹ Also, inhaled NO (40 ppm) improves neurological outcomes during concurrent use of hypothermia.¹⁶⁹

In contrast to NO, NO-donor compounds may induce systemic vasodilation and hypotension, frequently precluding their use in the setting of cardiac arrest-associated hemodynamic instability. On the other hand, inhaled NO is a selective pulmonary vasodilator that does not produce systemic hypotension when inhaled at concentrations of up to 80 ppm in multiple species, including man.¹⁷⁰ The absence of systemic vasodilation during NO inhalation is due to the rapid scavenging of NO by hemoglobin in the blood.

Some NO, once inhaled, may escape scavenging by hemoglobin and be converted to relatively stable NO metabolites (e.g., nitrite and S-nitrosothiols) that can regenerate NO in the periphery.¹⁷¹ NO inhalation has been associated with marked increases in the arterial blood concentration of NO metabolites.¹⁷² Also, regenerated NO may exert regional vasodilating effects. Indeed, a recent study by Terpolilli et al,¹⁷³ showed that NO inhalation prevented ischemic brain injury in mice and sheep by selective dilatation of collateral arterioles. The aforementioned, promising, experimental results provide a robust background for a possible, future evaluation of nitrates/NO in the clinical setting.

CONCLUSIONS

Our clinical knowledge and practices with respect to the management of cardiac arrest have substantially improved during the last 10-15 years. This has resulted in significant improvements in the survival with favorable neurological outcome. Furthermore, recent, promising study results may guide future research aimed at establishing definitive evidence for more effective therapeutic approaches during CPR and ALS, as well as during the postresuscitation period.

REFERENCES

1. Cobb LA, Fahrenbruch CE, Olsufka M, Copass MK. Changing incidence of out-of-hospital ventricular fibrillation. *JAMA* 2002; 288:3008-3013.
2. Merchant RM, Yang L, Becker LB, et al, American Heart Association Get With The Guidelines-Resuscitation Investigators. Incidence of treated cardiac arrest in hospitalized patients in the United States. *Crit Care Med* 2011; 39:2401-2406.
3. Ehlenbach WJ, Barnato AE, Curtis JR, et al. Epidemiologic study of in-hospital cardiopulmonary resuscitation in the elderly. *N Engl J Med* 2009;361:22-31.
4. Girotra S, Nallamothu BK, Spertus JA, et al. Trends in survival after in-hospital cardiac arrest. *N Engl J Med* 2012; 367:1912-1920.
5. Berg RA, Hemphill R, Abella BS, et al. Part 5: adult basic life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010; 122(Suppl 3):S685-S705.
6. Ornato JP, Garnett AR, Glauser FL Relationship between cardiac output and the end-tidal carbon dioxide tension. *Ann Emerg Med* 1990; 19:1104-1106.
7. Chandra NC, Gruben KG, Tsitlik JE. Observations of ventilation during resuscitation in a canine model. *Circulation* 1994; 90:3070-3075.
8. Sanders AB, Kern KB, Atlas M, Bragg S, Ewy GA. Importance of the duration of inadequate coronary perfusion pressure on resuscitation from cardiac arrest. *J Am Coll Cardiol* 1985; 6:113-118.
9. Berg RA, Sanders AB, Kern KB, et al. Adverse hemodynamic effects of interrupting chest compressions for rescue breathing during cardiopulmonary resuscitation for ventricular fibrillation cardiac arrest. *Circulation* 2001; 104:2465-2470.
10. Aufderheide TP, Sigurdsson G, Pirralo RG, et al. Hyperventilation-induced hypotension during cardiopulmonary resuscitation. *Circulation*. 2004; 109:1960-1965.
11. SOS-KANTO Study Group. Cardiopulmonary resuscitation by bystanders with chest compression only (SOS-KANTO): an observational study. *Lancet* 2007; 369:920-926.
12. Assar D, Chamberlain D, Colquhoun M, et al. Randomised controlled trials of staged teaching for basic life support: 1, Skill acquisition at bronze stage. *Resuscitation* 2000; 45:7-15.
13. Rea TD, Fahrenbruch C, Culley L, et al. CPR with chest com-

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- pression alone or with rescue breathing. *N Engl J Med* 2010; 363:423-433.
14. Heidenreich JW, Higdon TA, Kern KB, et al. Single rescuer cardiopulmonary resuscitation: “two quick breaths”: an oxymoron. *Resuscitation* 2004; 62:283-289.
 15. Weisfeldt ML, Becker LB. Resuscitation after cardiac arrest: a 3-phase time-sensitive model. *JAMA* 2002; 288:3035-3038.
 16. Wik L, Hansen TB, Fylling F, et al. Delaying defibrillation to give basic cardiopulmonary resuscitation to patients with out-of-hospital ventricular fibrillation: a randomized trial. *JAMA* 2003; 289:1389-1395.
 17. Bobrow BJ, Spaite DW, Berg RA, et al. Chest Compression-only CPR by lay rescuers and survival from out-of-hospital cardiac arrest. *JAMA* 2010; 304:1447-1454.
 18. Rea TD, Fahrenbruch C, Culley L, et al. CPR with chest compression alone or with rescue breathing. *N Engl J Med* 2010; 363:423-433.
 19. Nolan JP, Soar J, Zideman DA, et al, ERC Guidelines Writing Group. European Resuscitation Council Guidelines for Resuscitation 2010 Section 1. Executive summary. *Resuscitation* 2010; 81:1219-1276.
 20. Soar J, Perkins GD, Abbas G, et al. European Resuscitation Council Guidelines for Resuscitation 2010 Section 8. Cardiac arrest in special circumstances: Electrolyte abnormalities, poisoning, drowning, accidental hypothermia, hyperthermia, asthma, anaphylaxis, cardiac surgery, trauma, pregnancy, electrocution. *Resuscitation* 2010; 81:1400-1433.
 21. Martin GB, Carden DL, Nowak RM, Lewinter JR, Johnston W, Tomlanovich MC. Aortic and right atrial pressures during standard and simultaneous compression and ventilation CPR in human beings. *Ann Emerg Med* 1986; 15:125-130.
 22. Paradis NA, Martin GB, Rivers EP, et al. Coronary perfusion pressure and the return of spontaneous circulation in human cardiopulmonary resuscitation. *J Am Med Assoc* 1990; 263:1106-1113.
 23. Timerman S, Cardoso LF, Ramires JA, Halperin H. Improved hemodynamic performance with a novel chest compression device during treatment of in-hospital cardiac arrest. *Resuscitation* 2004; 61:273-280.
 24. Tomlinson AE, Nysaether J, Kramer-Johansen J, Steen PA, Dorph E. Compression force-depth relationship during out-of-hospital cardiopulmonary resuscitation. *Resuscitation* 2007; 72:364-370.
 25. Babbs CF, Kemeny AE, Quan W, Freeman G. A new paradigm for human resuscitation research using intelligent devices. *Resuscitation* 2008; 77:306-315.
 26. Edelson DP, Abella BS, Kramer-Johansen J, et al. Effects of compression depth and pre-shock pauses predict defibrillation failure during cardiac arrest. *Resuscitation* 2006; 71:137-145.
 27. Edelson DP, Litzinger B, Arora V, et al. Improving in-hospital cardiac arrest process and outcomes with performance debriefing. *Arch Intern Med* 2008; 168:1063-1069.
 28. Kramer-Johansen J, Myklebust H, Wik L, et al. Quality of out-of-hospital cardiopulmonary resuscitation with real time automated feedback: a prospective interventional study. *Resuscitation* 2006; 71:283-292.
 29. Travers AH, Rea TD, Bobrow BJ, et al. Part 4: CPR overview: 2010 American Heart Association Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2010; 122:S676-S684.
 30. Koster RW, Baubin MA, Bossaert LL, et al. European Resuscitation Council guide-lines for resuscitation 2010 Section 2. Adult basic life support and use of automated external defibrillators. *Resuscitation* 2010; 81:1277-1292.
 31. Vadeboncoeur T, Stolzb U, Panchal A, et al. Chest compression depth and survival in out-of-hospital cardiac arrest. *Resuscitation* 2014;85:182-188.
 32. Deakin CD, Nolan JP, Sunde K, Koster RW. European Resuscitation Council Guidelines for Resuscitation 2010 Section 3. Electrical therapies: automated external defibrillators, defibrillation, cardioversion and pacing. *Resuscitation* 2010; 81:1293-1304.
 33. American National Standard: automatic external defibrillators and remote controlled defibrillators (DF39). Arlington, Virginia: Association for the Advancement of Medical Instrumentation; 1993.
 34. Marengo JP, Wang PJ, Link MS, Homoud MK, Estes NA 3rd. Improving survival from sudden cardiac arrest: the role of the automated external defibrillator. *JAMA* 2001; 285:1193-1200.
 35. Deakin CD, Shewry E, Gray HH. Public access defibrillation remains out of reach for most victims of out-of-hospital sudden cardiac arrest. *Heart* 2014. doi: 10.1136/heartjnl-2013-305030.
 36. Kerber RE. External defibrillation: new technologies. *Ann Emerg Med* 1984;13:794-797.
 37. van Alem AP, Chapman FW, Lank P, Hart AA, Koster RW. A prospective, randomised and blinded comparison of first shock success of monophasic and biphasic waveforms in out-of-hospital cardiac arrest. *Resuscitation* 2003; 58:17-24.
 38. Carpenter J, Rea TD, Murray JA, Kudenchuk PJ, Eisenberg MS. Defibrillation waveform and post-shock rhythm in out-of-hospital ventricular fibrillation cardiac arrest. *Resuscitation* 2003; 59:189-196.
 39. Morrison LJ, Dorian P, Long J, et al. Out-of-hospital cardiac arrest rectilinear biphasic to monophasic damped sine defibrillation waveforms with advanced life support intervention trial (ORBIT). *Resuscitation* 2005; 66:149-157.
 40. Neumar RW, Otto CW, Link MS, et al. 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science. Part 8: Adult Advanced Cardiovascular Life Support. *Circulation* 2010;122:S729-S767.
 41. Freese JP, Jorgenson DB, Liu PY, et al. Waveform analysis-guided treatment versus a standard shock-first protocol for the treatment of out-of-hospital cardiac arrest presenting in ventricular fibrillation: results of an international randomized, controlled trial. *Circulation* 2013; 128:995-1002.
 42. Cave DM, Gazmuri RJ, Otto CW, et al. Part 7: CPR techniques and devices: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010; 122(18 Suppl 3):S720-S728.

43. Cohen TJ, Tucker KJ, Lurie KG, et al. Active compression-decompression: a new method of cardiopulmonary resuscitation. Cardiopulmonary Resuscitation Working Group. *JAMA* 1992; 267:2916–2923.
44. Plaisance P, Lurie KG, Vicaut E, et al. A comparison of standard cardiopulmonary resuscitation and active compression-decompression resuscitation for out-of-hospital cardiac arrest. French Active Compression-Decompression Cardiopulmonary Resuscitation Study Group. *N Engl J Med* 1999; 341:569–575.
45. Lurie K, Voelckel W, Plaisance P, et al. Use of an inspiratory impedance threshold valve during cardiopulmonary resuscitation: a progress report. *Resuscitation* 2000; 44:219–230.
46. Lurie KG, Coffeen P, Shultz J, et al. Improving active compression-decompression cardiopulmonary resuscitation with an inspiratory impedance valve. *Circulation* 1995; 91:1629–1632.
47. Segal N, Yannopoulos D, Truchot J. Improving vital organs perfusion by the respiratory pump: physiology and clinical use. *Ann Fr Anesth Reanim* 2013;32:572-579.
48. Plaisance P, Lurie KG, Ducros L, Soleil C, Payen D. Comparison of an active versus sham impedance threshold valve on survival in patients receiving active compression decompression cardiopulmonary resuscitation for treatment of out of hospital cardiac arrest. *Circulation* 2001; 104(Suppl II):765.
49. Wolcke BB, Mauer DK, Schoefmann MF, et al Prospective randomized controlled trial comparing standard CPR with active compression decompression cardiopulmonary resuscitation and an impedance threshold valve in patients with out of hospital Cardiac arrest. *Circulation* 2002; 106(Suppl II):538.
50. Aufderheide TP, Frascone RJ, Wayne MA., et al. Comparative effectiveness of standard CPR versus active compression decompression CPR with augmentation of negative intrathoracic pressure for treatment of out-of-hospital cardiac arrest: results from a randomized prospective study. *Lancet* 2011; 377: 301–311.
51. Aufderheide TP, Nichol G, Rea TD, et al., Resuscitation Outcomes Consortium (ROC) Investigators. A trial of an impedance threshold device in out-of-hospital cardiac arrest. *N Engl J Med* 2011; 365:798-806.
52. Olasveengen TM, Sunde K, Brunborg C, et al. Intravenous Drug Administration during out-of-hospital cardiac arrest: a randomized trial. *JAMA* 2009; 302:2222-2229.
53. Jacobs IG, Finn JC, Jelinek GA, Oxer HF, Thompson PL. Effect of adrenaline on survival in out-of-hospital cardiac arrest: A randomized double-blind placebo-controlled trial. *Resuscitation* 2011; 82:1138–1143.
54. Reardon PM, Magee K. Epinephrine in out-of-hospital cardiac arrest: a critical review. *World J Emerg Med* 2013; doi: 10.5847/wjem.j.1920–8642.2013.02.001.
55. Hagihara A, Hasegawa M, Abe T. Prehospital epinephrine use and survival among patients with out-of-hospital cardiac arrest. *JAMA* 2012; 307:1161-1168.
56. Ong ME, Tan EH, Ng FS, et al. Survival outcomes with the introduction of intravenous epinephrine in the management of out-of-hospital cardiac arrest. *Ann Emerg Med* 2007; 50:635–642.
57. Ohshige K, Shimazaki S, Hirasawa H, et al. Evaluation of out-of-hospital cardiopulmonary resuscitation with resuscitative drugs: a prospective comparative study in Japan. *Resuscitation* 2005; 66:53–61.
58. Holmberg M, Holmberg S, Herlitz J. Low chance of survival among patients requiring adrenaline (epinephrine) or intubation after out-of-hospital cardiac arrest in Sweden. *Resuscitation* 2002; 54:37–45.
59. Herlitz J, Ekstrom L, Wennerblom B, Axelsson A, Bang A, Holmberg S. Adrenaline in out-of-hospital ventricular fibrillation. Does it make any difference? *Resuscitation* 1995; 29:195–201.
60. Wang HE, Min A, Hostler D, Chang CC, Callaway CW. Differential effects of out-of-hospital interventions on short- and long-term survival after cardiopulmonary arrest. *Resuscitation* 2005; 67:69–74.
61. Yanagawa Y, Sakamoto T. Analysis of prehospital care for cardiac arrest in an urban setting in Japan. *J Emerg Med* 2010; 38:340–345.
62. Nakahara S, Tomio J, Nishida M, et al. Association between timing of epinephrine administration and intact neurologic survival following out-of-hospital cardiac arrest in Japan: a population-based prospective observational study. *Acad Emerg Med* 2012; 19:782–792.
63. Nakahara S, Tomio J, Takahashi H, et al. Evaluation of pre-hospital administration of adrenaline (epinephrine) by emergency medical services for patients with out of hospital cardiac arrest in Japan: controlled propensity matched retrospective cohort study. *BMJ* 2013; 347:f6829. doi: 10.1136/bmj.f6829.
64. Warren SA, Huszti E, Bradley SM, et al for the American Heart Association’s Get With the Guidelines-Resuscitation (National Registry of CPR) Investigators. Adrenaline (epinephrine) dosing period and survival after in-hospital cardiac arrest: A retrospective review of prospectively collected data. *Resuscitation* 2014;85:350-358.
65. Mentzelopoulos SD, Zakyntinos SG, Tzoufi M, et al. Vasopressin, epinephrine, and corticosteroids for in-hospital cardiac arrest. *Arch Intern Med* 2009; 169:15-24.
66. Adrie C, Adib-Conquy M, Laurent I, et al. Successful cardiopulmonary resuscitation after cardiac arrest as a “sepsis-like” syndrome. *Circulation* 2002; 106:562-568.
67. Mentzelopoulos SD, Malachias S, Chamos C, et al. Vasopressin, steroids, and epinephrine and neurologically favorable survival after in-hospital cardiac arrest: a randomized clinical trial. *JAMA* 2013; 310:270-279.
68. Ebell MH, Jang W, Shen Y, Geocadin RG; Get With the Guidelines-Resuscitation Investigators. Development and Validation of the Good Outcome Following Attempted Resuscitation (GO-FAR) Score to Predict Neurologically Intact Survival After In-Hospital Cardiopulmonary Resuscitation. *JAMA Intern Med* 2013; 173:1872-1878.
69. Meaney PA, Nadkarni VM, Kern KB, et al. Rhythms and outcomes of adult in-hospital cardiac arrest. *Crit Care Med* 2010;38:101-108.
70. Ballew KA. Combined vasopressin, steroids, and epinephrine

- improved survival in in-hospital cardiac arrest. *Ann Intern Med* 2013; 159:JC4.
71. Varvarousi G, Goulas S, Agrogiannis G, et al. Epinephrine, vasopressin, and nitroglycerin improve neurologic outcome in porcine asphyxial cardiac arrest. *Am J Emerg Med* 2012; 30:1549-1554.
 72. Xanthos T, Bassiakou E, Koudouna E, et al. Combination pharmacotherapy in the treatment of experimental cardiac arrest. *Am J Emerg Med* 2009; 27:651-659.
 73. Kitsou V, Xanthos T, Stroumpoulis K, et al. Nitroglycerin and epinephrine improve coronary perfusion pressure in a porcine model of ventricular fibrillation arrest: a pilot study. *J Emerg Med* 2009; 37:369-375.
 74. Koudouna E, Xanthos T, Bassiakou E, et al. Levosimendan improves the initial outcome of cardiopulmonary resuscitation in a swine model of cardiac arrest. *Acta Anaesthesiol Scand* 2007; 51:1123-1129.
 75. Opie LH. Reperfusion injury and its pharmacologic modification. *Circulation* 1989; 80:1049-1062.
 76. White BC, Grossman LI, Krause GS. Brain injury by global ischemia and reperfusion: a theoretical perspective on membrane damage and repair. *Neurology* 1993; 43:1656-1665.
 77. Neumar RW, Nolan JP, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognosis. A consensus statement from the ILCOR, AHA, ANZCR, ERC, HSFC, IAHF, RCA, & RCSA; the AHA ECC; the CCSA; the CCPCC; the CCC; and the SC. *Circulation* 2008; 118:2452-2483.
 78. Peberdy MA, Callaway CW, Neumar RW, et al; American Heart Association. Part 9: post-cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010; 122(Suppl 3):S768-S786.
 79. Marsala J, Marsala M, Vanicky I, Galik J, Orendacova J. Post cardiac arrest hyperoxic resuscitation enhances neuronal vulnerability of the respiratory rhythm generator and some brainstem and spinal cord neuronal pools in the dog. *Neurosci Lett* 1992; 146:121-124.
 80. Zwemer CF, Whitesall SE, D' Alecy LG. Cardiopulmonary-cerebral resuscitation with 100% oxygen exacerbates neurological dysfunction following nine minutes of normothermic cardiac arrest in dogs. *Resuscitation* 1994; 27:159-170.
 81. Liu Y, Rosenthal RE, Haywood Y, et al. Normoxic ventilation after cardiac arrest reduces oxidation of brain lipids and improves neurological outcome. *Stroke* 1998; 29:1679-1686.
 82. Vereczki V, Martin E, Rosenthal RE, et al. Normoxic resuscitation after cardiac arrest protects against hippocampal oxidative stress, metabolic dysfunction, and neuronal death. *J Cereb Blood Flow Metab* 2006; 26:821-835.
 83. Richards EM, Fiskum G, Rosenthal RE, Hopkins I, McKenna MC. Hyperoxic reperfusion after global ischemia decreases hippocampal energy metabolism. *Stroke* 2007; 38:1578-1584.
 84. Richards EM, Rosenthal RE, Kristian T, Fiskum G. Postischemic hyperoxia reduces hippocampal pyruvate dehydrogenase activity. *Free Radic Biol Med* 2006; 40:1960-1970.
 85. Sunde K, Pytte M, Jacobsen D, et al. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation* 2007; 73:29-39.
 86. Gaieski DF, Band RA, Abella BS, et al. Early goal-directed hemodynamic optimization combined with therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest. *Resuscitation* 2009; 80:418-424.
 87. Nolan JP, Laver SR, Welch CA, et al. Outcome following admission to UK intensive care units after cardiac arrest: a secondary analysis of the ICNARC Case Mix Programme Database. *Anaesthesia* 2007; 62:1207-1216.
 88. Losert H, Sterz F, Roine RO, et al. Strict normoglycaemic blood glucose levels in the therapeutic management of patients within 12h after cardiac arrest might not be necessary. *Resuscitation* 2008; 76:214-220.
 89. Mullner M, Sterz F, Binder M, et al. Blood glucose concentration after cardiopulmonary resuscitation influences functional neurological recovery in human cardiac arrest survivors. *J Cereb Blood Flow Metab* 1997; 17:430-436.
 90. Skrifvars MB, Pettila V, Rosenberg PH, Castrun M. A multiple logistic regression analysis of in-hospital factors related to survival at six months in patients resuscitated from out-of-hospital ventricular fibrillation. *Resuscitation* 2003; 59:319-328.
 91. Langhelle A, Tyvold SS, Lexow K, et al. In-hospital factors associated with improved outcome after out-of-hospital cardiac arrest. A comparison between four regions in Norway. *Resuscitation* 2003; 56:247-263.
 92. Krinsley JS, Grover A. Severe hypoglycemia in critically ill patients: risk factors and outcomes. *Crit Care Med* 2007; 35:2262-2267.
 93. Arabi YM, Tamim HM, Rishu AH. Hypoglycemia with intensive insulin therapy in critically ill patients: predisposing factors and association with mortality. *Crit Care Med* 2009; 37:2536-2544.
 94. Colbourne F, Corbett D. Delayed and prolonged post-ischemic hypothermia is neuroprotective in the gerbil. *Brain Res* 1994; 654:265-272.
 95. Sterz F, Safar P, Tisherman S, Radovsky A. Mild hypothermic cardiopulmonary resuscitation improves outcome after prolonged cardiac arrest in dogs. *Crit Care Med* 1991; 19:379-389.
 96. Logue ES, McMichael MJ, Callaway CW. Comparison of the effects of hypothermia at 33 degrees C or 35 degrees C after cardiac arrest in rats. *Acad Emerg Med* 2007; 14:293-300.
 97. Arrich J, Holzer M, Havel C, Müllner M, Herkner H. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. *Cochrane Database Syst Rev* 2012; 9:CD004128.
 98. Nielsen N, Friberg H, Gluud C, Herlitz J, Wetterslev J. Hypothermia after cardiac arrest should be further evaluated – a systematic review of randomised trials with meta-analysis and trial sequential analysis. *Int J Cardiol* 2011; 151:333-341.
 99. Fisher GC. Hypothermia after cardiac arrest: feasible but is it therapeutic? *Anaesthesia* 2008; 63:885-886.
 100. Moran JL, Solomon PJ. Therapeutic hypothermia after cardiac arrest – once again. *Crit Care Resusc* 2006; 8:151-154.
 101. Bernard SA, Gray TW, Buist MD, et al. Treatment of coma-

- tose survivors of out-of hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002; 346:557-363.
102. The Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002; 346:549-556.
 103. Nielsen N, Wetterslev J, Cronberg T, et al; TTM Trial Investigators. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med* 2013; 369:2197-2206.
 104. Grödsner 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:R61.
 105. Mooney MR, Unger BT, Boland LL, et al. Therapeutic hypothermia after out-of hospital cardiac arrest: evaluation of a regional system to increase access to cooling. *Circulation* 2011; 124:206-214.
 106. Tømte O, Andersen GO, Jacobsen D, et al. Strong and weak aspects of an established postresuscitation treatment protocol – a five year observational study. *Resuscitation* 2011; 82:1186-1193.
 107. Nielsen N, Hovdenes J, Nilsson F, et al. Outcome, timing and adverse events in therapeutic hypothermia after out-of-hospital cardiac arrest. *Acta Anaesthesiol Scand* 2009; 53:926-934.
 108. Lindner TW, Langorgen J, Sunde K, et al. Factors predicting the use of therapeutic hypothermia and survival in unconscious out-of-hospital cardiac arrest patients admitted to the ICU. *Crit Care* 2013; 17:R147.
 109. Adielsson A, Hollenberg J, Karlsson T, et al. Increase in survival and bystander CPR in out-of-hospital shockable arrhythmia: bystander CPR and female gender are predictors of improved outcome: experiences from Sweden in an 18-year perspective. *Heart* 2011; 97:1391-1396.
 110. Zeiner A, Holzer M, Sterz F, et al. Hyperthermia after cardiac arrest is associated with an unfavorable neurologic outcome. *Arch Intern Med* 2001; 161:2007-2012.
 111. Bernard SA, Smith K, Cameron P, et al. Rapid Infusion of Cold Hartmanns (RICH) Investigators. Induction of therapeutic hypothermia by paramedics after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest: a randomized controlled trial. *Circulation* 2010; 122:737-742.
 112. Kim F, Nichol G, Maynard C, et al. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest a randomized clinical trial. *JAMA* 2014;311:45-52.
 113. Grafton ST, Longstreth WT Jr. Steroids after cardiac arrest: a retrospective study with concurrent, nonrandomized controls. *Neurology* 1988; 38:1315-1316.
 114. Jastremski M, Sutton-Tyrrell K, Vaagenes P, et al. Glucocorticoid treatment does not improve neurological recovery following cardiac arrest. *JAMA* 1989; 262: 3427-3430.
 115. Kolliantzaki I, Zakynthinos S, Mentzelopoulos SD. The potential contribution of corticosteroids to positive cardiac arrest outcomes. In: Gullo A, Ristagno G, eds. *Resuscitation, Translational Research, Clinical Evidence, Education, Guidelines*. Springer-Verlag, Milan, Italy, 2013:143-155.
 116. Libby P, Maroko PR, Bloor CM, et al. Reduction of experimental myocardial infarct size by corticosteroid administration. *J Clin Invest* 1973; 52:599-607.
 117. Spath JA Jr, Lane DL, Lefer AM. Protective action of methylprednisolone on the myocardium during experimental myocardial ischemia in the cat. *Circ Res* 1974; 35: 44-51.
 118. Hammerman H, Kloner RA, Hale S, et al. Dose-dependent effects of short-term methylprednisolone on myocardial infarct extent, scar formation, and ventricular function. *Circulation* 1983; 68:446-452.
 119. Wynsen JC, Preuss KC, Gross GJ, et al. Steroid-induced enhancement of functional recovery of postischemic, reperfused myocardium in conscious dogs. *Am Heart J* 1988; 116:915-925.
 120. D'Amico M, Di Filippo C, La M, et al. Lipocortin 1 reduces myocardial ischemia-reperfusion injury by affecting local leukocyte recruitment. *FASEB J* 2000; 14:1867-1869.
 121. Valen G, Kawakami T, Tähepold P, et al. Glucocorticoid pretreatment protects cardiac function and induces cardiac heat shock protein 72. *Am J Physiol* 2000; 279: H836-H843.
 122. Sun L, Chang J, Kirchhoff SR, et al. Activation of HSF and selective increase in heat-shock proteins by acute dexamethasone treatment. *Am J Physiol* 2000; 278:H1091-H1097.
 123. Giugliano GR, Giugliano RP, Gibson CM, Kuntz RE. Meta-analysis of corticosteroid treatment in acute myocardial infarction. *Am J Cardiol* 2003; 91:1055-1059.
 124. Cronstein BN, Kimmel SC, Levin RI, et al. A mechanism for the anti-inflammatory effects of corticosteroids: the glucocorticoid receptor regulates leukocyte adhesion to endothelial cells and expression of endothelial-leukocyte adhesion molecule 1 and intercellular adhesion molecule 1. *Proc Natl Acad Sci* 1992; 89:9991-9995.
 125. Springer TA. Traffic signals for lymphocyte recirculation and leukocyte emigration: the multistep paradigm. *Cell* 1994; 76: 301-314.
 126. Filep JG, Delalandre A, Payette Y, et al. Glucocorticoid receptor regulates expression of L-selectin and CD11/CD18 on human neutrophils. *Circulation* 1997; 96:295-301.
 127. Nakagawa M, Bondy GP, Waisman D, et al. The effect of glucocorticoids on the expression of L-selectin on polymorphonuclear leukocyte. *Blood* 1999; 93:2730-2737.
 128. Radomski MW, Palmer RMJ, Moncada S. Glucocorticoids inhibit the expression of an inducible, but not the constitutive, nitric oxide synthase in vascular endothelial cells. *Proc Natl Acad Sci* 1990; 87:10043-10047.
 129. Amano Y, Lee SW, Allison AC. Inhibition by glucocorticoids of the formation of interleukin-1 alpha, interleukin-1 beta, and interleukin-6: mediation by decreased mRNA stability. *Mol Pharmacol* 1993; 43:176-182.
 130. Teoh KHT, Bradley CA, Gaudie J, et al. Steroid inhibition of cytokine-mediated vasodilation after warm heart surgery. *Circulation* 1995; 92(suppl II): 347-363.
 131. Williams CM, Coleman JW. Induced expression of mRNA for IL-5, IL-6, TNF-alpha, MIP-2 and IFN-gamma in immunologically activated rat peritoneal mast cells: inhibition by dexamethasone and cyclosporin A. *Immunology* 1995; 86:244-249.

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132. Meng X, Ao L, Brown JM, et al. LPS induces late cardiac functional protection against ischemia independent of cardiac and circulating TNF-alpha. *Am J Physiol* 1997; 42:H1894-H1904.
133. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2012. *Intensive Care Med* 2013; 39:165-228.
134. Adrie C, Laurent I, Monchi M, et al. Postresuscitation disease after cardiac arrest: a sepsis-like syndrome? *Curr Opin Crit Care* 2004; 10:208-212.
135. Hkımian G, Bagnon T, Thuong M, et al. Cortisol levels and adrenal reserve after successful cardiac arrest resuscitation. *Shock* 2004; 22:116-119.
136. Kim JJ, Hyun SY, Hwang SY, et al. Hormonal responses upon return of spontaneous circulation after cardiac arrest: a retrospective cohort study. *Crit Care* 2011; 15:R53.
137. Coba V, Jaehne AK, Suarez A, et al. The incidence and significance of bacteremia in out of hospital cardiac arrest. *Resuscitation* 2014;85:196-202.
138. Gaussergues P, Gueugniaud PY, Vedrinne JM, et al. Bacteremia following cardiac arrest and cardiopulmonary resuscitation. *Intensive Care Med* 1988; 14:575-577.
139. Lindner KH, Strohmenger HU, Ensinger H, et al. Stress hormone response during and after cardiopulmonary resuscitation. *Anesthesiology* 1992; 77:662-668.
140. Kosaka Y, Quillinan N, Bond C, et al. GPER1/GPR30 activation improves neuronal survival following global cerebral ischemia induced by cardiac arrest in mice. *Transl Stroke Res* 2012; 3:500-507.
141. Nademane K, Taylor R, Bailey WE, Rieders DE, Kosar EM. Treating electrical storm: sympathetic blockade versus advanced cardiac life support-guided therapy. *Circulation* 2000; 102:742-747.
142. Miwa Y, Ikeda T, Mera H, et al. Effects of landiolol, an ultra-short-acting beta1-selective blocker, on electrical storm refractory to class III antiarrhythmic drugs. *Circ J* 2010; 74:856-863.
143. de Oliveira FC, Feitosa-Filho GS, Ritt LE. Use of beta-blockers for the treatment of cardiac arrest due to ventricular fibrillation/pulseless ventricular tachycardia: a systematic review. *Resuscitation* 2012; 83:674-683.
144. Kudenchuk PJ, Cobb LA, Copass MK, et al. Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. *N Engl J Med* 1999; 341:871- 878.
145. Dorian P, Cass D, Schwartz B, et al. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. *N Engl J Med* 2002;346:884-890.
146. Manz M, Pfeiffer D, Jung W, Luederitz B. Intravenous treatment with magnesium in recurrent persistent ventricular tachycardia. *New Trends in Arrhythmias* 1991;7:437- 442.
147. Tzivoni D, Banai S, Schuger C, et al. Treatment of torsade de pointes with magnesium sulfate. *Circulation* 1988; 77:392-397.
148. Laver S, Farrow C, Turner D, Nolan J. Mode of death after admission to an intensive care unit following cardiac arrest. *Intensive Care Med* 2004; 30:2126-2128.
149. Neumar RW. Molecular mechanisms of ischemic neuronal injury. *Ann Emerg Med* 2000; 36:483-506.
150. Fujioka M, Taoka T, Matsuo Y, et al. Magnetic resonance imaging shows delayed ischemic striatal neurodegeneration. *Ann Neurol* 2003; 54:732-747.
151. Dezfulian C, Raat N, Shiva S, Gladwin MT. Role of the anion nitrite in ischemia-reperfusion cytoprotection and therapeutics. *Cardiovasc Res* 2007; 75:327-338.
152. Duranski MR, Greer JJ, Dejam A, et al. Cytoprotective effects of nitrite during in vivo ischemia-reperfusion of the heart and liver. *J Clin Invest* 2005; 115:1232-1240.
153. Jung KH, Chu K, Ko SY, et al. Early intravenous infusion of sodium nitrite protects brain against in vivo ischemia-reperfusion injury. *Stroke* 2006; 37:2744-2750.
154. Gonzalez FM, Shiva S, Vincent PS, et al. Nitrite anion provides potent cytoprotective and antiapoptotic effects as adjunctive therapy to reperfusion for acute myocardial infarction. *Circulation* 2008; 117:2986-2994.
155. Pluta RM, Dejam A, Grimes G, et al. Nitrite infusions to prevent delayed cerebral vasospasm in a primate model of subarachnoid hemorrhage. *JAMA* 2005; 293:1477-1484.
156. Shiva S, Wang X, Ringwood LA, et al. Ceruloplasmin is a NO oxidase and nitrite synthase that determines endocrine NO homeostasis. *Nat Chem Biol* 2006; 2:486-493
157. Bryan NS, Calvert JW, Elrod JW, et al. Dietary nitrite supplementation protects against myocardial ischemia-reperfusion injury. *Proc Natl Acad Sci U S A* 2007; 104:19144-19149.
158. Dejam A, Hunter CJ, Tremonti C, et al. Nitrite infusion in humans and nonhuman primates. Endocrine effects, pharmacokinetics, and tolerance formation. *Circulation* 2007; 116:1821-1831.
159. Bloch KD, Ichinose F, Roberts JD, Jr, Zapol WM. Inhaled NO as a therapeutic agent. *Cardiovasc Res* 2007; 75:339-348.
160. Kubes P, Suzuki M, Granger DN. Nitric oxide: an endogenous modulator of leukocyte adhesion. *Proc Natl Acad Sci U S A* 1991;88:4651-4655.
161. Huang Z, Huang PL, Ma J, et al. Enlarged infarcts in endothelial nitric oxide synthase knockout mice are attenuated by nitro-L-arginine. *J Cereb Blood Flow Metab* 1996; 16:981-987.
162. Jones SP, Girod WG, Palazzo AJ, et al. Myocardial ischemia-reperfusion injury is exacerbated in absence of endothelial cell nitric oxide synthase. *Am J Physiol* 1999; 276:H1567-H1573.
163. Nishida T, Yu JD, Minamishima S, et al. Protective effects of nitric oxide synthase 3 and soluble guanylate cyclase on the outcome of cardiac arrest and cardiopulmonary resuscitation in mice. *Crit Care Med* 2009; 37:256-262.
164. Dezfulian C, Shiva S, Alekseyenko A, et al. Nitrite therapy after cardiac arrest reduces reactive oxygen species generation, improves cardiac and neurological function, and enhances survival via reversible inhibition of mitochondrial complex I. *Circulation* 2009; 120:897-905.
165. Beiser DG, Orbelyan GA, Inouye BT, et al. Genetic deletion of NOS3 increases lethal cardiac dysfunction following mouse cardiac arrest. *Resuscitation* 2011; 82:115-121.
166. Minamishima S, Kida K, Tokuda K, et al. Inhaled Nitric Oxide Improves Outcomes After Successful Cardiopulmonary Resus-

- citation in Mice. *Circulation* 2011; 124:1645–1653.
167. Nagasaka Y, Buys E, Spagnoli E, et al. Soluble guanylate cyclase alfa 1 is required for the cardioprotective effects of inhaled nitric oxide. *Am J Physiol Heart Circ Physiol* 2011; 300:H1477-H1483.
 168. Dezfulian C, Alekseyenko A, Dave KR, et al. Nitrite therapy is neuroprotective and safe in cardiac arrest survivors. *Nitric Oxide* 2012; 26:241–250.
 169. Kida K, Shirozu K, Yu B, et al. Beneficial effects of nitric oxide on outcomes after cardiac arrest and cardiopulmonary resuscitation in hypothermia-treated mice. *Anesthesiology* 2014; doi: 10.1097/ALN.000000000000149.
 170. Ichinose F, Roberts JD, Jr, Zapol WM. Inhaled nitric oxide: a selective pulmonary vasodilator: current uses and therapeutic potential. *Circulation* 2004; 109:3106–3111.
 171. Cannon RO, 3rd, Schechter AN, Panza JA, et al. Effects of inhaled nitric oxide on regional blood flow are consistent with intravascular nitric oxide delivery. *J Clin Invest* 2001; 108:279–287.
 172. Nagasaka Y, Fernandez BO, Garcia-Saura MF, et al. Brief periods of nitric oxide inhalation protect against myocardial ischemia-reperfusion injury. *Anesthesiology* 2008; 109:675–182.
 173. Terpolilli NA, Kim SW, Thal SC, et al. Inhalation of nitric oxide prevents ischemic brain damage in experimental stroke by selective dilatation of collateral arterioles. *Circ Res* 2012; 110:727-738.