The Egyptian Journal of Hospital Medicine (January 2018) Vol. 70 (3), Page 439-445

Early Epinephrine Administration in Patients with Cardiac Arrest in Case of Shockable Rhythm in ER

1Khalid Yahya Alzahrani, 1Abdulaziz Saud Alghamdi, 1Omar Hussain Alghamdi, 2Yasser Musallam Alrehaili, 3Mahmoud Shehab Halawani, 4Saleh Jameel Almatrafi, 4Abdulkareem Khaled Almotairi, 5Bayan Jamal AlMulhim, 6Naif Khaled Alomar, 7Aman Abdullah Alkishi, 8Abeer Abdullah Alreshidi, 9 Basil Mohammed Alrajhi

[1]King Abdulaziz University,[2]King Fahad Hospital,[3]Ohud Hospital,[4]Ibn Sina National College
[5]King Faisal University, [6]Imam Mohammed Bin Saud Islamic University,[7]Alfaisal University
[8]International Academy for Health Science, [9] Albatterjee Medical College, SA

ABSTRACT

The objective of the review was to investigate the scientific production and evaluate the effectiveness of epinephrine in the treatment of cardiac arrest in terms of survival and neurological status. PubMed, Embase, and Google Scholar databases were searched up till November 2017 for published studies in English language and human subjects discussing early epinephrine administration in patients with cardiac arrest in case of shockable rhythm in emergency medicine. Prehospital epinephrine management may increase short-term survival (ROSC) yet does not improve survival to release, or neurologic results after out-of-hospital cardiac arrest OHCA. Although there is no clear proof of long-lasting advantages complying with the use of epinephrine in OHCA, there is insufficient evidence to sustain altering present guidelines which recommend its management (1 mg every 3-5 min) throughout resuscitation. As a result, there is a need for additional clinical trials to analyze whether lower dosages or alternative regimes of epinephrine administration. Furthermore, one of the most important aspects of care in cardiac arrest is basic life support (BLS) measures, consisting of adequate compressions and early defibrillation.

Keywords: Epinephrine , Cardiac Arrest , Shockable Rhythm.

INTRODUCTION

The cardiorespiratory arrest is the sudden and unexpected cessation of breathing and spontaneous circulation, that can be restored to a previous condition, in those in whom a deadly outcome was not anticipated back then [1].This is a major issue worldwide because the occurrence is approximated at around 55 out-of-hospital cardiac arrests in adults every 100,000 individuals, of whom only 7% survive [2]. As concerns in-hospital cardiac arrests, pertinent searching for in the literature were scarce, but estimates suggest that the occurrence could be between 1 and 5 situations each 1.000 admissions each year, and the total survival ranges 10% and 42% [3].

The treatment of cardiorespiratory apprehension follows suggestions released every 5 years, based on a variety of reviews by the International Liaison Committee on Resuscitation (ILCOR), a company developed by leading international councils and Resuscitation associations. Exceptional amongst them are the American Heart Association (AHA) and European Resuscitation Council (ERC). Both AHA and ERC suggestions, from 2010 and 2015, have suggested that regulated clinical trials of vasopressors vs. placebo are required. With the present proof, the use of epinephrine in cardiac arrest is advised as class IIb [4]. This needs to be thought about, as the advantages could exceed the dangers; consequently, both organizations recommend using 1 mg of epinephrine every 3-5 min. Nonetheless, AHA has indicated that 40UI of vasopressin could change the very first or 2nd dose of epinephrine [5].

Epinephrine is among three natural catecholamines, together with norepinephrine and dopamine, that has a potent stimulatory activity on α and β receptors distributed throughout the body; in the heart raises the circulation rate, the heart rate and the force of tightening (chronotropic and inotropic results on the heart) therefore raises the quantity per minute, the systolic blood pressure and at the same time the myocardial oxygen intake. High dosages generate extrasystoles and cardiac arrhythmias; they (high doses) also produce a surge in high blood pressure (especially diastolic) that assists in venous return and ventricular filling during diastole by boosting α and β receptors. This raises overall outer resistance, thus triggering a boost in differential

Received: 16/10/2017
Accepted: 26/10/2017
DOI: 10.12816/0043484

tension and tachycardia. If hypertension is high it can create response bradycardia. Excessive and prolonged activation of the myocardium threatens; this can cause improperly increased oxygen consumption and micro-injuries that could show up in the vessels and myofibrils [6]. Based on the foregoing discussion, the question arises regarding the effect of epinephrine on the survival of patients enduring cardiac arrest and on the neurological condition of survivors of these cardiac events.

Although epinephrine is necessary for the successful return of spontaneous circulation (ROSC), the impact of this medicine on recuperation during the post-cardiac arrest phase is debatable.

The objective of the review was to investigate the scientific production and evaluate the effectiveness of epinephrine in the treatment of cardiac arrest in terms of survival and neurological status.

METHODOLOGY

- **Data Sources and Search terms**

We conducted this review using a comprehensive search of MEDLINE, PubMed, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials up till November, 2017 for published studies in English language and human subjects discussing early epinephrine administration in patients with cardiac arrest in case of shockable rhythm in emergency medicine. Moreover, we included reviews and randomized control studies, we excluded all case reports, in our search strategy we scanned the references list of our included studies for more relevant articles.

- **Data Extraction**

Two reviewers independently reviewed studies, abstracted data, and resolved disagreements by consensus. Studies were evaluated for quality. A review protocol was followed throughout.

The study was done according to the ethical board of King Abdul-Aziz university.

DISCUSSION

- **Cardiac arrest**

The actual reason for cardiac arrest is typically difficult to uncover in the individual patient. Two general causes appear crucial, anoxia and response restraint. Anoxia, or more precisely hypoxia, could commonly be proved or realistically assumed to be present. Speculative work bears out the influence of anoxia. **Sloan** [7] defined recently the effects of reduced oxygen tension in dogs, discovering that severe hypoxia or asphyxia frequently resulted in arrest while hypercapnia did not. Youthful, Sealy, **Harris and Botwin** [8] found that hypercapnia boosted and hypoxia reduced the effect of vagal stimulation in dogs, although continued cardiac arrest was not generated. **Ramamoorthy *et al.*** [9] showed that Children with HD were sicker compared with those without HD at the time of anesthesia-related CA and had a higher mortality after arrest. These arrests were reported most frequently from the general operating room and were likely to be from cardiovascular causes. The identification of causes and factors relating to anesthesia-related CA suggests possible strategies for prevention. Several causes of anoxia exist clinically. Excessive sedative drugs, excessively deep anesthesia and blockage of the airway and circulatory failing prevail reasons. Particularly if the heart is already infected, one or several of these or various other reasons might precipitate arrest. Vagal response inhibition is usually implicated, although **Sloan** might not recreate arrest by this means in dogs unless hypoxia was present [7]. **Shumacker and Hampton** [10] reported 5 instances of sudden death due to cardiac arrest as endotracheal extubation and suction were done. Whether this was due to a response or to hypoxia or to a combination is unknown. It is identified that breakdown in the mediastinum and concerning the lung origins and aortic arch may result in arrhythmias and arrest. From the practical point of view then, problems leading to anoxia and causing response inhibition could generate apprehension. Extreme sedation, rapid induction and maintenance of deep anesthetic, interference with the airway, and previous cardiac disease seem essential contributing reasons.

Cardiac arrest causes anoxia as circulation stops and offered oxygen is used. Cells vary intolerance of anoxia, the neurons of the brain being earliest damaged and recuperating last. Weinberger, **Gibbon and Gibbon** [11], in their review, note that Brown-Sequard in 1858 located that the cerebrum, medulla, cord, and peripheral nerves were influenced in that order by temporary disruption of blood supply. Stewart, Guthrie, **Burns and Pike** [12] in 1960 located total recuperation in dogs after 5 minutes interruption of cerebral blood circulation, and one recuperated totally after 15 mins. None recuperated after 20 mins.

- **Diagnosis**

Due to the short time which may elapse in between circulatory arrest and resumption if brain damage is to be prevented, quick medical diagnosis is necessary.

Lengthy treatments are pointless and only simple steps are feasible. Pulse and blood pressure are the most evident diagnostic requirements. The anesthetist typically finds these absent at the time that apnea happens or soon after that. If the personnel direct exposure permits, palpation of the heart or a great vessel will certainly result in a prompt diagnosis. Otherwise, the peripheral vessels are utilized. The capillaries do not refill after pressure. The electrocardiogram works but not totally accurate, showing arrhythmias however, not the actual time of mechanical arrest. **According to Rea** [13] Agonal respirations have physiologic and care implications. Efforts to identify agonal respirations and integrate this information into resuscitation care may improve outcome from cardiac arrest. **Ziegler** [14] located electrocardiographic activity after clinical arrest in 7 patients operated after for pulmonic stenosis. He suggested its usefulness in caution of upcoming arrest by arrhythmias and bradycardia. If bradycardia of 50 or less did not respond to atropine or if it persisted after atropine was utilized, it was frequently a pre-terminal sign in that series. **Rea** believed that Agonal respirations originate from lower brainstem neurons as higher centers become increasingly hypoxic during cardiac arrest. No single layperson descriptor consistently identifies agonal respirations; rather, laypersons use a collection of terms to describe the abnormal breathing of agonal respirations. Animal studies demonstrate that agonal respirations can produce clinically important ventilation, oxygenation, and circulation. In human studies, agonal respirations are apparent in 40% of persons suffering out-of-hospital cardiac arrest. Agonal respirations are associated with witnessed events, ventricular fibrillation, and survival, suggesting that agonal respirations are a marker of an arrest's early phase and may potentially directly affect cardiopulmonary function. Although agonal respirations appear to exert favorable cardiopulmonary effects, they may paradoxically inhibit rescue efforts by preventing arrest recognition. A standardized dispatch approach can help dispatchers identify agonal respirations by distinguishing normal and abnormal breathing in the unconscious patient. **Salsburg and Melvin** [15] described the appearance of the veins as a busted column of blood whose motion gradually stops numerous minutes after the heart quits. From the functional viewpoint, medical diagnosis generally is based on lack of pulse and blood pressure associated with apnea. If this happens when a wonderful vessel is not instantly available for palpation, a minimum of time is available for stethoscopic auscultation of the precordium. Belongings time may be lost questioning the opportunities of therapy. It could be necessary to open the chest or abdomen after the strong suspicion of cardiac arrest, verifying this by palpation. The heart will be motionless, contracting extremely feebly, or fibrillating, the latter giving an experience of a "bag of worms" in the hand. **Fauteux** [16] explained that a strange ventricular rhythm with auricular fibrillation might be confused with ventricular fibrillation and thinks this might make up some of the reports of spontaneous defibrillation. Periodically as the upper body wall surface or pleura is incised, respirations may instantly resume and the heart is found to be acquiring regularly. It appears most likely that the resumption results from strong stimuli originating in the incision, considering that various other energetic stimuli, such as sharply striking the precordium, have been hardly ever successful in resuscitation.

- **Beneficial effects of epinephrine**

The results from randomized trials and observational studies show that epinephrine raises coronary perfusion pressure and the likelihood of ROSC throughout CPR [17]. Providing epinephrine during CPR boosts the probability of restoring cardiac task with pulses, which is a crucial intermediate action towards long-lasting survival [18]. The possible beneficial effects are associated with the stimulation of α-receptors, which restrict the arterioles and raise aortic pressure during chest compressions [19]. When CPR fails to generate a coronary perfusion pressure > 15- 20 mmHg (1 mmHg = 0.133 kPa), return of cardiac mechanical activity hardly ever or never happens [20]. Epinephrine, with its powerful vasopressor and inotropic properties, could quickly increase diastolic blood pressure to assist in coronary perfusion and assistance bring back arranged myocardial contractility. In a methodical review and meta-analysis, private investigators addressed an advantage of standard-dose adrenaline (SDA) over placebo and high-dose adrenaline (HDA) over SDA in overall survival to admission and ROSC, which follows previous reviews [21].

In the first and up to date, just randomized, double-blind, placebo-controlled test of adrenaline in patients with out-of-hospital cardiac arrest (OHCA), **Jacobs *et al.*** [22] reported a substantial rise in ROSC related to epinephrine and a non-significant rise in survival to healthcare facility discharge or even worse

neurological outcomes in patients carried out epinephrine. **Nakahara *et al.*** [23] reported that patients getting early (<10 min) adrenaline had dramatically greater rates of neurologic undamaged survival and any type of survival compared to those who did not get early adrenaline, after readjusting for possible confounders. **Hayashi *et al.*** [24] reported that the effectiveness of adrenaline in patients with OHCA relied on the time of its administration. When adrenaline was carried out in the early phase, there was an improvement in the neurologic end result from OHCA secondary to VF. **Atiksawedparit *et al.*** [25] released a meta-analysis reporting a greater rate of prehospital ROSC in the epinephrine group while no distinction in survival to discharge was discovered. Research in patients with cardiac arrest outside hospital have continually found that epinephrine enhances aortic relaxation pressure and raises coronary perfusion pressure, raising the chances of attaining ROSC.

- **Detrimental effects of epinephrine**

Epinephrine enhances coronary perfusion pressure by reducing blood circulation to all various other body organs, an effect that could continue after the remediation of pulses [26]. On the basis of observational data and restricted medical trials, standard-dose epinephrine does not enhance and could actually reduce lasting survival and neurological recuperation after CPR. Potentially hazardous impacts are α- and β-receptor moderated and include decreased cerebral microvascular blood circulation and worsening of neurological result. Cardiovascular instability, such as boosted myocardial work and boosted risk of tachydysrhythmia, promotes thrombogenesis and platelet activation after ROSC and adverse immunomodulatory and metabolic results [26]. Experimental researches have revealed that β-blocker treatment might mitigate a few of these negative effects. An animal study indicated that epinephrine minimized capillary blood flow in swine brain. Epinephrine-induced cerebral hypoperfusion lingered throughout CPR was attributable to the α-1 agonist impacts of minimized cerebral microcirculatory blood circulation and raised cerebral ischemia, determined by reduced brain tissue pO2 and boosted pCO2 [27]. Epinephrine likewise has negative results on myocardium mediated by β-receptor stimulation [27]. Epinephrine impairs myocardial function despite enhancing coronary perfusion pressure [27]. Epinephrine is known to increase the frequency of transitions from PEA to ROSC and expand the time home window for the advancement of ROSC at a price of higher cardiovascular instability after ROSC, with a greater rate of rearresting. Similarly, the total dosage of epinephrine is associated with damaged lactate clearance for hours and gastric mucosal perfusion after CPR in human beings [26].

Hagihara et al. carried out a potential nonrandomized analysis of over 400,000 patients with OHCA in Japan, discovering an increase in ROSC with epinephrine, yet no rise in survival or functional outcome. Greater ROSC happened in the epinephrine group, although this was connected with lower survival at one month and even worse neurologic result. **Dumas *et al.*** [28] analyzed an accomplice of patients that achieved ROSC and located that prehospital adrenaline was associated with a reduced possibility of survival. Private investigators likewise reported that adrenaline management was related to worse survival and neurological end result that was not enhanced by postresuscitation hypothermia [28]. In a trial post hoc analysis, Olasveengen et al. [29] located that" adrenaline was associated with short-time survival yet also with reduced survival to health center discharge and survival with favorable neurological results." A research conducted by **Sanghavi *et al.*** [30] in 2015 reported that no proof indicates epinephrine related to enhanced neurologic result, survival to release, and total survival. There is clashing evidence on long-term survival and functional recuperation, specifically neurological end results, in patients with cardiac arrest outside health center.

- **Effect of dosage, timing subgroups of patients**

The total dose and timing of epinephrine impact patient result [31].The current 1 mg bolus dosage of adrenaline was derived from animal researches in the 1960s. The optimal dosage of epinephrine is not known, although increasing the cumulative dosage could intensify survival and neurological outcome. **Lin *et al.*** [32] contrasted SDA(1 mg every 3- 5 min) with placebo, SDA with HDA (> 1 mg/dose), SDA with the mix of adrenaline and vasopressin, and SDA with vasopressin alone. There was no benefit of adrenaline in survival to discharge or neurological end results [32].There were enhanced rates of survival to admission and ROSC in the SDA versus placebo and HDA versus SDA researches [32].Nevertheless, there are no researches examining smaller doses (e.g., 1 μg/ kg) or infusions of adrenaline in clinical reports.

Some research studies recommended that the earlier epinephrine is administered in cardiac arrest, especially in nonshockable OHCA, the better its effect.

A number of research studies have determined different etiologies in subgroups with shockable and nonshockable rhythms, and it appears practical that there are differences in treatment methods [33]. In the first shockable rhythm accomplice, the ratios of prehospital ROSC, 1-month survival, and 1-month favorable neurological outcomes in the nonepinephrine group were considerably more than those in the epinephrine team [34]. However, in the preliminary nonshockable rhythm accomplice, the ratios of prehospital ROSC and 1-month survival in the epinephrine team were significantly greater than those in the nonepinephrine team, and there was no considerable difference in between the epinephrine and nonepinephrine teams for 1-month favorable neurological results [34].

Several research studies have recognized different etiologies in shockable and nonshockable subgroups and it seems sensible to assume that distinctions in treatment techniques will emerge. Nevertheless, future studies should consider whether different impacts of epinephrine are observed in clinically distinct parts of patients, such as those with non-VF cardiac arrest, or at distinct times after cardiac arrest.

Table 1. Summary of studies evaluating the effects of epinephrine. ROSC: Return of spontaneous circulation; SDA: Standard-dose adrenaline; HDA: High-dose adrenaline; CPC: Cerebral performance category.

Study	Year	Description	Outcomes	Findings
Sanghavi *et al.* [35]	2015	Retrospective cohort study	Survival to hospital discharge, to 30 days, and to 90 days; neurological performance	No epinephrine associated with improved neurologic outcome, survival to discharge, and total survival
Lin *et al.* [36]	2014	Systematic review and meta-analysis	Primary: Survival to hospital discharge Secondary: ROSC, survival to hospital admission, and neurological outcome at hospital discharge	No benefit of epinephrine in survival to discharge or neurological outcomes. There were improved rates of survival to admission and ROSC with SDA over placebo and HDA over SDA
Atiksawedparit *et al.* [37]	2014	Meta-analysis	ROSC and survival to discharge	A higher rate of prehospital ROSC in the epinephrine group while no difference in survival to discharge
Dumas *et al.* [38]	2014	Prospective cohort study	Survival to hospital admission, and neurological outcome at hospital discharge	Prehospital epinephrine was associated with a lower chance of survival and worse neurological outcomes
Nakahara *et al.* [39]	2013	Retrospective cohort study	Overall and neurologically intact survival at 1 month or at discharge	Significant increase in neurologic intact survival and survival at 1 month
Hayashi *et al.* [40]	2012	Prospective cohort study	neurological outcome at hospital discharge	When epinephrine was administered in the early phase, there was an improvement in neurologic outcome

CONCLUSION

Prehospital epinephrine management may increase short-term survival (ROSC) yet does not improve survival to release or neurologic results after out-of-hospital cardiac arrest OHCA. Although there is no clear proof of long-lasting advantages complying with the use of epinephrine in OHCA, there is insufficient evidence to sustain altering present guidelines which recommend its management (1 mg every 3-5 min) throughout resuscitation. As a result, there is a need for additional clinical trials to analyze whether lower dosages or alternative regimes of epinephrine administration. Furthermore, one of the most important aspects of care in cardiac arrest is basic life support (BLS) measures, consisting of adequate compressions and early defibrillation.

REFERENCE

1. **Montero Pérez FJ and Jiménez Murillo L (2014):** Medicina de Urgencias y Emergencias. https://oncouasd.files.wordpress.com/2015/../medicina-de-urgencias-y-emergencias.p
2. **Berdowsky J, Berg RR, Tijssen JGP and Koster RW (2010):** Global incidences of out-of-hospital cardiac arrest and survival rates Systematic review of 67 prospective studies. Resuscitation, 81:1479–1487.
3. **Sandroni C, Nolan J, Cavallaro F, Antoneli M(2007):** In-hospital cardiac arrest incidence, prognosis and possible measures to improve survival. Intensive Care Med., 33(2):237–245.
4. **Oxford Center for Evidence Based Medicine (2015):** http://www.cebm.net/index.aspx?o=5653
5. **Deakin CD, Morrison LJ, Morley PT, Callaway CW, Kerber RE, Kronick SL(2010):** International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Resuscitation,81(1):e93–e174.
6. **Meana JJ, García-Sevilla JA. Meana JJ, García-Sevilla JA(2014):** Transmisión catecolaminérgica. Farmacología Humana Jesús Flórez,34: 243–260.
7. **Sloan H (1950):** The Vagus Nerve in Cardiac Arrest. Gynec. & Obst., 91: 257, 1950.
8. **Young W, Sealy W, Harris J and Botwin A(1951):** The Effects of Hypercapnia and Hypoxia on the Response of the Heart to Vagal Stimulation. Gynec. & Obst., 93: 51.
9. **Ramamoorthy C, Haberkern CM, Bhananker SM *et al.* (2010):** Anesthesia-related cardiac arrest in children with heart disease: Data from the pediatric perioperative cardiac arrest (POCA) registry. Anesth Analg.,110:1376–82.
10. **Schumacker H and Hampton L (1951):** Sudden Death Occurring Immediately After Operation in Patients with Cardiac Disease with Particular Reference to the Role of Aspiration Through the Endotracheal Tube and Extubation. J. Thoracic Surg., 21: 48.
11. **Weinberger L, Gibbon M and Gibbon J (1940):** Temporary Arrest of the Circulation to the Central Nervous System: I. Physiologic Effects. Arch. Neurol. & Psychiat., 43: 615.
12. **Stewart G, Guthrie C, Burns L and Pike F(1960):** The Resuscitation of the Central Nervous System of Mammals. J. Exper. Med., 8: 289.
13. **Rea TD (2005):** Agonal respirations during cardiac arrest. Current opinion in critical care, 11(3):188-91.
14. **Ziegler R (1984):** The Cardiac Mechanism During Anesthesia and Operation in Patients with Congenital Heart Disease and Cyanosis. Bull. Johns Hopkins Hosp., 83: 236.
15. **Salsburg C and Melvin C (1963):** Obhthqlmosconic Signs of Death. Brit. M. J., 1: 1249.
16. **Fauteux M (1974):** Cardiac Resuscitation. J. Thoracic Surg., 16: 623.
17. **Callaway CW(2013):** Epinephrine for cardiac arrest. Curr Opin Cardiol., 28:36–42.
18. **Callaway C(2012):** Questioning the use of epinephrine to treat cardiac arrest. JAMA., 307:1198–200.
19. **Paradis NA, Martin GB, Rosenberg J, Rivers EP, Goetting MG, Appleton TJ *et al.*(1991):** The effect of standard- and high-dose epinephrine on coronary perfusion pressure during prolonged cardiopulmonary resuscitation. JAMA.,265:1139–44.
20. **Paradis NA, Martin GB, Rivers EP, Goetting MG, Appleton TJ, Feingold M *et al.* (1990):**Coronary perfusion pressure and the return of spontaneous circulation in human cardiopulmonary resuscitation. JAMA., 263:1106–13.
21. **Lin S, Callaway CW, Shah PS, Wagner JD, Beyene J, Ziegler CP *et al.*(2014):** Adrenaline for out-of-hospital cardiac arrest resuscitation: A systematic review and meta-analysis of randomized controlled trials. Resuscitation, 214;85:732–40.
22. **Jacobs IG, Finn JC, Jelinek GA, Oxer HF, Thompson PL(2011):** Effect of adrenaline on survival in out-of-hospital cardiac arrest: A randomised double-blind placebo-controlled trial. Resuscitation,82:1138–43.
23. **Nakahara S, Tomio J, Takahashi H, Ichikawa M, Nishida M, Morimura N *et al.* (2013):**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., 347:f6829.
24. **Hayashi Y, Iwami T, Kitamura T, Nishiuchi T, Kajino K, Sakai T *et al.*(2012):** Impact of early intravenous epinephrine administration on outcomes following out-of-hospital cardiac arrest. Circ J., 76:1639–45.
25. **Atiksawedparit P, Rattanasiri S, McEvoy M, Graham CA, Sittichanbuncha Y, Thakkinstian A(2014):** Effects

of prehospital adrenaline administration on out-of-hospital cardiac arrest outcomes: A systematic review and meta-analysis. Crit Care,18:463.

26. **Callaway CW(2012):** Questioning the use of epinephrine to treat cardiac arrest. JAMA.,307:1198–200.
27. **Nolan JP, Perkins GD(2013):** Is there a role for adrenaline during cardiopulmonary resuscitation? Curr Opin Crit Care,19:169–74.
28. **Dumas F, Bougouin W, Geri G, Lamhaut L, Bougle A, Daviaud F *et al*.(2014):** Is epinephrine during cardiac arrest associated with worse outcomes in resuscitated patients? J Am Coll Cardiol., 64:2360–7.
29. **Olasveengen TM, Wik L, Sunde K, Steen PA(2011):** Outcome when adrenaline (epinephrine) was actually given vs. not given – *Post hoc* analysis of a randomized clinical trial. Resuscitation, 83:327–32.
30. **Sanghavi P, Jena AB, Newhouse JP, Zaslavsky AM(2015):** Outcomes after out-of-hospital cardiac arrest treated by basic vs. advanced life support. JAMA Intern Med., 175:196–204.
31. **Koscik C, Pinawin A, McGovern H, Allen D, Media DE, Ferguson T *et al*.(2013):** Rapid epinephrine administration improves early outcomes in out-of-hospital cardiac arrest. Resuscitation,84:915–20.
32. **Lin S, Callaway CW, Shah PS, Wagner JD, Beyene J, Ziegler CP *et al.*(2014):** Adrenaline for out-of-hospital cardiac arrest resuscitation: A systematic review and meta-analysis of randomized controlled trials. Resuscitation,85:732–40.
33. **Machida M, Miura S, Matsuo K, Ishikura H, Saku K(2012):** Effect of intravenous adrenaline before arrival at the hospital in out-of-hospital cardiac arrest. J Cardiol., 60:503–7.
34. **Goto Y, Maeda T, Goto Y(2013):** Effects of prehospital epinephrine during out-of-hospital cardiac arrest with initial non-shockable rhythm: An observational cohort study. Crit Care, 17:R188.
35. **Sanghavi P, Jena AB, Newhouse JP, Zaslavsky AM(2015):** Outcomes after out-of-hospital cardiac arrest treated by basic vs. advanced life support. JAMA Intern Med., 175:196–204.
36. **Lin S, Callaway CW, Shah PS, Wagner JD, Beyene J, Ziegler CP *et al.*(2014):** Adrenaline for out-of-hospital cardiac arrest resuscitation: A systematic review and meta-analysis of randomized controlled trials. Resuscitation,85:732–40.
37. **Atiksawedparit P, Rattanasiri S, McEvoy M, Graham CA, Sittichanbuncha Y, Thakkinstian A(2014):** Effects of prehospital adrenaline administration on out-of-hospital cardiac arrest outcomes: A systematic review and meta-analysis. Crit Care,18:463.
38. **Dumas F, Bougouin W, Geri G, Lamhaut L, Bougle A, Daviaud F *et al.*(2014):** Is epinephrine during cardiac arrest associated with worse outcomes in resuscitated patients? J Am Coll Cardiol., 64:2360–7.
39. **Nakahara S, Tomio J, Takahashi H, Ichikawa M, Nishida M, Morimura N *et al.*(2013):** 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., 347:f6829.
40. **Hayashi Y, Iwami T, Kitamura T, Nishiuchi T, Kajino K, Sakai T *et al.*(2012):** Impact of early intravenous epinephrine administration on outcomes following out-of-hospital cardiac arrest. Circ J., 76:1639–45.