An Update on Cardio-Pulmonary Resuscitation

Paranjpe J S*

Abbreviations:

ACLS - Advanced Cardiac Life Support, AED - Automated External Defibrillator, AHA - American Heart Association, BLS - Basic Life Support, BVM - bag - valve - mask, CPR - Cardiopulmonary Resuscitation, COCPR - com pression - only CPR, EMS - emergency medical services, ILCOR- International Liaison Committee on Resuscitation

Abstract:

Cardiac arrest represents one of the most devastating medical conditions for which improved outcomes have, for decades, eluded medical practitioners. A realization that large variations in outcome exist in different EMS and hospital systems has led to the concept of strengthening and lengthening the chain of survival. The major change in 2010 AHA guidelines is that CPR commences with chest compressions rather than rescue breaths. When a sudden cardiac arrest occurs, immediate CPR is a vital link in the chain of survival. Another important link is early defibrillation, which has improved greatly with the widespread availability of AEDs. AHA 2010 guidelines have increased emphasis on continuous quantitative waveform capnography to verify endotracheal tube placement, optimization of CPR quality and detection of return of Spontaneous circulation (ROSC). In addition, intra-arrest care can be optimised by focusing on chest compression quality and increasing chest compression fraction, early defibrillation and optimal post-arrest care which has been added as the 5th link in the chain of survival.

Key words: *ACLS, BLS, CPR*

Introduction:

CPR is an emergency procedure consisting of external cardiac massage and artificial respiration; the first treatment for a person who has collapsed and has no pulse and has stopped breathing; attempts to restore circulation of the blood and prevent death or brain damage due to lack of oxygen.

However, when a patient has an advanced life-threatening illness (such as advanced stages of cancer) and is dying, CPR may not be the best option. Hence it is important for the patient, family members and doctor to talk about this issue before the need arises.

Electric stimulation to the chest with AED and cardiac drugs are used to resuscitate a person whose heart has stopped beating. This is usually done for 15 to 30 minutes. An endotracheal tube or Laryngeal mask airway is inserted and is connected to a mechanical ventilator in the intensive care unit (ICU) to help the victim breathe for a while after he receives CPR.

The Importance of CPR Training:

CPR training helps in medical emergencies like drowning, suffocation, drug overdose, hypothermia and electrocution other than sudden cardiac arrest. It is an important life saving first aid skill, practised throughout the world. It is the only known effective method of keeping a victim of cardiac arrest alive long enough till emergency medical assistance arrives.

The victim's chance for survival is greatest if CPR is started as soon as the medical emergency occurs[1]. Even though a number of people are CPR-trained, many are reluctant to administer this procedure for fear of doing it wrong.

History:

In 1954, James Elam was the first to demonstrate experimentally that cardiopulmonary resuscitation (CPR) was a sound technique. Peter Safar wrote the book 'ABC of resuscitation' in 1957. In the United States, it was first promoted as a technique for the public to learn in the 1970s.

The first city to teach and promote resuscitation was Amsterdam a city of canals - therefore a city with many drownings – as many as 400 per year. Death from cardiac

*Associate Professor, Dept. of Anesthesiology, Bharati Vidyapeeth University Medical College & Hospital, Sangli.

Address for Correspondence :
Dr. Paranjpe J S, Associate Professor Dept. of Anesthesiology, Bharati Vidyapeeth University Medical College & Hospital, Sangli, Maharashtra, India E-mail : san_jyotsna@yahoo.co.in

disease was still not prevalent and sudden deaths were mostly from accidents.

Consensus on Resuscitation Science: The AHA and other member councils of ILCOR make a complete review of resuscitation science every 5 years. To achieve unbiased evidence evaluation and management of potential or perceived conflicts of interest, no industry support was accepted for C2005 or C2010. The ILCOR 2010 International Consensus on CPR and ECC science simultaneously published in Circulation and Resuscitation documented review of tens of thousands of peer-reviewed resuscitation studies with treatment recommendations[2-10].

BLS consists of an emergency medical care provided without medical equipments usually in pre-hospital setting; which is used for patients who are unresponsive and not breathing; until the patient can be given full medical care at a hospital.

AHA 2010 guidelines for CPR [2, 3, 4] :

- 'Look, listen, and feel' is no longer recommended. This minimizes delay to action.
- The initial sequence of steps is changed from ABC (airway, breathing, chest compressions) to CAB (chest compressions, airway, breathing). The sequence begins with skill that everyone can perform without any equipment. Chest Compressions are Critical. Without effective chest compressions, Oxygen flow to brain & heart stops. Drugs go nowhere.
- Compression depth: At least 2 inches in adults, 2 inches in children & 1.5 inches in infants or 1/3 of the chest diameter antero-posteriorly.
- Compression to ventilation ratio: 30:2 in adults, 15:2 in children & infants
- The compression rate should be at least 100/min. Absolute numbers of compressions delivered per minute & uninterrupted high quality compressions are independent predictors of survival. [11]
- Routine use of cricoid pressure during CPR is generally NOT recommended. Cricoid pressure can interfere with ventilation and advanced airway placement. Not proven to prevent aspiration or gastric insufflation during cardiac arrest.
- The precordial thump should not be used for unwitnessed out-of-hospital cardiac arrest. It may be considered for patients with witnessed, monitored, unstable or pulseless VT if a defibrillator is not immediately ready for use, but it should not delay CPR and shock delivery.

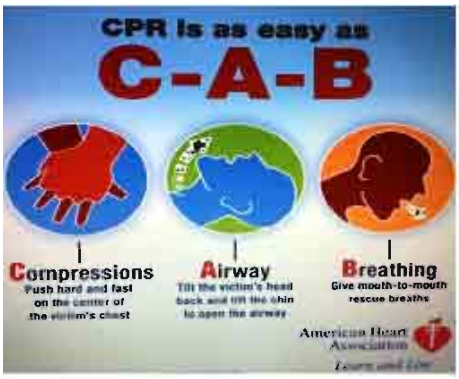

Figure 1 : Algorithm of BLS

The major change in 2010 AHA guidelines is that CPR commences with chest compressions rather than rescue breaths. When a sudden cardiac arrest occurs, immediate CPR is a vital link in the chain of survival[1]. Continue chest compression hard and fast, counting aloud at a rate of 100 compressions per minute for all age groups, allowing chest to recoil in between. Continue for five cycles or two minutes before re-assessing pulse.

Another important link is early defibrillation, which has improved greatly with the widespread availability of AEDs. If an AED is available it should be activated immediately and its directives followed and call for clearance before defibrillation/shock should be given. If defibrillation is done, begin chest compression immediately after shock.

Figure 2 : use of AED

BLS protocols continue until (1) the patient regains a pulse (2) the rescuer is relieved by another rescuer of equivalent or higher training (3) the rescuer is too physically tired to continue CPR or (4) the patient is pronounced dead by a medical doctor[12].

Several large randomized controlled and prospective cohort trials have shown that survival falls by 10-15% for each minute of cardiac arrest without CPR delivery[13-15]. Bystander CPR initiated within minutes of the onset of arrest has been shown to improve survival

rates 2- to 3-fold, as well as improve neurologic outcomes at 1 month[16].

It has also been demonstrated that out-of hospital cardiac arrests occurring in public areas are more likely to be associated with initial ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) and have better survival rates than arrests occurring at home[17].

Foundation of successful ACLS is good BLS.

ACLS refers to a set of clinical interventions for the urgent treatment of cardiac arrest, stroke and other life threatening medical emergencies, as well as the knowledge and skills to deploy those interventions. Extensive medical knowledge and rigorous hands-on training and practice are required to master ACLS. Only qualified health care providers (physician, nurse, paramedic) can provide ACLS, as it requires the ability to manage the patient's airway, initiate IV access, read and interpret electrocardiograms, insertion of a chest tube, drugs, diagnosis and treatment of reversible causes with survival at 1 hour after resuscitation.

ACLS algorithm revised recommendations[5]:

- De-emphasis of Devices, Drugs and other Distracters
- Focus on high-quality CPR and defibrillation
- Atropine no longer recommended for routine use in management of pulseless electrical activity (PEA)/ asystole.
- Chronotropic drug infusions now recommended as alternative to pacing in symptomatic and unstable bradycardia.
- Adenosine recommended as safe and potentially effective for treatment and diagnosis in initial management of undifferentiated regular monomorphic wide-complex tachycardia.
- Routine use of Sodium Bicarbonate or Calcium not recommended. However, in PEA arrests associated with hyperkalemia, hypocalcemia or Ca2+ channel blocking drug overdose, IV calcium chloride is indicated.
- Exercise caution before using epinephrine in arrests associated with cocaine or other sympathomimetic drugs. Epinephrine is not required until after the second DC shock in standard ACLS management as DC shock in itself releases significant quantities of epinephrine. Epinephrine can be substituted with Vasopressin.
- Consider amiodarone for ventricular fibrillation/ pulseless ventricular tachycardia after 3 attempts at defibrillation, as there is evidence it improves response in refractory VF / VT.
- For torsades de pointes, refractory VF in patients with digoxin toxicity or hypomagnesemia, IV magnesium sulfate is recommended.
- Search for and correct potentially reversible causes of arrest, brady/tachycardia.

Figure 3 : Treatable causes of Cardiac arrest

Several studies concluded that stopping compressions in order to give ventilations may be detrimental to the patient's outcome[18]. While a bystander halts compressions to give 2 breaths, blood flow also stops, and this cessation of blood flow leads to a quick drop in the blood pressure that had been built up during the previous set of compressions.

Loss of effective cardiac activity is generally due to the spontaneous initiation of a nonperfusing arrhythmia, sometimes referred to as a malignant arrhythmia. The most common nonperfusing arrhythmias include the following:

- VF
- Pulseless VT
- PEA
- Asystole
- Pulseless bradycardia

CPR should be started before the rhythm is identified and should be continued while the defibrillator is being applied and charged. Additionally, CPR should be resumed immediately after a defibrillatory shock until a pulsatile state is established.

Contraindications

The only absolute contraindication to CPR is a do-not-resuscitate (DNR) order or other advanced directive indicating a person's desire to not be resuscitated in the event of cardiac arrest.

A relative contraindication to performing CPR may arise if a clinician justifiably feels that the intervention would be medically futile, although this is clearly a complex issue that is an active area of research[7].

Anaesthesia

Because a person in cardiac arrest is almost invariably unconscious, anaesthetic agents are not typically required for cardiopulmonary resuscitation (CPR).

Equipment

CPR, in its most basic form, can be performed anywhere without the need for specialized equipment. Regardless of the equipment available, proper technique is essential.

Some hospitals and EMS systems employ devices to provide mechanical chest compressions, although until relatively recently, such devices had not been shown to be more effective than high-quality manual compressions[16].

AHA 2010 Guidelines recommend high-quality manual compressions at a rate of at least 100 compressions per minute. Animal and human studies have reported that blood flow is greatest with chest compression rates near 120/min. A recent study has supported the view that increase in chest compression rate is associated with return of spontaneous circulation but not with survival to hospital discharge in out-of hospital cardiac arrest [19].

Positioning

CPR is most easily and effectively performed by laying the patient supine on a hard surface, often on the floor, with the CPR provider kneeling over him or her to achieve sufficient leverage, so that he or she can use body weight to adequately compress the chest.

Figure 4 : Method of chest compression

Technique

In its full, standard form, cardiopulmonary resuscitation (CPR) comprises 3 steps: chest compressions, airway, and breathing (CAB).

Chest compression

The heel of one hand is placed on the centre of patient's sternum, and the other hand is placed on top of the first, fingers interlaced. The elbows are extended and the provider leans directly over the patient. The provider presses down fast and hard, compressing the chest at least 2 inches at a rate of 100 compressions per minute. The chest is released and allowed to recoil completely. Care should be taken to not lean on the patient between compressions, as this prevents chest recoil and worsens blood flow.

Airway

Open the airway using the head-tilt/chin-lift maneuver and determine if the patient is breathing. If the victim has suspected neck trauma, the airway should be opened with the jaw-thrust technique. If the jaw-thrust is ineffective at opening/maintaining the airway, Laryngeal Mask airway can be inserted.

Before beginning ventilations, rule out airway obstruction by looking in the patient's mouth for a foreign body blocking the patient's airway. Blind finger-sweeps should never be performed, as they may push foreign objects deeper into the airway and increase chances of an obstruction. CPR in the presence of an airway obstruction results in ineffective ventilation/oxygenation and may lead to worsening hypoxemia.

Breathing (Ventilation)

If the patient is not breathing, 2 ventilations are given after 30 compressions, via the provider's mouth or a bag-valve-mask (BVM).

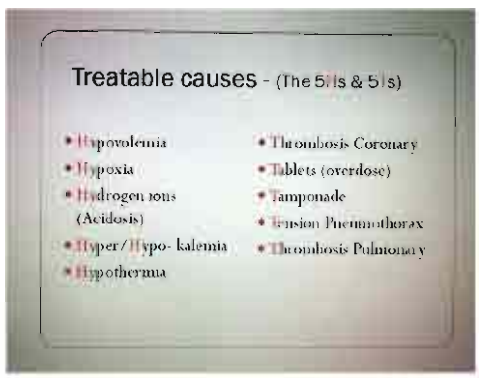

Figure 6 : Delivering mouth-to-mouth ventilations

The mouth-to-mouth technique is performed as follows:

- The nostrils of the patient are pinched closed to assist with an airtight seal.
- The provider puts his mouth completely over the

patient's mouth.

- The provider gives a breath for approximately 1 second with enough force to make the patient's chest rise.

Effective mouth-to-mouth ventilation is determined by observation of chest rise during each exhalation of the provider. Failure to observe chest rise indicates an inadequate mouth seal or airway occlusion. As noted, 2 such exhalations should be given in sequence after 30 compressions (the 30:2 cycle of CPR). When breaths are completed, compressions are restarted. If available, a barrier device (pocket mask or face shield) should be used.

More commonly, health care providers use a BVM, which forces air into the lungs when the bag is squeezed. Several adjunct devices may be used with a BVM, including oropharyngeal and nasopharyngeal, laryngeal mask airways.

The BVM or invasive airway technique is performed as follows:

- The provider ensures a tight seal between the mask and the patient's face or the bag is attached to endotracheal tube (if inserted), cuff is inflated.
- The bag is squeezed with one hand for approximately 1 second, forcing at least 500 ml of air into the patient's lungs.

Next, the provider checks for a carotid or femoral pulse. If the patient has no pulse, chest compressions are begun.

Figure 5 : CPR with Bag-Mask ventilation

This delivery of compressions continues until the arrival of medical professionals or until another rescuer is available to continue compressions. When done properly, CPR can be quite fatiguing for the provider. If possible, in order to give consistent, high-quality CPR, another rescuer should continue chest compressions. The victim should receive continuous compressions while ventilations are given 8-10 times per minute. This entire process is repeated until a pulse returns or the patient is transferred to definitive care[20].

A recent study in patients resuscitated from cardiac arrest for determining optimal position for external chest compression during CPR has suggested that compression of the sternum at the sternoxiphoid junction is more effective than compression at the centre of the sternum (performed according to the current guidelines) to compress the ventricles. They analysed generation of a maximal haemodynamic effect by measuring the area of each cardiac chamber under the sternum using cross-sectional CT chest[21].

Physiologic Monitoring During CPR:

Since unacceptably high incidence of unrecognized ET tube misplacement or displacement was noted, AHA 2010 guidelines have increased emphasis on continuous quantitative waveform capnography to verify endotracheal tube placement, optimization of CPR quality and detection of ROSC.

Capnography by detecting exhaled carbon dioxide, gives high sensitivity and specificity to identify correct endotracheal tube placement in cardiac arrest. Highest value of EtCO2 is obtained at end-expiration.

Signs of ROSC(return of Spontaneous circulation):

Palpable pulse, recordable BP, abrupt and sustained rise in EtCO2>40 mmHg, spontaneous arterial pressure wave with intraarterial monitoring.

Complications:

- Chest compressions- may result in the fracturing of ribs or the sternum, though the incidence of such fractures is widely considered to be low.
- Defibrillation - repeated several times cause electrical burns.
- Artificial respiration-using noninvasive ventilation methods (eg, mouth-to-mouth, bag-valve-mask [BVM]) can often result in gastric insufflations, vomiting, which can further lead to airway compromise or aspiration.

Post-Cardiac Arrest Care (New 5th link in the chain of survival) [6,22] :

It emphasizes importance of comprehensive multidisciplinary care through hospital discharge and beyond. It includes:

- Optimizing vital organ perfusion
- Titration of FiO2 to maintain O2 sat = 94% and < 100%

- Transport to comprehensive post-arrest system of care
- Emergent coronary reperfusion for STEMI or high suspicion of AMI
- Temperature control
- Anticipation, treatment, and prevention of multiple organ dysfunction

However, the optimal bundle of postarrest care has yet to be elucidated and may include hemodynamic optimization, early percutaneous coronary interventions, glucose and electrolyte management, and appropriately timed neuroprognostication.

Pediatric Basic Life Support [8]:

Some differences between pediatric BLS and adult BLS

- Chest compression depth-at least 1/3 of the anterior-posterior diameter of chest, Infants: about 1½ inches, Children: about 2 inches
- Lone rescuer provides 2 minutes of CPR before activating emergency response, two rescuers use 15:2 compression to ventilation ratio. Traditional CPR (compressions and ventilations) by bystanders associated with higher survival than chest compressions alone.
- Cardiac arrests in children are typically asystole or pulseless electrical activity(PEA). Because of better survival after asystole and PEA, children had better outcomes than adults despite fewer cardiac arrests due to VF or pulseless VT[23].

Pediatric Advanced Life Support(PALS) [9]:

- Optimal energy dose for defibrillation of children is unknown. Initial dose 2-4 J/kg. Subsequent dose = 4 J/kg
- Post-ROSC: titrate oxygen to limit hyperoxemia.
- Therapeutic hypothermia (to 32°C to 34°C) may be beneficial (studies in progress)
- Young victims of sudden, unexpected cardiac arrest should have a complete autopsy with genetic analysis of tissue to look for inherited disorders.

Note: some treatments (eg, therapeutic hypothermia, amiodarone for pediatric cardiac arrest) in AHA Guidelines are not approved by US FDA.

Neonatal Resuscitation [10]:

- For babies born at term, begin resuscitation with room air rather than 100% oxygen.
- Any oxygen administered should be blended with room air, titrated based on oxygen saturation measured from right upper extremity.
- Suctioning after birth reserved for infants with obvious airway obstruction, those requiring ventilation or non-vigorous babies with meconium.
- Therapeutic hypothermia recommended for babies near term with evolving moderate to severe hypoxic-ischemic encephalopathy.

Ethics:

- Prehospital BLS and ALS termination of resuscitation rules are provided.
- Indicators of poor outcome after cardiac arrest used in the past may not be valid when therapeutic hypothermia is used.
- Assessment of clinical neurologic signs, electrophysiologic studies, biomarkers and imaging are recommended where available 3 days after cardiac arrest.

Chain of survival:

- Rapid access-call for help
- Rapid cardiopulmonary resuscitation (BLS)
- Rapid defibrillation
- Rapid advanced care (ACLS)
- Integrated post-cardiac arrest care

A strong Chain of Survival can improve chances of survival and recovery for victims of heart attack, stroke and other emergencies.

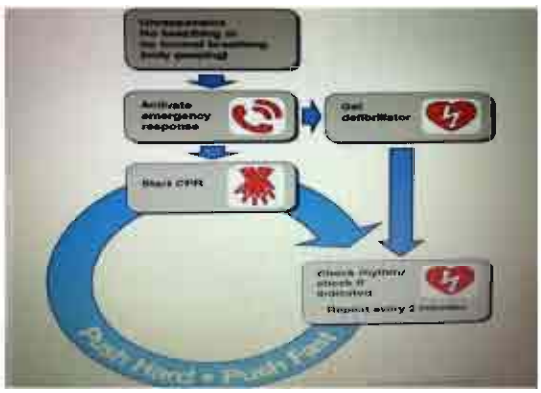

Figure 7 : Chain of Survival

Summary:

- Many resuscitation systems and communities have documented improved survival from cardiac arrest.

- Too few victims of cardiac arrest receive bystander CPR.
- CPR quality must be high.
- Victims require excellent post-cardiac arrest care by organized, integrated teams.
- Education and frequent refresher training key to improving resuscitation performance.
- We must rededicate ourselves to improving the frequency of bystander CPR, the quality of all CPR and the quality of post-cardiac arrest care.

References:

1. Ogawa T, Akahane M, Koike S, Tanabe S, Mizoguchi T, Imamura T. Outcomes of chest compression only CPR versus conventional CPR conducted by lay people in patients with out of hospital cardiopulmonary arrest witnessed by bystanders: nationwide population based observational study. BMJ 2011;342:c7106.
2. Berg RA, Hemphill R, Abella BS, Aufderheide TP, Cave DM, Hazinski MF, Lerner EB, Rea TD, Sayre MR, Swor RA. Part 5: Adult Basic Life Support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010;122:S685-S705.
3. Field JM, Hazinski MF, Sayre MR, Chameides L, Schexnayder SM, Hemphill R et al. Part 1: executive summary: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010;122(18 Suppl 3):S640-56.
4. Peberdy MA, Kaye W, Ornato JP, Larkin GL, Nadkarni V, Mancini ME et al. Cardiopulmonary resuscitation of adults in the hospital: a report of 14720 cardiac arrests from the National Registry of Cardiopulmonary Resuscitation. Resuscitation 2003;58:297-308.
5. Neumar RW, Otto CW, Link MS, Kronick SL, Shuster M, Callaway CW et al. Part 8: Adult Advanced Cardiovascular Life Support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010;122(18 Suppl 3):S729-67.
6. Peberdy MA, Callaway CW, Neumar RW, Geocadin RG, Zimmerman JL, Donnino M et al. Part 9: post-cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010;122(18 Suppl 3):S768-86.
7. Morrison LJ, Verbeek PR, Vermeulen MJ, Kiss A, Allan KS, Nesbitt L, Stiell I. Derivation and evaluation of a termination of resuscitation clinical prediction rule for advanced life support providers. Resuscitation 2007;74:266-75.
8. Berg MD, Schexnayder SM, Chameides L, Terry M, Donoghue A, Hickey RW et al. Part 13: pediatric basic life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010;122(18 Suppl 3):S862-75.
9. Kleinman ME, Chameides L, Schexnayder SM, Samson RA, Hazinski MF, Atkins DL et al. Part 14: pediatric advanced life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010;122(18 Suppl 3):S876-908.
10. Kattwinkel J, Perlman JM, Aziz K, Colby C, Fairchild K, Gallagher J et al. Part 15: neonatal resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010;122(18 Suppl 3):S909-19.
11. Morley PT. Monitoring the quality of cardiopulmonary resuscitation. Curr Opin Crit Care 2007;13:261-7.
12. Lick CJ, Aufderheide TP, Niskanen RA, Steinkamp JE, Davis SP, Nygaard SD et al. Take Heart America: A comprehensive, community-wide, systems-based approach to the treatment of cardiac arrest. Crit Care Med 2011;39:26-33.
13. Rea TD, Fahrenbruch C, Culley L, Donohoe RT, Hambly C, Innes J, et al. CPR with Chest Compression Alone or with Rescue Breathing. N Engl J Med 2010;363:423-33.
14. Bobrow BJ, Spaite DW, Berg RA, Stolz U, Sanders AB, Kern KB et al. Chest compression-only CPR by lay rescuers and survival from out-of-hospital cardiac arrest. JAMA 2010;304:1447-54.
15. Hupfl M, Selig HF, Nagele P. Chest Compression-Only CPR: A Meta-Analysis. Lancet 2010;376(9752):1552-7.

16. Yasunaga H, Horiguchi H, Tanabe S, Akahane M, Ogawa T, Koike S, Imamura T. Collaborative effects of bystander-initiated cardiopulmonary resuscitation and prehospital advanced cardiac life support by physicians on survival of out-of-hospital cardiac arrest: a nationwide population-based observational study. Crit Care 2010;14(6):R199.
17. Weisfeldt ML, Everson-Stewart S, Sitlani C, Rea T, Aufderheide TP, Atkins DL et al. Ventricular tachyarrhythmias after cardiac arrest in public versus at home. N Engl J Med 2011;364:313-21.
18. Ewy GA, Kellum M. Advancing resuscitation science. Curr Opin Crit Care 2012;18: 221-7.
19. Hallstrom A, Rea TD, Sayre MR, Christenson J, Anton AR, Mosesso VN et al. Manual Chest Compression vs Use of an Automated Chest Compression Device During Resuscitation Following Out-of-Hospital Cardiac Arrest: a randomized trial. JAMA 2006;295:2620-8. Idris AH, Guffey D, Aufderheide TP, Brown S, Morrison LJ, Nichols P et al. Relationship Between Chest Compression Rates and Outcomes From Cardiac Arrest.Circulation 2012;125:3004-12.
20. Rea TD, Fahrenbruch C, Culley L, Donohoe RT, Hambly C, Innes J, et al. CPR with Chest Compression Alone or with Rescue Breathing. N Engl J Med 2010;363:423-33.
21. Cha KC, Kim YJ, Shin HJ, Cha YS, Kim H, Lee KH, Kwon W, Hwang SO. Optimal position for external chest compression during cardiopulmonary resuscitation: an analysis based on chest CT in patients resuscitated from cardiac arrest. Emerg Med J doi:10.1136/emermed-2012-201556.
22. Gaieski DF, Abella BS, Goyal M.CPR and Postarrest Care: Overview, Documentation, and Databases. Chest 2012;141:1082-9.
23. Nadkarni VM, Larkin GL, Peberdy MA, Carey SM, Kaye W, Mancini ME et al. First documented rhythm and clinical outcome from in-hospital cardiac arrest among children and adults. JAMA 2006;295:50-7.