ZIMNICKI, Patryk, LATO, Marta, IBERSZER, Konrad, LITWINIUK, Maria, ZANIUK, Marcin, HURKAŁA, Kamil, ANTONIK, Dominika, DENYS, Barbara, GÓRA, Karolina & ZDZIENNICKI, Wojciech. The use of adrenaline in cardiac arrest - impact on survival to discharge from the hospital. Journal of Education, Health and Sport. 2023;30(1):68-78. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2023.30.01.006
https://apcz.umk.pl/JEHS/article/view/43693
https://zenodo.org/record/7938011

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32343.
Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences).
Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. L.p. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159.
Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 25.04.2023. Revised: 10.05.2023. Accepted: 15.05.2023. Published: 15.05.2023.

The use of adrenaline in cardiac arrest - impact on survival to discharge from the hospital

Patryk Zimnicki[1], Marta Lato[2], Konrad Iberszer[3], Maria Litwiniuk[4], Marcin Zaniuk[5], Kamil Hurkała[6], Dominika Antonik[7], Barbara Denys[8], Karolina Góra[9], Wojciech Zdziennicki[10]

[1] Samodzielny Publiczny Zakład Opieki Zdrowotnej MSWiA w Lublinie, ul. Grenadierów 3, 20-331 Lublin, Poland
[2] Szpital Specjalistyczny im. J.Dietla w Krakowie, ul. Skarbowa 1, 31-121 Kraków, Poland
[3] Samodzielny Publiczny Szpital Kliniczny nr 4, ul. Jaczewskiego 8, 20-954 Lublin, Poland
[4] Wojewódzki Szpital Specjalistyczny im. Stefana Kardynała Wyszyńskiego Samodzielny Publiczny Zakład Opieki Zdrowotnej w Lublinie, Al. Kraśnicka 100, 20-718 Lublin, Poland
[5] Samodzielny Publiczny Zakład Opieki Zdrowotnej MSWiA w Lublinie, ul. Grenadierów 3, 20-331 Lublin, Poland
[6] Samodzielny Publiczny Szpital Wojewódzki im. Papieża Jana Pawła II w Zamościu, ul. Aleje Jana Pawła II 10, 22-400 Zamość, Poland
[7] 5 Wojskowy Szpital Kliniczny z Polikliniką w Krakowie, ul. Wrocławska ⅓, 30-901 Kraków, Poland
[8] Wojewódzki Szpital Specjalistyczny im. Stefana Kardynała Wyszyńskiego Samodzielny Publiczny Zakład Opieki Zdrowotnej w Lublinie, Al. Kraśnicka 100, 20-718 Lublin, Poland
[9] Samodzielny Publiczny Szpital Kliniczny nr 4, ul. Jaczewskiego 8, 20-954 Lublin, Poland
[10] Uniwersytecki Szpital Kliniczny w Poznaniu - ul. Przybyszewskiego 49, 60-355 Poznań, Poland

Karolina Góra, ORCiD: https://orcid.org/0000-0002-5377-3010; e-mail: gora.karolina7@gmail.com
Barbara Denys, ORCiD: https://orcid.org/0009-0003-1951-1142; e-mail: barbaradenys11@gmail.com
Dominika Antonik, ORCiD: https://orcid.org/0009-0004-7575-8016; e-mail: antonikdominika97@gmail.com
Kamil Hurkała, ORCiD: https://orcid.org/0009-0007-5961-9894; e-mail: kamilhurkala@gmail.com
Konrad Iberszer, ORCiD: https://orcid.org/0000-0002-4290-9883; e-mail: konrad.iberszer@gmail.com
Marcin Zaniuk, ORCiD: https://orcid.org/0000-0003-4643-0594; e-mail: marcin.zaniuk@gmail.com
Maria Litwiniuk, ORCiD: https://orcid.org/0009-0004-5396-7482; e-mail: litwiniuk.mm@gmail.com
Marta Lato, ORCiD: https://orcid.org/0000-0003-4121-3400; e-mail:coronarysulcus@gmail.com
Patryk Zimnicki, ORCiD: https://orcid.org/0000-0002-5808-8661; e-mail: patryk.zimnicki.97@o2.pl
Wojciech Zdziennicki, ORCiD: https://orcid.org/0009-0005-1254-9740; e-mail: wojtekzdziennicki@gmail.com

Abstract
Introduction and objective: Epinephrine is the most important and primary drug that resuscitation team use to reverse cardiac arrest. The provision of epinephrine is currently suggested by both the American Heart Association and the European Resuscitation Council. It is vital to improving the return of spontaneous circulation (ROSC), however the evidence for the use of adrenaline in resuscitation is inconclusive.
Materials and methods: The literature was reviewed in the Pubmed database, in the Via Medica Journals database, and in the guidelines of the Polish Society of Anesthesiology, European Resuscitation Council and the American Heart Association with the use of keywords.
State of knowledge: There is a clear evidence of an association between epinephrine and increased return of spontaneous circulation (ROSC). Its action is based on stimulation of alpha- and beta-adrenergic receptors. Epinephrine have a role in resuscitation, during CPR it increases the probability of restoring cardiac activity with pulses, which is intermediate step toward long-term survival. However, there are conflicting results regarding long-term survival and functional recovery, particularly neurological outcome.
Conclusions: Research shows that epinephrine administration in patients with cardiac arrest increases the chance of restoring spontaneous circulation and patient survival to hospital admission and discharge. However, there are arguments questioning the validity of using epinephrine in resuscitation. Publications show that the compound contributes to post-resuscitation syndrome, which reduces a patient's chance of long-term survival. There are a number of conflicting studies that vary widely in the results presented. The current evidence is insufficient to either confirm or exclude the efficacy of epinephrine, which is why it is still recommended in the latest resuscitation guidelines by the European Resuscitation Council (ERC 2021) and the American Heart Association (AHA 2020).

Keywords: adrenaline, cardiac arrest, resuscitation, rosc, epinephrine, cpr

1. Introduction

Epinephrine is the most important and primary drug that resuscitation team use to reverse cardiac arrest. It has been the cornerstone of cardiac resuscitation and advanced cardiac life support (ACLS) from the birth of modern cardiopulmonary resuscitation (CPR) in the early 1960s. [1] The provision of epinephrine is currently suggested by both the American Heart Association (AHA) and the European Resuscitation Council in both shockable and nonshockable rhythms.[2]

Cardiopulmonary resuscitation is a team activities performed by the affected person to sudden cardiac arrest, one of the main ones causes of death in Europe. Correct resuscitation increases the victim's chances of survival four times [3-8], which is why it is extremely important adequate knowledge of the procedure and take action quickly. Medications during

resuscitation are administered in accordance with the guidelines and depending from the current heart rate.

Adrenaline is given in any case of cardiac arrest as a medicine first line. [9] It is an endogenous catecholamine showing affinity for α-receptors and β-adrenergic, belonging to sympathetic amines metrics - stimulating the sympathetic nervous system. [10] It is commonly referred to as the fight and flight hormone. [11] It makes an impact for the functioning of many organs. In layout breathing causes muscle relaxation of bronchial tree. In the circulatory system, it accelerates heart function and improves the conduction of stimuli. Administration of adrenaline during circulatory resuscitation respiratory system causes an increase in flow blood through the coronary vessels by stimulation α1 receptors. β-adrenergic effects are more pronounced at low doses while α-adrenergic effects are more pronounced at higher doses. [21] The factor determining the coronary flow is the perfusion pressure of the heart muscle which is defined as the difference between the pressure aortic diastolic pressure and diastolic pressure of right atrium. [12] Epinephrine has beneficial effects in patients during cardiac arrest, primarily because of its α-adrenergic effects, resulting in improved coronary perfusion pressure which is associated with an increased probability of ROSC in animals and humans [22,23]. When it comes to circulatory arrest and cell hypoxia myocardium (anaerobic metabolism is non- sufficient to cover the demand for ATP), resistance vessels are maximally dilated, decreasing vascular resistance, which also causes a drop in blood pressure diastolic aorta and lowering the pressure gradient between the aorta and the right atrium, which is related is with reduced blood flow through the heart. During cardiopulmonary resuscitation, the non-perfusion of the heart should take a higher value than 15-20 mmHg, because in the case of lower pressure values are rarely restored spontaneous circulation. [13]

Many conditions may cause cardiac arrest. Myocardial ischemia resulting in ventricular fibrillation is the most common cause of cardiac arrest. Cardiomyocytes have a high demand for oxygen due to intensive ventricular work during fibrillation. There is an imbalance between supply and demand for this compound, particularly in the subendocardium of the left ventricle. In a study on a group of fourteen dogs with ventricular fibrillation conducted in Los Angeles and published in 1978 in The Journal of Thoracic and Cardiovascular Surgery it was shown that epinephrine, through an inotropic effect exacerbates fibrillation and contributes to the increasing intraventricular pressure and increasing myocardial oxygen demand. [14,15] However, at the same time, it impedes blood flow through coronary vessels of the left ventricle especially through the subendocardial layer, greater distribution of blood flow

toward the epicardium and a decrease in the endocardial/subendocardial blood flow ratio. [16] Increased oxygen consumption in ventricular fibrillation under the influence of β1 receptor stimulation was also noted in studies conducted on groups of dogs, which were published in 1960 in Circulation Research, and in 1990 in the Journal of the American College of Cardiology. [17] The effect of epinephrine on β1 receptors is also responsible for dysfunctional myocardial dysfunction, which can persist in the post-resuscitation period. In 1998, Ditchey and Lindenfeld conducted a study on a group of dogs with ventricular fibrillation, in which they observed that epinephrine supply caused a significant reduction in ATP stores and lactate accumulation in the myocardium heart. These effects were the result of an increase in the demand for cardiomyocytes' need for oxygen under the influence of the positive inotropic and chronotropic effects. [18,19] The described consequences of stimulation of β-adrenergic receptors have important relevance to cardiac dysfunction. Relating to cardiac dysfunction, as the decrease in cardiac ATP in the heart is correlated with the intensity of damage to the myocardium. [20]

Epinephrine is vital to improving the return of spontaneous circulation (ROSC), however the evidence for the use of adrenaline in out-of-hospital and in-hospital resuscitation is inconclusive.

We conducted a systematic review on the clinical efficacy of adrenaline in adult OHCA patients to evaluate whether epinephrine provides any overall benefit for patients. Some of the articles and say that adrenaline may be harmful for prognosis of surviving the patient in health good enough to be discharged from the hospital. However, standard-dose epinephrine does not increase and may actually reduce long-term survival and neurological recovery after CPR.

2. The arguments for the use of epinephrine in cardiac arrest

Epinephrine increases the rate of Return of Spontaneous Circulation (ROSC). [24] This is demonstrated by animal studies and many retrospective analyses. In a systematic review and meta-analysis, researchers noted the superiority of standard-dose epinephrine (SDA) over placebo and high-dose epinephrine (HDA) over SDA in overall survival to admission and ROSC, which is consistent with previous reviews.[31] Administration of epinephrine during CPR increases the likelihood of pulse-mediated restoration of cardiac function, a necessary intermediate step toward long-term survival. [27] The beneficial effects of epinephrine are attributed to stimulation of α-receptors, which are responsible for arteriolar constriction and increase aortic pressure when the chest is compressed. [28] Epinephrine has strong

vasopressor and inotropic properties, which can increase diastolic blood pressure to facilitate coronary perfusion and help restore proper and coordinated cardiac function.[29] When coronary perfusion pressures >15-20 mmHg (1 mmHg = 0. 133 kPa) are not achieved during resuscitation efforts, the return of cardiac mechanical function occurs very rarely or not at all. [30] In the first and, to date, only randomized, double-blind, placebo-controlled study of epinephrine use in patients with out-of-hospital cardiac arrest (OHCA), Jacobs et al [25] reported a significant increase in ROSC associated with epinephrine administration and a nonsignificant increase in survival to hospital discharge or worse neurological outcomes in patients who received epinephrine. Studies in patients with out-of-hospital cardiac arrest have consistently found that epinephrine increases aortic relaxation pressure and raises coronary perfusion pressure, increasing the chances of achieving ROSC. In December 2013, a study was conducted in a porcine model comparing the effects of epinephrine, vasopressin and placebo. [26] Resuscitative measures with the above-mentioned drugs were undertaken in the animals studied in three groups with ventricular fibrillation. The results obtained were: 83% of the pigs with epinephrine achieved ROSC and two-hour survival, 50% in the vasopressin group and 25% in the placebo group. A decrease in the effect of epinephrine increase on blood pressure increase was also observed after the third dose, while the increase in blood pressure after vasopressin application was maintained after each of the six doses.

The use of epinephrine during OHCA has also been shown to increase survival to hospital discharge. This conclusion was reached by researchers in a systematic review and meta-analysis including 20716 patients published in 2019. [32] The survival rate to hospital discharge is significantly higher with epinephrine compared to placebo. The positive effect of high-dose epinephrine was also highlighted, where more frequent ROSCs and higher survival to hospital discharge were achieved.

Some studies have indicated an appropriate time for epinephrine administration of up to 10 minutes [33], while others specify as up to 20 minutes [34] after cardiac arrest. Most researchers, however, conclude that the timing of epinephrine administration is very important and emphasize the importance of administering CPR as soon as possible and note the increased ROSC rate with faster epinephrine administration. Reduced neurological loss with earlier epinephrine administration is also indicated. In 2013, similar conclusions were reached by Japanese researchers [35], where they found that with each minute elapsed between cardiac arrest and epinephrine administration, the probability of a favorable neurological outcome increases 1.1 times. A 2014 study [36] where patients with cardiac arrest in the hospital in a non-defibrillation rhythm were put under the microscope, summarized that

administration of epinephrine at 1 to 3 minutes led to a higher probability of leading to ROSC, increased the survival rate to hospital discharge along with a good neurological picture of the patient. Two, large randomized trials, PARAMEDIC2 [37] and PACA (Placebo-Controlled Trial of Adrenaline in Cardiac Arrest), proved a higher rate of ROSC in patients with out-of-hospital cardiac arrest. Epinephrine was shown to be more effective in non-defibrillable rhythms (electrical activity without pulse - PEA and asystole), but its effect in defibrillable rhythms (ventricular fibrillation - VF and ventricular tachycardia - pVT without pulse wave) was also significant.

3. The arguments for not using epinephrine in cardiac arrest

Epinephrine increases coronary perfusion pressure, reducing blood flow to all other organs, and this effect may persist after circulation is restored. [40] This may reduce long-term survival and neurological recovery after cardiopulmonary resuscitation. [39] Standard-dose epinephrine reduces cerebral microvascular blood flow by affecting α- and β-receptors. This promotes an unfavorable prognosis for patient survival after successful resuscitation and worsens neurological outcomes.

Studies conducted on pigs have shown a reduction in capillary blood flow through the brain. [50] This effect is attributed to α-1 agonist effects resulting in decreased microvascular blood flow in the brain, its increased ischemia. This was determined by decreased p02 flow in brain tissue and increased pCO2. [32] Epinephrine impairs myocardial function despite increased coronary perfusion pressure. [32]. This is an effect of β-receptor stimulation [32]. Epinephrine also leads to increased myocardial work, increases the risk of tachyarrhythmias, which in turn affects platelet activation and promotes thrombogenesis. It also leads to adverse immunomodulatory and metabolic effects. [38,40,48]

Dumas et al [53] studied a cohort of patients who reached ROSC and found that prehospital epinephrine was associated with a lower chance of survival. The researchers also reported that epinephrine administration was associated with worse survival and neurological outcome, which was not improved by post-resuscitation hypothermia.[53] Receiving epinephrine is also associated with impaired lactate clearance for hours and gastric mucosal perfusion after CPR in humans. [39,40]

Epinephrine increases the rate of transitions from PEA to ROSC and lengthens the time window for the development of ROSC at the cost of greater cardiovascular instability after ROSC, with higher rates of re-arrest. [51] Japanese researchers Haginafara et al. performed a

prospective, non-randomized analysis of more than 400,000 patients with out-of-hospital cardiac arrest. They observed an increase in ROSC with epinephrine, but no increase in survival or functional outcome. Greater ROSC occurred in the epinephrine group, although this was associated with lower one-month survival and worse neurological outcome.[52] The study by Sanghavi et al [53] in 2015 reported that no evidence suggests that epinephrine is associated with better neurological outcome, survival to hospital discharge and overall survival. There is conflicting evidence regarding long-term survival and return of blood circulation.

In a post hoc analysis of the study, Olasveengen et al [54] found that "epinephrine was associated with short-term survival, but also with reduced survival to hospital discharge and survival with favorable neurological outcome." functional outcome, particularly neurological outcome, in patients with out-of-hospital cardiac arrest.

4. Summa

Epinephrine, according to the 2021 European Resuscitation Council guidelines, is the drug of choice for advanced resuscitation procedures. Its action is based on stimulation of alpha- and beta-adrenergic receptors. Research shows that epinephrine administration in patients with out-of-hospital cardiac arrest increases the chance of restoring spontaneous circulation and patient survival to hospital admission and discharge. This is due to its effect on alpha receptors, which is responsible for increasing myocardial perfusion through vasoconstriction of peripheral vessels and increasing diastolic pressure. However, there are arguments questioning the validity of using epinephrine in cardiopulmonary resuscitation. Scientific publications show that the compound contributes to post-resuscitation syndrome, which reduces a patient's chance of long-term survival. Its symptoms include brain damage caused by microcirculatory disruption as a result of alpha receptor stimulation. Myocardial dysfunction associated with beta receptors and organ ischemia caused by vasoconstriction of peripheral vessels as a result of alpha receptor stimulation can also be observed. There are a number of conflicting studies that vary widely in the results presented. Some of the studies have been conducted on animals, which differ in structure and function from the human body, so we have no confidence that the results obtained will be similar in humans. The current evidence is insufficient to either confirm or exclude the efficacy of epinephrine, which is why it is still recommended in the latest resuscitation guidelines by the European Resuscitation

Council (ERC 2021) [53] and the American Heart Association (AHA 2020) [54]. It is advisable to continue to conduct reliable randomized trials involving large groups of patients.

References:

1. Nolan JP, Perkins GD. Is there a role for adrenaline during cardiopulmonary resuscitation? Curr Opin Crit Care. 2013;19:169–74.
2. Andersen LW, Kurth T, Chase M, Berg KM, Cocchi MN, Callaway C, et al. Early administration of epinephrine (adrenaline) in patients with cardiac arrest with initial shockable rhythm in hospital: Propensity score matched analysis. BMJ. 2016;353:i1577.
3. Waalewijn RA, Tijssen JG, Koster RW. Bystander initiated actions in out-of-hospital cardiopulmonary resuscitation: results from the Amsterdam Resuscitation Study (ARRESUST). Resuscitation. 2001;50(3):273-9.
4. Valenzuela TD, Roe DJ, Cretin S, Spaite DW, Larsen MP. Estimating effectiveness of cardiac arrest interventions: a logistic regression survival model. Circulation. 1997;96(10):3308-13.
5. Holmberg M, Holmberg S, Herlitz J, Gårdelöv B. Survival after cardiac arrest outside hospital in Sweden. Swedish Cardiac Arrest Registry. Resuscitation. 1998;36(1):29-36.
6. Holmberg M, Holmberg S, Herlitz J, Swedish Cardiac Arrest Registry. Factors modifying the effect of bystander cardiopulmonary resuscitation on survival in out-of-hospital cardiac arrest patients in Sweden. Eur Heart J. 2001;22(6):511-9.
7. Wissenberg M, Lippert FK, Folke F, Weeke P, Hansen CM, Christensen EF, i wsp. Association of national initiatives to improve cardiac arrest management with rates of bystander intervention and patient survival after out-of-hospital cardiac arrest. JAMA. 2013;310(13):1377-84.
8. Hasselqvist-Ax I, Herlitz J, Svensson L. Early CPR in Out-of-Hospital Cardiac Arrest. N Engl J Med. 15 2015;373(16):1573-4.
9. Polish Resuscitation Council. ERC resuscitation guidelines 2021 [Internet]. Available at: https://www.prc.krakow.pl/wytyczne_2021.html
10. Overgaard CB, Dzavík V. Inotropes and vasopressors: review of physiology and clinical use in cardiovascular disease. Circulation. 2008;118:1047-56
11. D.U.Silverthorn. Communication, integration and homeostasis. In Ponikowska B (ed.). Human physiology, an integrated approach. Warsaw: PZWL Wydawnictwo Lekarskie; 2018:96
12. Callaway CW. Epinephrine for cardiac arrest. Curr Opin Cardiol. 2013;28(1):36-42
13. Shao H, Li CS. Epinephrine in Out-of-hospital Cardiac Arrest: Helpful or Harmful?. Chin Med J (Engl). 2017;130:2112-2116
14. Livesay JJ, Follette DM, Fey KH, Nelson RL, DeLand EC, Barnard RJ i wsp. Optimizing myocardial supply/demand balance with alpha-adrenergic drugs during cardiopulmonary resuscitation. J Thorac Cardiovasc Surg. 1978;76(2):244-51
15. Midei MG, Sugiura S, Maughan WL, Sagawa K, Weisfeldt ML. Preservation of ventricular function by treatment of ventricular fibrillation with phenylephrine. J Am Coll Cardiol. 1990;16(2):489-94

16. Ditchey RV, Lindenfeld J. Failure of epinephrine to improve the balance between myocardial oxygen supply and demand during closed-chest resuscitation in dogs. Circulation. 1988;78(2):382-9
17. Monroe RG, French G. Ventricular pressure-volume relationships and oxygen consumption in fibrillation and arrest. Circ Res. 1960;8:260-6.
18. Ditchey RV, Lindenfeld J. Failure of epinephrine to improve the balance between myocardial oxygen supply and demand during closed-chest resuscitation in dogs. Circulation. 1988;78(2):382-
19. Tang W, Weil MH, Sun S, Noc M, Yang L, Gazmuri RJ. Epinephrine increases the severity of postresuscitation myocardial dysfunction. Circulation. 1995;92(10):3089-93
20. Callaway CW. Epinephrine for cardiac arrest. Curr Opin Cardiol. 2013;28(1):36-42
21. Overgaard CB, Dzavík V. Inotropes and vasopressors: Review of physiology and clinical use in cardiovascular disease. Circulation. 2008;118:1047–56.
22. Niemann JT, Criley JM, Rosborough JP, Niskanen RA, Alferness C. Predictive indices of successful cardiac resuscitation after prolonged arrest and experimental cardiopulmonary resuscitation. Ann Emerg Med. 1985;14:521–8.
23. Michael JR, Guerci AD, Koehler RC, Shi AY, Tsitlik J, Chandra N, et al. Mechanisms by which epinephrine augments cerebral and myocardial perfusion during cardiopulmonary resuscitation in dogs. Circulation. 1984;69:822–35.
24. Callaway CW. Epinephrine for cardiac arrest. Curr Opin Cardiol. 2013;28:36–42.
25. Jacobs IG, Finn JC, Jelinek GA, Oxer HF, Thompson PL. Effect of adrenaline on survival in out-of-hospital cardiac arrest: A randomised double-blind placebo-controlled trial. Resuscitation. 2011;82:1138–43. [PubMed] [Google Scholar]
26. Palácio MÂG, Paiva EF de, Azevedo LCP de, Timerman A. Experimental cardiac arrest treatment with adrenaline, vasopressin, or placebo. Arq Bras Cardiol. 2013;101(6):536-44.
27. Callaway CW. Questioning the use of epinephrine to treat cardiac arrest. JAMA. 2012;307:1198–200. [PubMed] [Google Scholar]
28. Paradis NA, Martin GB, Rosenberg J, Rivers EP, Goetting MG, Appleton TJ, et al. The effect of standard- and high-dose epinephrine on coronary perfusion pressure during prolonged cardiopulmonary resuscitation. JAMA. 1991;265:1139–44. [PubMed] [Google Scholar]
29. Overgaard CB, Dzavík V. Inotropes and vasopressors: Review of physiology and clinical use in cardiovascular disease. Circulation. 2008;118:1047–56. [PubMed] [Google Scholar]
30. Paradis NA, Martin GB, Rivers EP, Goetting MG, Appleton TJ, Feingold M, et al. Coronary perfusion pressure and the return of spontaneous circulation in human cardiopulmonary resuscitation. JAMA. 1990;263:1106–13. [PubMed] [Google Scholar]
31. Lin S, Callaway CW, Shah PS, Wagner JD, Beyene J, Ziegler CP, et al. Adrenaline for out-of-hospital cardiac arrest resuscitation: A systematic review and meta-analysis of randomized controlled trials. Resuscitation. 2014;85:732–40. [PubMed] [Google Scholar]
32. Vargas M, Buonanno P, Iacovazzo C, Servillo G. Epinephrine for out of hospital cardiac arrest: A systematic review and meta-analysis of randomized controlled trials. Resuscitation. 2019;145:151-7
33. Nakahara S, Tomio J, Nishida M, Morimura N, Ichikawa M, Sakamoto T. 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 Off J Soc Acad Emerg Med. 2012;19(7):782-92.

34. Goto Y, Maeda T, Goto Y. Effects of prehospital epinephrine during out-of-hospital cardiac arrest with initial non-shockable rhythm: an observational cohort study. Crit Care Lond Engl. 2013;17(5):R188
35. Hayakawa M, Gando S, Mizuno H, Asai Y, Shichinohe Y, Takahashi I, i wsp. Effects of epinephrine administration in out-of-hospital cardiac arrest based on a propensity analysis. J Intensive Care. 2013;1(1):12.
36. Donnino MW, Salciccioli JD, Howell MD, Cocchi MN, Giberson B, Berg K, i wsp. Time to administration of epinephrine and outcome after in-hospital cardiac arrest with non-shockable rhythms: retrospective analysis of large in-hospital data registry. BMJ. 2014;348:g3028
37. Perkins GD, Ji C, Deakin CD, Quinn T, Nolan JP, Scomparin C, i wsp. A Randomized Trial of Epinephrine in Out-of-Hospital Cardiac Arrest. N Engl J Med. 2018;379(8):711-21.
38. Link MS, Berkow LC, Kudenchuk PJ, Halperin HR, Hess EP, Moitra VK, et al. Part 7: Adult advanced cardiovascular life support: 2015 American heart association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2015;132(18 Suppl 2):S444–64. [PubMed] [Google Scholar]
39. Callaway CW. Epinephrine for cardiac arrest. Curr Opin Cardiol. 2013;28:36–42. [PubMed] [Google Scholar]
40. Callaway CW. Questioning the use of epinephrine to treat cardiac arrest. JAMA. 2012;307:1198–200. [PubMed] [Google Scholar]
41. Paradis NA, Martin GB, Rosenberg J, Rivers EP, Goetting MG, Appleton TJ, et al. The effect of standard- and high-dose epinephrine on coronary perfusion pressure during prolonged cardiopulmonary resuscitation. JAMA. 1991;265:1139–44. [PubMed] [Google Scholar]
42. Paradis NA, Martin GB, Rivers EP, Goetting MG, Appleton TJ, Feingold M, et al. Coronary perfusion pressure and the return of spontaneous circulation in human cardiopulmonary resuscitation. JAMA. 1990;263:1106–13. [PubMed] [Google Scholar]
43. Lin S, Callaway CW, Shah PS, Wagner JD, Beyene J, Ziegler CP, et al. Adrenaline for out-of-hospital cardiac arrest resuscitation: A systematic review and meta-analysis of randomized controlled trials. Resuscitation. 2014;85:732–40. [PubMed] [Google Scholar]
44. Jacobs IG, Finn JC, Jelinek GA, Oxer HF, Thompson PL. Effect of adrenaline on survival in out-of-hospital cardiac arrest: A randomised double-blind placebo-controlled trial. Resuscitation. 2011;82:1138–43. [PubMed] [Google Scholar]
45. Nakahara S, Tomio J, Takahashi H, Ichikawa M, Nishida M, Morimura N, 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. [PMC free article] [PubMed] [Google Scholar]
46. Hayashi Y, Iwami T, Kitamura T, Nishiuchi T, Kajino K, Sakai T, et al. Impact of early intravenous epinephrine administration on outcomes following out-of-hospital cardiac arrest. Circ J. 2012;76:1639–45. [PubMed] [Google Scholar]

47. Atiksawedparit P, Rattanasiri S, McEvoy M, Graham CA, Sittichanbuncha Y, Thakkinstian A. Effects of prehospital adrenaline administration on out-of-hospital cardiac arrest outcomes: A systematic review and meta-analysis. Crit Care. 2014;18:463. [PMC free article] [PubMed] [Google Scholar]
48. Perkins GD, Quinn T, Deakin CD, Nolan JP, Lall R, Slowther AM, et al. Pre-hospital assessment of the role of adrenaline: Measuring the effectiveness of drug administration in cardiac arrest (PARAMEDIC-2): Trial protocol. Resuscitation. 2016;108:75–81. [PMC free article] [PubMed] [Google Scholar]
49. 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;83:674–83. [PubMed] [Google Scholar]
50. Ristagno G, Tang W, Huang L, Fymat A, Chang YT, Sun S, et al. Epinephrine reduces cerebral perfusion during cardiopulmonary resuscitation. Crit Care Med. 2009;37:1408–15. [PubMed] [Google Scholar]
51. Sun S, Tang W, Song F, Yu T, Ristagno G, Shan Y, et al. The effects of epinephrine on outcomes of normothermic and therapeutic hypothermic cardiopulmonary resuscitation. Crit Care Med. 2010;38:2175–80. [PubMed] [Google Scholar]
52. Hagihara A, Hasegawa M, Abe T, Nagata T, Wakata Y, Miyazaki S. Prehospital epinephrine use and survival among patients with out-of-hospital cardiac arrest. JAMA. 2012;307:1161–8. [PubMed] [Google Scholar]
53. Polish Resuscitation Council. ERC resuscitation guidelines 2021 [Internet]. https://www.prc.krakow.pl/wytyczne_2021.html
54. American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care 2020 [Internet]. https://www.ahajournals.org/toc/circ/142/16_suppl_