

# The amplitude spectrum area correctly predicts improved resuscitation and facilitated defibrillation with head cooling

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**Objectives:** When systemic hypothermia was maintained before inducing cardiac arrest, the likelihood of successful defibrillation and meaningful survival was increased. When hypothermia is induced during cardiopulmonary resuscitation, mortality is also improved. With the introduction of the amplitude spectrum area as a predictor of the success of electrical defibrillation, we investigated the effect of preferential head cooling initiated coincident with cardiopulmonary resuscitation on amplitude spectrum area as a predictor. We hypothesized that rapid head cooling initiated coincident with cardiopulmonary resuscitation improves amplitude spectrum area, and therefore is predictive of successful defibrillation.

**Design:** Prospective randomized controlled study.

**Setting:** University-affiliated research institute.

**Subjects:** Domestic pigs.

**Interventions:** Sixteen pigs, weighing  $40.6 \pm 1.4$  kg, were randomized to the hypothermia ( $n = 8$ ), or control ( $n = 8$ ) group. Ventricular fibrillation was induced and untreated for 10 mins. Cardiopulmonary resuscitation was then initiated for 5 mins followed by attempted defibrillation with a biphasic 150-J electric shock. Coincident with starting cardiopulmonary resuscitation, hypothermia was induced with evaporative intranasal cooling using a perfluorochemical. If spontaneous circulation was not restored after defibrillation, cardiopulmonary resuscitation was resumed for 1 min before the next defibrillation attempt until the animal was either successfully resuscitated or for a total of 15

mins. The target core temperature was  $34^{\circ}\text{C}$ . Control animals were identically treated except for hypothermia.

**Measurements and Main Results:** Five seconds of ventricular fibrillation waveform were recorded immediately preceding delivery of a shock. The ventricular fibrillation waveforms were analyzed using the amplitude spectrum area algorithm. A smaller epinephrine dose ( $60 \pm 32.1$  vs.  $30 \pm 0$  mg/mL,  $p = .01$ ) and shorter cardiopulmonary resuscitation duration ( $365 \pm 42$  sec vs.  $600 \pm 243$  sec,  $p = .01$ ) were required to achieve return of spontaneous circulation in the hypothermia group, compared with control. Five minutes after starting cardiopulmonary resuscitation, head temperature was reduced from  $38^{\circ}\text{C}$  to  $34^{\circ}\text{C}$  in the hypothermia group ( $p = .028$ ). Hypothermia improved the success of electrical shocks before return of spontaneous circulation ( $88 \pm 18\%$  vs.  $66 \pm 19\%$ ,  $p = .034$ ). Both the amplitude spectrum area values of initial shock ( $26.1 \pm 5.3$  vs.  $21.4 \pm 2.16$  mV-Hz,  $p = .049$ ) and total shocks ( $26.1 \pm 5.3$  vs.  $21.4 \pm 2.16$  mV-Hz,  $p = .006$ ) were significantly higher in the hypothermia group than control.

**Conclusions:** Amplitude spectrum area served as a useful predictor for improved resuscitation and facilitated defibrillation in the setting of rapid head cooling initiated coincident with cardiopulmonary resuscitation. (Crit Care Med 2008; 36: [Suppl.]:S413–S417)

**KEY WORDS:** amplitude spectrum area; cardiac arrest; cardiopulmonary resuscitation; electrical shock; hypothermia

**T**herapeutic hypothermia has been used to improve neurologic outcomes and decrease injury in patients with various neurologic defects, including cardiac arrest, traumatic brain injury, and stroke (1–5). On the basis of data from two recent randomized clinical studies (2, 3),

the most recent American Heart Association guidelines of cardiopulmonary resuscitation (CPR) now stipulate that unconscious, adult patients successfully resuscitated from an out-of-hospital ventricular fibrillation (VF) cardiac arrest should be cooled to  $32^{\circ}$  to  $34^{\circ}\text{C}$  for 12 to 24 hrs (6).

Hypothermia has also been documented to decrease ischemia/reperfusion injury of the heart and improve resuscitation outcome (7–11). In a murine cardiac arrest model, Abella et al. (8) previously showed that systemic cooling initiated during the arrest period had a beneficial impact on survival as compared with delayed cooling initiated only 15 mins after return of spontaneous circulation (ROSC). Early application of mild hypothermia with cold saline during prolonged CPR also enabled survival in dogs (11). Systemic hypothermia established before cardiac arrest in a porcine cardiac arrest model actually improved the likelihood of successful defibrillation and meaningful survival suggesting hypothermia may be beneficial to the resuscitation efforts (10).

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Although the impact of systemic cooling on the myocardium is recognized in cardiac arrest and whether amplitude spectrum area (AMSA) serves as a useful predictor of successful defibrillation and improved resuscitation in the setting of hypothermia are still unknown. Our hypothesis was that rapid head cooling initiated coincident with CPR improves AMSA, and therefore is predictive of successful defibrillation. In the present study, we sought to investigate the effect of preferential head cooling initiated coincident with CPR on AMSA as a predictor.

## METHODS

Experiments were performed in an established swine model of cardiac arrest and CPR. All animals received humane care in compliance with the *Principles of Laboratory Animal Care* formulated by the National Society for Medical Research and the *Guide for the Care and Use of Laboratory Animals* prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (NIH publication 86-32, 146 revised 1985). The protocol was approved by the Institutional Animal Care and Use Committee of the Weil Institute of Critical Care Medicine. The animal laboratories of the Weil Institute are fully accredited by the American Association for Accreditation of Laboratory Animal Care International.

**Animal Preparation.** Sixteen male domestic pigs weighing between  $42 \pm 3$  kg were fasted overnight except for free access to water. Anesthesia was initiated by intramuscular injection of ketamine (20 mg/kg) and completed by auricular venous injection of sodium pentobarbital (30 mg/kg). Additional doses of sodium pentobarbital (8 mg/kg) were intravenously injected to maintain anesthesia at intervals of 1 hr. Animals were mechanically ventilated with a volume-controlled ventilator (Model MA-1, Puritan-Bennett, Carlsbad, CA). End-tidal  $P_{CO_2}$  was monitored with an infrared analyzer (Model 01R-7101A, Nihon Kohden Corp., Tokyo, Japan). Respiratory frequency was adjusted to maintain end-tidal  $P_{CO_2}$  between 35 and 40 mm Hg. For the measurement of aortic pressure, a fluid-filled catheter was advanced from the right femoral artery into the thoracic aorta. A 7F thermodilution-tipped catheter was advanced from the right femoral vein and flow directed into the pulmonary artery for the measurements of right atrial and pulmonary arterial pressures, and blood temperature. Coronary perfusion pressure (CPP), the difference between diastolic pressure in the aorta and the diastolic pressure in the right atrium, was used as a surrogate for coronary blood flow, and thus an indirect indicator of myocardial perfusion dur-

ing CPR (12, 13). Threshold levels of CPP are identified as major determinants of successful cardiac resuscitation (14–17). Our previous study showed CPP threshold of 15 mm Hg in our porcine model of cardiac arrest (18). Another 5F thermodilution-tipped catheter was placed in the internal jugular vein (5 cm from the insertion point) to measure the head temperature. Three adhesive electrodes were applied to the shaved skin of the limbs for measurements of the electrocardiogram signal. A 5F pacing catheter (EP Technologies Inc., Mountain View, CA) was advanced from the right cephalic vein into the right ventricle for inducing VF. The position of catheters was confirmed by characteristic pressure morphology and/or fluoroscopy. Echocardiographic measurements were obtained with the aid of a S7-20mni, 3.5 MHz transthoracic echocardiographic transducer (HD11XE, Ultrasound System Specification, Philips Medical Systems, Eindhoven, The Netherlands). At the view of the short axis, the left ventricular (LV) end-systolic and end-diastolic volumes were obtained by the method of discs. Left ventricular ejection fractions were then calculated.

**Experimental Protocol.** Fifteen minutes before inducing cardiac arrest, baseline measurements were obtained and animals were then randomized. VF was induced by 1 mA alternating current delivered to right ventricular endocardium through the pacing catheter. Mechanical ventilation was discontinued after onset of VF. Before starting resuscitation procedure, the pacing catheter was withdrawn to avoid injury during chest compression. After 10 mins of untreated VF, CPR was started with a pneumatic piston-driven chest compressor (Thumper 1000, Michigan Instruments, Grand Rapids, MI). Chest compression was programmed to provide 100 compressions per minute and synchronized to provide a compression/ventilation ratio of 30:2 with equal compression-relaxation intervals, i.e., a 50% duty cycle. The compression depth was adjusted to decrease the anteroposterior diameter by 25%. Coincident with starting precordial compression, the animal was mechanically ventilated with tidal volume of 15 mL/kg and  $F_{IO_2}$  of 1.0. After 2 mins of chest compression, one dose of epinephrine (30  $\mu$ g/kg) was injected into the right atrium. Repeat doses of epinephrine were given at the 7th, 10th, and 12th min after the start of CPR. After a total 5 mins of chest compression, one 150-J biphasic electrical shock was delivered between the right infraclavicular electrode and the apical electrode with a Heartstart XL defibrillator (Philips Medical Systems, Andover, MA). If an organized cardiac rhythm with mean aortic pressure of more than 60 mm Hg persisted for an interval of 5 mins or more, the animal was regarded as successfully resuscitated. If ROSC was not achieved, CPR was resumed for 1 min before the next defibrillation attempts. This sequence was repeated until the animal was either successfully resuscitated or pronounced dead after a total of 15 mins of CPR. The total

number of electrical shocks was defined as that required to attain ROSC. A successful electrical shock was defined as return of organized cardiac rhythm with minimal mean aortic pressure  $>60$  mm Hg.

**Induction of Hypothermia.** Before the onset of cardiac arrest, the core temperature of all the animals was kept at 38°C by using warm or cold water bags. Head cooling was induced by using the Rhinohill (Benechill Inc, San Diego, CA) nasal catheter system. The Rhinohill device sprays a liquid six-chain perfluorocarbon (PFC) into the nasal cavity. The liquid is volatile and evaporates instantaneously, thereby removing heat from the nasal cavity. The cold is transmitted to the brain predominantly hematogenously, through the submucosal nasal venous plexuses and also by direct convection. Body cooling occurs later. The intranasal catheters were positioned in the animal's nostrils, and PFC was delivered in an amount of 1 mL/kg/min with oxygen flow of 1 L/kg/min. The cooling was initiated at the same time as precordial compression and stopped once core temperature reached 34°C. The temperature of the control group was not altered after induction of VF.

**AMSA and Median Frequency Measurements.** The electrocardiographic signal was continuously recorded at a frequency of 300 Hz and digitized with the aid of a data acquisition system (Model Windaq 200, Dataq, Akron, OH). AMSA was calculated in real-time using a USB-1208FS data acquisition system (Measurement Computing, Middleboro, MA) and the Matlab software (MathWorks, Natick, MA) (19–21). A 5-sec window of electrocardiogram recording was captured and the signal was filtered between 5 Hz and 48 Hz to minimize low-frequency artifacts produced by precordial compression and to exclude the electrical interference of ambient noise at frequencies greater than 48 Hz. Analog electrocardiogram signals were digitalized and converted from a time to a frequency domain by fast Fourier transform. The resulting AMSA representing the area under the curve relating amplitude to frequency was then computed, i.e.,  $AMSA = \sum A_i \cdot F_i$ , where  $A_i$  represents the amplitude at  $i$ th frequency  $F_i$ . The median frequency was determined from the power spectrum using the method of Brown et al. (22). The power spectrum was obtained by squaring the amplitude of each sinusoidal component from the amplitude frequency spectrum. The median frequency is represented by  $MF = \frac{\sum F_i \cdot P_i}{\sum P_i}$ , where  $F_i$  is the  $i$ th frequency component and  $P_i$  the relative power at  $F_i$ .

**Statistical Analyses.** The chi-square test and Fisher's exact test were used for the comparison of the binomial variables. Continuous variables were presented as mean  $\pm$  sd, and analysis of variance was used to check the difference between groups. A value of  $p < .05$  was considered significant. Analyses were carried out using SPSS V.11.0 software (Chicago, IL).

## RESULTS

Baseline characteristics, including animal weight, heart rate, mean arterial pressure, arterial blood gas analyses, cardiac output, and left ventricular ejection fractions before inducing cardiac arrest were indistinguishable between the two groups (Table 1). At baseline, head and core temperatures were the same in both groups (head:  $38.1 \pm 0.3^\circ\text{C}$  in hypothermia group and  $38.0 \pm 0.3^\circ\text{C}$  in the control group,  $p = \text{NS}$ ; core:  $38.0 \pm 0.2^\circ\text{C}$  in hypothermia group and  $38.0 \pm 0.1^\circ\text{C}$  in the control group,  $p = \text{NS}$ ). Head temperature started falling within 1 min of initiation of cooling and CPR. At 5 mins, head temperature was  $34.2 \pm 4.5^\circ\text{C}$  in the hypothermia group and  $38.1 \pm 0.3^\circ\text{C}$  in the control group ( $p = .028$ ). The core temperature, however, was at baseline value ( $38.3 \pm 0.1^\circ\text{C}$  in the hypothermia group and in the control group ( $38.3 \pm 0.2^\circ\text{C}$ ;  $p = \text{NS}$ ) (Fig. 1).

The hypothermia group had a smaller dose of epinephrine ( $30 \pm 0 \mu\text{g}/\text{kg}$  vs.  $60 \pm 32.1 \mu\text{g}/\text{kg}$ ,  $p = 0.009$ ) and shorter duration of CPR ( $364.6 \pm 42.4$  sec vs.  $600.4 \pm 243.2$  sec,  $p = .01$ ) required for resuscitation than control. There was also a trend of fewer numbers of defibrillation shocks required to achieve ROSC in the hypothermia group ( $8.1 \pm 4.6$  vs.  $14.8 \pm 8.8$ ,  $p = .073$ ). CPP, before initial defibrillation, was  $21.3 \pm 9.6$  mm Hg in the hypothermia group and  $17.7 \pm 5.6$  mm Hg in the control group ( $p = \text{NS}$ ). Throughout the CPR process, CPP was not significantly different between these two groups and was above the threshold of 15 mm Hg. The hypothermia group had a higher success rate for the total number of shocks in each experimental animal than the control group ( $88 \pm 18\%$  vs.  $66 \pm 19\%$ ,  $p = .034$ ), whereas the success rate of initial shock did not achieve statistical significance between these two groups due to the limitation of the number of animals ( $75\%$  vs.  $38\%$ ,  $p = .315$ ) (Table 2).

Before the initial shock, the hypothermia group had a higher AMSA value than controls ( $26.1 \pm 5.3$  mV-Hz vs.  $21.4 \pm 2.16$  mV-Hz,  $p = .049$ ). A higher AMSA value before overall electrical shocks was also noted in the cooled animals ( $25.3 \pm 5.2$  mV-Hz vs.  $21.3 \pm 2.9$  mV-Hz,  $p = .006$ ) (Fig. 2). The median frequency before the initial shock did not differ in these two groups ( $9.2 \pm 2.9$  Hz vs.  $9.8 \pm 2.2$  Hz,  $p = .692$ ), nor before total shocks

Table 1. Baseline characteristics before resuscitation of the two groups

	Control, N = 8	Hypothermia, N = 8	$p^a$
Weight (kg)	$40.8 \pm 1.9$	$40.4 \pm 0.7$	NS
Heart rate (/min)	$119.8 \pm 21.4$	$104.0 \pm 13.5$	NS
Mean arterial pressure (mm Hg)	$122.9 \pm 13.6$	$115.5 \pm 12.1$	NS
Arterial blood pH	$7.51 \pm 0.04$	$7.52 \pm 0.03$	NS
Arterial blood Pao <sub>2</sub> (mm Hg)	$101.3 \pm 15.5$	$102.9 \pm 9.8$	NS
Cardiac output (L/min)	$6.5 \pm 1.2$	$7.8 \pm 1.6$	NS
Left ventricular ejection fraction (%)	$63.9 \pm 3.7$	$64.8 \pm 3.6$	NS

NS, not significant.

<sup>a</sup> $p < .05$  was considered significant.

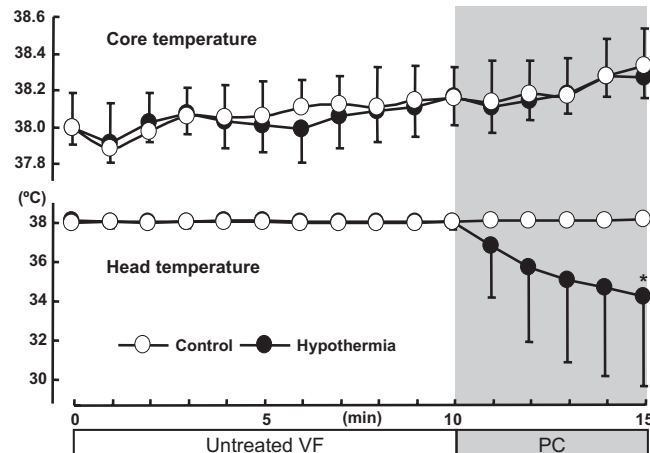


Figure 1. Head and core temperatures of the experimental groups. The head temperature of the hypothermia group was significantly lower than the control group at PC 5 mins.  $*p < 0.05$ ; PC, precordial compression; VF, ventricular fibrillation.

Table 2. Resuscitation events of the two groups

	Control, N = 8	Hypothermia, N = 8	$p^a$
CPP before initial electric shock (mm Hg)	$17.7 \pm 5.6$	$21.3 \pm 9.6$	NS
CPR duration (sec)	$612.9 \pm 227.3$	$364.5 \pm 42.4$	0.009
Epinephrine dosage ( $\mu\text{g}/\text{kg}$ )	$60 \pm 32.1$	$30 \pm 0$	0.010
No. of electric shock	$14.8 \pm 8.8$	$8.1 \pm 4.6$	0.073
Initial electric shock success (%)	38	75	0.315
Total electric shock success (%)	$66 \pm 19$	$88 \pm 18$	0.034
ROSC	7 (88%)	8 (100%)	NS

CPP, coronary perfusion pressure; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; NS, not significant.

<sup>a</sup> $p < .05$  was considered significant.

( $8.4 \pm 3.2$  Hz vs.  $7.8 \pm 2.5$  Hz,  $p = .529$ ) (Fig. 3).

ROSC was achieved in eight of eight (100%) of the hypothermic animals and in seven of eight of the controls (88%) ( $p = \text{NS}$ ).

## DISCUSSION

In the present study, we demonstrated that rapid head cooling during CPR improves the success of defibrillation and reduces the chances of rebrillation in a porcine model of prolonged cardiac ar-

rest. AMSA served as a useful predictor for improved resuscitation and successful defibrillation in the setting of rapid head cooling initiated coincident with CPR in which a higher AMSA value was associated with greater success in restoring a viable rhythm.

Systemic hypothermia has been documented to reduce the transventricular defibrillation threshold in experimental settings (23, 24). Boddicker et al. (10) demonstrated that moderate or severe systemic hypothermia established before resuscitation improved the success of de-

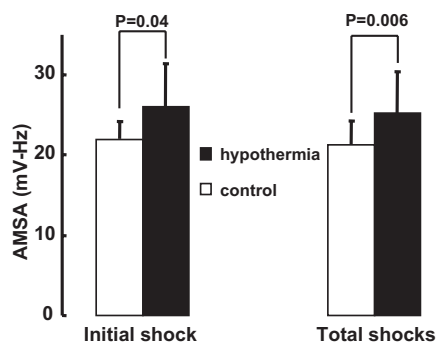


Figure 2. The amplitude spectral area (AMSA) value of ventricular fibrillation before initial shock and total shocks in the experimental groups. The hypothermia group had higher AMSA values before initial shock and total shocks compared with controls.  $p < .05$  was considered significant.

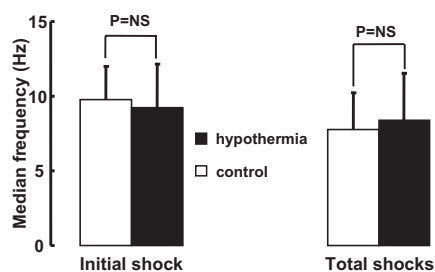


Figure 3. The median frequency of ventricular fibrillation before initial shock and total shocks in the experimental groups. The median frequency did not differ between these two groups either before initial shock or total shocks. NS, not significant.

fibrillation and ROSC in a porcine model of cardiac arrest after 8 mins of untreated VF. In the current study, head cooling initiated coincident with the starting of CPR facilitated defibrillation and reduced the occurrence of refrillation. The beneficial effect of hypothermia on successful defibrillation could not be attributed to a direct effect of cooling on the myocardium. The initial defibrillation occurred 15 mins after arrest and 5 mins into CPR, at which point the head temperature in the hypothermic animals was 4°C below baseline value, whereas core temperature was not different from baseline.

The mechanism by which selective head cooling improves resuscitation and facilitates defibrillation may involve modulation of sympathetic efferent activity and neurohumoral changes. Reduction of splenic, renal, and adrenal sympathetic activity during systemic cooling has been previously demonstrated in rats (25). Systemic hypothermia has also been shown to reduce myocardial interstitial norepi-

nephrine and acetylcholine release induced by ischemia or nerve stimulation (24). Increased cardiac sympathetic activity is thought to be important in generating ventricular tachyarrhythmias (26, 27), and isolated cerebral cooling may facilitate resuscitation by reducing recurrent VF by inhibiting cervical sympathetic firing. Neurohumoral factors may also ease resuscitation during cooling. Horiguchi et al. showed increased extracellular adenosine concentration during forebrain ischemia/reperfusion in the animals that were cooled to 32°C compared with animals maintained at 37°C (28), and adenosine was also documented to attenuate the time-dependent deterioration of VF (29).

Our group has previously documented that the AMSA value of VF waveform can predict the probability of successful defibrillation and thus optimize timing of electrical defibrillation in animal and human experiments (19, 20). In the current study, higher AMSA values before initial shocks and total shocks in the hypothermia group were compatible to the higher success rate of electrical defibrillation. However, the median frequency failed to show correlation with improved defibrillation success and mitigated resuscitation effort. Marn-Pernat et al. (21) demonstrated that an AMSA value of >21 mV-Hz predicted restoration of perfusing rhythm with satisfactory sensitivity and specificity of about 90% in an animal experiment. Human data revealed that successful defibrillation at an AMSA value of >13 mV-Hz yielded a sensitivity of 91% and a specificity of 94% (20). The negative predictive value of AMSA was comparable with median frequency. However, the positive predictive values of AMSA (78%) were greatly improved compared with median frequency (29%) (19).

There are several limitations to our study. First and foremost, we used high jugular venous temperature as a surrogate for head temperature and pulmonary artery temperature for myocardial temperature. We cannot rule out the possibility that at least some of the cooling occurred in the neck rather than the head and that any alteration in sympathetic input to the heart may have resulted from local cooling of the neck. Second, this particular method of cooling involves PFCs and high volumes of oxygen to enhance evaporation in the nasal cavity. PFCs are known to enhance oxygenation. The relative contribution of the three components—the cold, the PFC, and the

oxygen—need to be explored. Third, the study was not blinded. It is difficult to blind the investigators in the study since touching the animals during the experiments allowed the investigators to differentiate between the hypothermic and the control groups. We attempted to account for this by fixing chest compression and ventilation rates. Chest compression was performed by the Thumper device, and the CPP was not different during resuscitation between the two groups. Finally, the potential vectoral changes of electrocardiogram, variable skin contact and conduction with electrodes, and different chest configurations in each animal were not evaluated. However, earlier study showed that the power spectrum of the time-domain waveform from which frequency parameters were extracted was not significantly affected by differences in electrode position or chest configurations (30).

In conclusion, we have shown that the AMSA correctly predicts the improved success rate of electrical defibrillation and mitigates resuscitation efforts in animals receiving head cooling through the nasal cavity during cardiac arrest in which a higher AMSA value was associated with greater success of defibrillation.

## REFERENCES

- Kim F, Olsufka M, Carlbom D, et al: Pilot study of rapid infusion of 2 L of 4°C normal saline for induction of mild hypothermia in hospitalized, comatose survivors of out-of-hospital cardiac arrest. *Circulation* 2005; 112:715–719
- 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
- Bernard SA, Gray TW, Buist MD, et al: Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002; 346:557–563
- Schwab S, Schwarz S, Spranger M, et al: Moderate hypothermia in the treatment of patients with severe middle cerebral artery infarction. *Stroke* 1998; 29:2461–2466
- Fritz HG, Bauer R: Secondary injuries in brain trauma: Effects of hypothermia. *J Neurosurg Anesthesiol* 2004; 16:43–52
- Nolan JP, Morley PT, Vanden Hoek TL, et al: Therapeutic hypothermia after cardiac arrest: An advisory statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation. *Circulation* 2003; 108:118–121
- Dixon SR, Whitbourn RJ, Dae MW, et al: Induction of mild systemic hypothermia with endovascular cooling during primary percu-

- taneous coronary intervention for acute myocardial infarction. *J Am Coll Cardiol* 2002; 40:1928–1934
8. Abella BS, Zhao D, Alvarado J, et al: Intra-arrest cooling improves outcomes in a murine cardiac arrest model. *Circulation* 2004; 109:2786–2791
  9. Shao ZH, Chang WT, Chan KC, et al: Hypothermia-induced cardioprotection using extended ischemia and early reperfusion cooling. *Am J Physiol Heart Circ Physiol* 2007; 292:H1995–H2003
  10. Boddicker KA, Zhang Y, Zimmerman MB, et al: Hypothermia improves defibrillation success and resuscitation outcomes from ventricular fibrillation. *Circulation* 2005; 111:3195–3201
  11. Nozari A, Safar P, Stezoski SW, et al: Critical time window for intra-arrest cooling with cold saline flush in a dog model of cardiopulmonary resuscitation. *Circulation* 2006; 113:2690–2696
  12. Deshmukh HG, Weil MH, Gudipati CV, et al: Mechanism of blood flow generated by precordial compression during CPR. I. Studies on closed chest precordial compression. *Chest* 1989; 95:1092–1099
  13. Yu T, Weil MH, Tang W, et al: Adverse outcomes of interrupted precordial compression during automated defibrillation. *Circulation* 2002; 106:368–372
  14. Sanders AB, Kern KB, Atlas M, et al: Importance of the duration of inadequate coronary perfusion pressure on resuscitation from cardiac arrest. *J Am Coll Cardiol* 1985; 6:113–118
  15. Sanders AB, Ogle M, Ewy GA: Coronary perfusion pressure during cardiopulmonary resuscitation. *Am J Emerg Med* 1985; 3:11–14
  16. Brandtitz FK, Kern KB, Campbell SC: Continuous transtracheal oxygen delivery during cardiopulmonary resuscitation: An alternative method of ventilation in a canine model. *Chest* 1989; 95:441–448
  17. Paradis NA, Martin GB, Rivers EP, et al: Coronary perfusion pressure and the return of spontaneous circulation in human cardiopulmonary resuscitation. *JAMA* 1990; 263:1106–1113
  18. Tang W, Weil MH, Sun S, et al: Cardiopulmonary resuscitation by precordial compression but without mechanical ventilation. *Am J Respir Crit Care Med* 1994; 150:1709–1713
  19. Li Y, Ristagno G, Bisera J, et al: Electrocardiogram waveforms for monitoring effectiveness of chest compression during cardiopulmonary resuscitation. *Crit Care Med* 2008; 36:211–215
  20. Young C, Bisera J, Gehman S, et al: Amplitude spectrum area: Measuring the probability of successful defibrillation as applied to human data. *Crit Care Med* 2004; 32:S356–S358
  21. Marn-Pernat A, Weil MH, Tang W, et al: Optimizing timing of ventricular defibrillation. *Crit Care Med* 2001; 29:2360–2365
  22. Brown CG, Griffith RF, Van Ligten P, et al: Median frequency—A new parameter for predicting defibrillation success rate. *Ann Emerg Med* 1991; 20:787–789
  23. Tacker WA, Babbs CF, Abendschein DR, et al: Transchest defibrillation under conditions of hypothermia. *Crit Care Med* 1981; 9:390–391
  24. Arredondo MT, Armayor MR, Clavin OE, et al: Effect of body hypothermia on transventricular simple-capacitor discharge defibrillation thresholds. *Am J Physiol* 1980; 238:H675–H681
  25. Helwig BG, Parimi S, Ganta CK, et al: Aging alters regulation of visceral sympathetic nerve responses to acute hypothermia. *Am J Physiol Regul Integr Comp Physiol* 2006; 291:R573–R579
  26. Kawada T, Kitagawa H, Yamazaki T, et al: Hypothermia reduces ischemia- and stimulation-induced myocardial interstitial norepinephrine and acetylcholine releases. *J Appl Physiol* 2007; 102:622–627
  27. Jardine DL, Charles CJ, Frampton CM, et al: Cardiac sympathetic nerve activity and ventricular fibrillation during acute myocardial infarction in a conscious sheep model. *Am J Physiol Heart Circ Physiol* 2007; 293:H433–H439
  28. Janse MJ, Wit A: Electrophysiological mechanisms of ventricular arrhythmias resulting from myocardial ischemia and infarction. *Physiol Rev* 1989; 69:1049–1169
  29. Horiguchi T, Shimizu K, Ogino M, et al: Neuroprotection role of adenosine under hypothermia in the rat global ischemia involves inhibition of not dopamine release but delayed postschemic hypoperfusion. *Brain Res* 2002; 952:222–231
  30. Carlisle EJ, Allen JD, Kernohan WG, et al: Fourier analysis of ventricular fibrillation of varied aetiology. *Eur Heart J* 1990; 11:173–181