

EARLY EPINEPHRINE TREATMENT FOR CARDIOVASCULAR COMPLICATIONS  
DURING NEURAXIAL ANESTHESIA

By

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ABSTRACT

Spinal and epidural anesthesia [cumulatively referred to as neuraxial anesthesia] carry a low associated risk of bradycardia that could progress to asystolic cardiac arrest. Neuraxial anesthesia may inadvertently exceed anticipated therapeutic dermatomes and anesthetize nerves related to maintaining cardiovascular stability; instability may progress to cardiovascular collapse. The aim of this integrative review is to examine available evidence of epinephrine administration in response to predictive signs and symptoms of cardiovascular compromise. Current ACLS guidelines provide an emergent and reactive dose of epinephrine in response to a cardiac arrest. Could a proactive and more conservative administration of epinephrine mitigate deteriorating cardiovascular complications? The focus of this review includes: 1) signs and symptoms of impending cardiac arrest for prevailing commonality, 2) the timing of epinephrine administration, and 3) the dose of epinephrine to determine if low doses of epinephrine are more favorable for improved patient outcome. Databases (MEDLINE, Embase, and Pubmed) were searched using search terms *epinephrine*, *cardiac arrest*, *neuraxial anesthesia*, *ACLS*, *guidelines*, *high spinal anesthesia*, and *asystole*. Twenty-five articles were reviewed. Vigilant monitoring for cardiovascular compromise is a crucial component of the treatment process prior to the development of adult cardiac arrest. Early identification of patients at risk for developing cardiovascular symptoms that may progress to cardiac arrest is vital to preventing and treating these patients. Early intervention with epinephrine, a potent sympathomimetic agent, mitigates cardiovascular shortcomings during neuraxial anesthesia. Administering a low dose of epinephrine early in the recognition of cardiovascular compromise has been shown to be most effective in returning spontaneous circulation. Delayed administration of epinephrine produces unfavorable patient outcomes. Identifying early signs and symptoms of cardiovascular

compromise is a critical component to treating cardiac arrest during neuraxial anesthesia. Vigilant monitoring of heart rate, blood pressure, and sensory level of blockade are easily identifiable cues regarding cardiovascular function. Prompt recognition allows early intervention with epinephrine. Administering a conservative dose of exogenous epinephrine at the earliest opportunity provides sympathetic support that may prevent full cardiovascular collapse.

*Keywords:* cardiac arrest, neuraxial anesthesia, ACLS guidelines, epinephrine

TABLE OF CONTENTS

INTRODUCTION.....	6
Variables.....	6
Focused Review Questions.....	7
METHOD.....	8
Elements of Population.....	8
Inclusion and Exclusion Criteria .....	8
Search Strategies.....	8
Evidence Appraisal .....	10
Data Analysis.....	10
RESULTS.....	11
Recognition of Signs and Symptoms.....	11
Timing of epinephrine administration.....	12
Dose of epinephrine.....	14
Guidelines.....	17
<i>Table 1: Articles Reviewed for Dosing Recommendations of Epinephrine.....</i>	<i>19</i>
DISCUSSION.....	20
Limitations.....	21
CONCLUSION.....	22
REFERENCES.....	23
APPENDICES.....	28
<i>Figure 1: Critique of Literature.....</i>	<i>28</i>

Bradycardia followed by asystolic cardiac arrest during neuraxial anesthesia is a serious complication. The incidence of cardiac arrest during neuraxial anesthesia has been reported as high as 2.73 per 10,000 in a review of 40,271 cases (Charuluxananan et al., 2008). Advanced cardiac life support (ACLS) provides a nationwide recommendation for the dose of epinephrine to be given during bradycardia and cardiac arrest. However, the ACLS recommendation does not specify patient symptom criteria other than bradycardia in which to administer the recommended dose of epinephrine or recommend an epinephrine dose to administer during neuraxial anesthesia. The current standard of practice is for healthcare providers to follow the ACLS guidelines under their discretion of what symptoms require actions and the magnitude of epinephrine dosing. Epinephrine is administered during 25-40 percent of cardiac arrests resulting from neuraxial anesthesia. The mortality rate of cardiac arrest during neuraxial anesthesia is 25 percent (Sostaric & Orenus, 2013). The aim of this integrative review is to review current accepted practice regarding epinephrine administration in response to predictive signs and symptoms of cardiovascular compromise.

### *Variables*

Neuraxial anesthesia is defined as spinal anesthesia, epidural anesthesia and peripheral nerve blocks. For the purpose of this review, neuraxial anesthesia will be defined as spinal anesthesia and epidural anesthesia due to the decreased incidence of bradycardia and cardiac arrest during peripheral nerve block (Limongi & Lins, 2011). Epinephrine is a sympathomimetic medication that increases the sympathetic nervous system response, causing an increase in heart rate and blood pressure. The use of epinephrine to prevent the progression of bradycardia to cardiac arrest was attributed to the positive chronotropic effects of epinephrine (Caplan, Ward, Posner, & Chesney, 1988). Low dose of epinephrine will be defined as less than one milligram

administered every three to five minutes. Standard dose of epinephrine will be defined as one milligram administered every three to five minutes, and high dose of epinephrine will be defined as greater than one milligram administered every three to five minutes. These definitions are created based upon the ACLS guidelines of recommended dosage of epinephrine during cardiac arrest. Limongi et al (2011) and Caplan et al (1988) accredit, the potent alpha-agonist, epinephrine to be a vital component to circulatory resuscitation.

Bradycardia will be defined as a heart rate less than 60 beats per minute (BPM), to correspond with ACLS' definition. Bradycardia, hypotension, and sensory level blockade greater than or equal to T4 during neuraxial anesthesia are serious indications that need to be addressed immediately as they may be the initial signs of impending cardiac arrest. Not all cardiac arrests during neuraxial anesthesia can be prevented, but optimizing the approach to treating these situations is crucial to patient survival. Management and treatment of bradycardia or cardiac arrest can be achieved by administration of sympathomimetic medications, elevating the patients' leg to optimize venous blood return to the heart, and diligent oxygenation monitoring.

#### *Focused Review Questions*

1) What are the cardiac and neuraxial symptoms that prompt administration of epinephrine? 2) Does earlier administration of epinephrine improve patient outcome? 3) Does the lower dose of epinephrine improve patient outcome and mortality?

## Method

### *Elements of Population*

The elements of the population reviewed are dependent upon the experience of bradycardia and asystolic cardiac arrest during neuraxial anesthesia. Cardiac arrests experienced by in-hospital and out-of-hospital patients will be reviewed to compensate for the scarcity of information relating to cardiac arrests during neuraxial anesthesia.

### *Inclusion and Exclusion Criteria*

Inclusion criteria for this study include human studies, case reports, literature reviews, meta-analyses, case series, and systematic reviews. Exclusion criteria for this study included non-English abstract or manuscripts. Pediatric populations of 18 years age or younger will be excluded from this review. The articles of research to be evaluated will be published no earlier than 1980.

Sources to be reviewed include case reports, meta-analyses, systematic reviews, and integrative reviews. This approach allows for a wide variety of research to be reviewed. Analyzing case reports allows for specific instances to thoroughly reviewed and determine methods of medication administration that will help improve patient outcomes.

### *Search Strategies*

MEDLINE was searched using the EBSCOhost provider on 08/22/2015.

- 1 (cardiac arrest OR asystole OR bradycardia) AND (epinephrine OR adrenaline) (NOT animals)(1,111)
- 2 1 AND (dosage OR dose) (807)
- 3 2 NOT (pediatric, PEA, complications, ambulatory, out-of-hospital) (506)
- 4 (neuraxial anesthesia OR spinal anesthesia) AND (epinephrine OR adrenaline) (500)



- 5 2 AND (total spinal blockade OR high spinal) (7)
- 6 (total spinal blockade OR high spinal) AND (epinephrine OR adrenaline) (44)
- 7 (total spinal blockade OR high spinal) AND (cardiac arrest OR bradycardia OR asystole) (80)
- 8 Total= 3 + 4 + 5 + 6 + 7 = 1,137

From MEDLINE 24 articles were relevant. 1,113 did not meet criteria and were discarded.

Embase was searched on 08/24/2015.

- 1 (epinephrine OR adrenaline) AND (cardiac arrest) (2,077)
- 2 1 AND (dose OR dosage) (696)
- 3 (high spinal blockade OR total spinal blockade) (18)
- 4 Total= 2 + 3 = 714

From Embase 18 articles met the inclusion criteria and were relevant. 696 articles did not meet criteria, were not relevant, and discarded.

Pubmed was searched on 09/03/2015.

- 1 (epinephrine) AND (cardiac arrest) (1813)
- 2 1 AND spinal anesthesia (15)
- 3 (ACLS) AND (epinephrine) AND (cardiac arrest) (52)
- 4 (high spinal anesthesia) (2009)
- 5 4 AND (epinephrine) (82)
- 6 Total = 2 + 3 + 5 = 149

From Pubmed 22 articles met the inclusion criteria and were relevant. 127 articles did not meet criteria, were not relevant and were discarded.

Hand-picked search from references in relevant articles. Saturation point was met. Discarded duplicate references. Resulting in 25 articles meeting the research criteria and relevancy to research.

### *Evidence Appraisal*

The Johns Hopkins Nursing Evidence-Based Practice Research Evidence Appraisal (JHNEBP) was used to evaluate the validity of the existing literature (Dearholt & Dang, 2012). The strength of evidence was ranked from highest level (Level I) to lowest level (Level III). The quality of evidence is ranked from high quality of consistent and generalized results to low quality of inconsistent results with little evidence. *Figure 1: Critique of Literature* displays the ranking of the research articles by strength of evidence and quality of evidence.

### *Data Analysis*

The data for this review was categorized by their application to the focus questions being reviewed. Literature reviews and studies relating to signs and symptoms of impending cardiac arrest were reviewed for prevailing commonality and early recognition of symptoms. The literature that meets the inclusion criteria was reviewed for the timing of epinephrine administration. Articles (or sources or literatures) regarding the dose of epinephrine were examined to determine if low doses of epinephrine are more favorable for improved patient outcome especially if given as an early intervention for bradycardia and/or hypotension.

## Results

### *Recognition of Signs and Symptoms*

Initial symptoms of cardiovascular involvement from neuraxial anesthesia include paresthesias of the upper extremities, hypotension, bradycardia, dyspnea, cyanosis, reduction in oxygen saturation, nausea, vomiting, anxiety and loss of consciousness (Caplan et al., 1988). Bradycardia and hypotension, the more critical symptoms, are attributed to the impact of the vasovagal response. The vasovagal response is the sudden activation of the parasympathetic nervous system predominating the sympathetic nervous system. There is a direct relationship between the level of spinal blockade and the impact on the sympathetic nervous system. The higher the blockade, the greater the number of spinal nerves involved, and thus the degree of sympathectomy is increased. Sensory neuraxial blockade, as assessed by dermatomes, may be two to four levels higher than sympathectomy. A sympathetic block of T1 to T5 impacts the cardio-accelerator nerves (Reese, 2012) (See *Figure 1*).

Identifying patients at risk for potential vagal predominance will aid in the prompt recognition of cardiovascular compromise. Pollard (2000) identified patients undergoing neuraxial anesthesia that are at higher susceptibility to vagal predominance, which may lead to cardiovascular collapse and asystolic cardiac arrest. The risk factors for moderate bradycardia (<59 BPM) during neuraxial anesthesia include ASA physical status I, the use of beta receptor blocking drugs, a sensory level achieved >T6, age <50 years old, and a prolonged PR interval. Identifying patients with these risk factors who are more susceptible to vagal predominance during spinal anesthesia promotes early intervention.

Bradycardia during spinal anesthesia is a potential indicator of high/complete neuraxial blockade. Furthermore, bradycardia and asystolic cardiac arrest may occur even without high

neuraxial blockade (Lovstad, Granhus, & Hetland, 2000). Therefore heart rate alone is not an adequate measurement of the cardiovascular system, with or without sympathetic compromise.

Vigilant monitoring prior to the development of cardiac arrest is predictive of favorable outcomes. Geffin & Shapiro (1998) identified in their analysis of case reports that bradycardia and asystolic cardiac arrest occurred 15 minutes or longer after the initial administration of neuraxial anesthesia. Heightened level of awareness of the potential complications of sympathetic nervous system compromise requires early recognition of symptoms and immediate and aggressive treatment to reverse cardio-accelerator nerve impairment. Jang, Do & Song (2012) also concluded, from a case report of a gravid woman who experienced cardiac arrest during a cesarean section, that vigilant monitoring for patient symptoms of cardiovascular compromise is critical.

#### *Timing of epinephrine administration*

Caplan et al. (1988) analyzed closed claims involving cardiac arrest during spinal anesthesia and came across 14 cases of unexpected and sudden cardiac arrest in healthy adults. The average level of blockage before cardiac arrest was T3-T5. Two or more initial symptoms or clues were recognized before the onset of cardiac arrest in each of the fourteen patients in order of most occurring to least occurring: bradycardia, hypotension, cyanosis, loss of consciousness, and asystole. During the treatment and management of cardiac arrest ephedrine and atropine were given within two minutes of the initial symptoms or clue. Epinephrine was given five or more minutes after the initial symptoms, with an average of eight minutes at a dose of 0.1 to 2 mg. Caplan et al. (1988) concluded the immediate use of ephedrine after initial symptoms, was not sufficient to treat and manage degree of the sympathetic blockade level. If epinephrine had been used as the initial treatment medication, the duration of cardiac arrest could potentially have

been decreased because following the administration of epinephrine spontaneous rhythm and perfusion returned, on average, within three minutes.

Caplan et al. (1988) concluded that upon recognition of sudden bradycardia, epinephrine should be administered early, and epinephrine should be administered immediately upon onset of cardiac arrest. Prompt recognition is the first step in treatment of bradycardia and impending cardiac arrest. Administering epinephrine promptly upon recognition of symptoms helps improve patient outcome. The delay of administration of epinephrine in cardiac arrest is associated with worse patient outcomes (Dumas et al., 2014).

Donnino, Saliccioli, Howell, Cocchi, Giberson, Berg, Gautam, and Callaway (2014) performed a retrospective cohort study to determine early administration of epinephrine is associated with an increased ROSC, survival and favorable neurological outcomes. The results of this study indicated that there is a decrease in patient survival with every minute until the first dose of epinephrine administered. For the interquartile range of 7 – 9 minutes, there was a statistically significant decrease in patient survival ( $p < 0.001$ ). The authors concluded that the shorter the time before the first dose of epinephrine is associated with more favorable patient outcomes for cardiac arrests that occurred in the hospital (Donnino et al., 2014).

Congruent with the implication that sudden bradycardia is indicative of a compromised sympathetic nervous system, Lovstad et al. (2000) concluded that bradycardia would be better treated with the early administration of epinephrine. Limongi et al. (2011) confirmed the importance of early administration of epinephrine to be a critical component of maintaining coronary perfusion pressure. Pollard (2000) recommended an early dose of 0.2 to 0.3 mg of epinephrine to treat bradycardia during neuraxial anesthesia and full resuscitation epinephrine

doses for patients with severe bradycardia or cardiac arrest, based upon the mechanics of epinephrine to vasoconstrict and increase heart rate.

### *Dose of epinephrine*

Larabee, Liu, Campbell, & Little (2012) investigated the outcomes of various vasopressor drugs during cardiac arrest in a systematic review. The therapeutic outcomes investigated were (1) outcomes comparing any vasopressor to placebo, (2) outcomes comparing vasopressin (alone or in combination with epinephrine) to epinephrine, (3) outcomes comparing high dose epinephrine (4 – 40 mg) to standard dose epinephrine (1 mg), (4) outcomes comparing any alternative vasopressor to epinephrine. Based on the data analysis of the 17 articles related to high dose and standard dose epinephrine, the authors concluded that high dose epinephrine does not improve long-term patient outcomes when compared to standard dose epinephrine (Larabee et al., 2012) (See *Table 1*).

Stiell et al. (1992) conducted a randomly assigned quantitative study examining the use of high dose epinephrine (7 mg) compared to standard dose of epinephrine (1 mg) during cardiac arrest of adults in or outside the hospital. 650 patients who met the research design protocol were assigned either to the high-dose group (N=317) or the standard-dose group (N=333). The high-dose group received 7 mg of epinephrine and the standard dose group received 1 mg of epinephrine. Each group could receive up to five doses of their allotted dosage at five-minute intervals. The average number of epinephrine doses each group received was 2.5 doses. The average standard dose of epinephrine patient received 2.5 mg (0.015 mg/kg) The average high dose epinephrine patient received 17.8 mg (0.10 mg/kg) There was not a statistically significant higher resuscitation rate for patients receiving high dose epinephrine compared to standard dose epinephrine ( $p = 0.15$ ). The results of their findings indicated that the high-dose epinephrine did

not improve survival or the neurological outcomes of adult patients who experienced cardiac arrest in or outside the hospital. The authors acknowledged that a limitation to their study was it did not identify an adult subgroup that would benefit from high-dose epinephrine. This research article reveals the standard dose of 1 mg epinephrine in five-minute intervals is the recommended dosage. The findings of this study are applicable to the population of patients receiving neuraxial anesthesia.

Behringer et al. (1998) reported the finding of a retrospective cohort study analyzing the neurological outcomes of cumulative epinephrine administration during cardiopulmonary resuscitation. The authors collected data of the patients admitted to an emergency department for cardiac arrest in or outside the hospital and 178 patients met the criteria for analysis. Even though this study analyzed the cumulative doses of epinephrine, data from this analysis can be applicable to this review by extrapolating data from the interquartile ranges that correlated to standard and high dose epinephrine. The median cumulative dose of epinephrine for the interquartile range of 0.6 mg to 2.1 mg was 1.2 mg administered every five minutes; the median cumulative dose for interquartile range of 1 mg to 6 mg was 4 mg administered every five minutes. When comparing the frequencies of favorable and unfavorable neurological outcomes after ROSC incorporating the no-flow duration and low-flow duration, the standard dose of epinephrine patients had greater favorable outcomes when compared to the high dose patients. The results concluded that during cardiac resuscitation increasing the cumulative epinephrine dose is independently associated with unfavorable neurological outcomes. The authors recommended that more investigation should be done to clearly define the epinephrine dose limitations during CPR in adult patients.

Arrich, Sterz, Herkner, Testori, & Behringer (2012) conducted a retrospective cohort study to determine the impact of unfavorable outcomes and in-hospital mortality on patients connected to the cumulative dose of epinephrine during cardiac arrest. The median dose of epinephrine from 946 patients was 2 mg. The range of cumulative epinephrine dose was 1 to 50 mg. Patients that received greater than 2 mg of epinephrine had a statistically longer low-flow duration than patients that received less than 2 mg of epinephrine. The higher cumulative dose of epinephrine patients had statistically significantly greater unfavorable functional outcomes ( $p < 0.001$ ). Analysis of the results concluded with an increased cumulative epinephrine dose, there is a statistically significant increase in the risk for unfavorable outcomes (Arrich et al., 2012).

Brown et al. (1992) conducted a randomized controlled trial to compare the patient outcomes of cardiac arrests outside the hospital in relation to administration of standard dose and high dose epinephrine. The standard dose of epinephrine was 0.02 mg per kilogram of patient body weight, and the high dose of epinephrine was 0.2 mg per kilogram. The authors were unable to determine a statistically significant difference between the patient outcomes comparing standard dose to high dose epinephrine. The authors attributed their results to the fact that 60 percent of the cardiac arrests were unwitnessed and outside the hospital. This increased the timing of initial epinephrine treatment administration. The authors determined that high dose epinephrine did not show any patient benefits or negative consequences.

Arrich et al. and Behringer et al. both concluded that the increase in cumulative dose of epinephrine increased the unfavorable outcomes in patients who experienced cardiac arrest. Larabee et al. determined there are no survival benefits to high dose epinephrine during cardiac arrest. Stiell et al. determined there is no difference between the administration of standard dose and high dose of epinephrine, concluding that high dose epinephrine does not improve patient



outcomes. Brown et al. was unable to determine the effects of high dose epinephrine regarding patient outcomes.

### *Guidelines*

The American Heart Association (AHA) Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care recommends administering 1 mg of epinephrine every 3 to 5 minutes during cardiac arrest. The AHA does not recommend administering higher doses of epinephrine unless indicated for specific problems: beta-blocker or calcium channel blocker overdose, or used to maintain hemodynamic stability with proper monitoring. The research conducted by the AHA concluded that high dose epinephrine does not improve survival benefits during cardiac arrest (Neumar et al., 2010). If ACLS guidelines are diligently followed, epinephrine should be administered following the first five rounds of CPR taking approximately two minutes following the recognition of asystolic cardiac arrest.

ACLS guidelines provided by the AHA are the foundation for treatment during cardiac arrest. Healthcare providers utilize the ACLS guidelines to determine treatment and dosage during cardiac arrest. However, the ACLS guidelines are not always followed strictly. Johansson et al. (2004) conducted a retrospective cohort study to determine whether ACLS guidelines were adhered to during cardiac arrest. The results of this study found that 36 of the 53 patients reviewed (68%) had a longer between dose of epinephrine interval than the recommended 3 to 5 minutes by ACLS. The median between dose interval was 6 minutes and 30 seconds. Eight percent of the patients did not receive epinephrine as part of their treatment. The authors concluded that the majority of the cases reviewed did not follow the current ACLS guidelines. Johansson et al. (2004) offered possible explanations for lack of ACLS adherence: lack of

outcome expectancy, lack of familiarization with the current guidelines, lack of clinical experience, and lack of a strategy to adhere to the guidelines.

*Table 1: Articles Reviewed for Dosing Recommendations of Epinephrine*

Author (s)	Level of Evidence	Conclusion
Arrich et al. (2012)	Level III = Good quality of evidence	Increased cumulative dose of epinephrine increased unfavorable patient outcomes. Median epinephrine dose 2 mg Range 1-50 mg pValue < 0.001 Cumulative low dose= < 2mg Cumulative high dose= >2 mg
Behringer et al. (1998)	Level III = Good quality of evidence	Increased cumulative dose increased unfavorable patient outcomes. pValue <0.001 Cumulative low dose= < 5 mg Cumulative high dose= > 5 mg
Brown et al. (1992)	Level I = High quality of evidence	Unable to determine effects of increased dose of epinephrine. pValue= N/A Standard dose= 0.02 mg/kg High dose= 0.2 mg/kg
ARC & NZRC (2011)	Level I = High quality of evidence National Guideline	No studies have shown that high dose epinephrine improves long-term patient outcomes. Standard dose 1 mg every 3-5 minutes
Larabee et al. (2012)	Level I = High quality of evidence	No survival benefits to high dose epinephrine. pValue= N/A Low dose= 1 mg High dose= 4 – 40 mg
Neumar et al. (2010)	Level I = High quality of evidence AHA National Guideline	No studies have shown that high dose epinephrine is more beneficial to patient outcomes. Standard dose 1 mg every 3-5 minutes
Stiell et al. (1992)	Level I = High quality of evidence	Patient outcomes not different between standard dose and high dose, therefore high dose epinephrine does not improve patient outcome. pValue= 0.15 Low dose= 1 mg High dose= 7 mg

### Discussion

The ACLS guidelines appear underutilized and lack adherence during cardiac arrest in the studies reviewed. The ACLS guidelines recommend a standard epinephrine dose of 1 mg every 3 to 5 minutes during cardiac arrest. However, the ACLS guidelines do not address the progression of initial symptoms in which to administer epinephrine or a plan of treatment specifically for hemodynamic compromise due to neuraxially-induced sympathectomy. Guidelines provide a foundation for treatment of cardiac derangements but diagnostic cause and effect within the context of individual care remains the responsibility of the healthcare provider. Anesthesia provider's treatment plans are initiated by their assessment and interpretation of patient status. The lack of a range of doses may preclude earlier administration of epinephrine. A study by Stiell et al. (1992) found that there was not a statistically significantly higher resuscitation rate for patients receiving high dose epinephrine compared to low dose epinephrine ( $p = 0.15$ ). Studies by Arrich et al. (2012) and Behringer et al. (1998) found that patients who received a higher cumulative dose of epinephrine had significantly greater unfavorable outcomes: Arrich et al. (2012) found a statistical significance of  $p < 0.001$ . Treatment of cardiac arrest with high dose epinephrine (0.2 mg/kg) was not found to be associated with worse patient outcomes compared to low dose epinephrine (0.02 mg/kg) (Brown et al., 1992). Donnino et al. (2014) found that administering epinephrine after 7 minutes from the onset of cardiac arrest was statistically significant in decreasing patient survival. Johansson et al. (2004) found that 68% of the patients in their study had a longer between doses of epinephrine than the recommended 3 to 5 minutes by ACLS.

Timing is not adhered to currently by the ACLS recommendations of administering epinephrine every 3 to 5 minutes during cardiac arrest. A prolonged interval between epinephrine doses does not coincide with the recommendations provided by the American Heart Association.

The research conducted for this review reveals that higher doses of epinephrine are positively correlated with unfavorable patient outcomes or provided no additional survival benefits. Due to the fact that ACLS recommends a low dose of epinephrine and only to administer high doses during specific problems and the evidence that supports higher epinephrine doses does not improve patient outcomes, why is high dose epinephrine still administered during cardiac arrest? An additional inquiry is why early and low doses of epinephrine are not administered during the first sign of cardiovascular compromise. Further areas of research should explore ACLS adherence guidelines in all settings in which cardiac arrest occurs.

### *Limitations*

Limitations within this review are due to the lack of literature of cardiac arrest during neuraxial anesthesia. There are large quantities of literature surrounding cardiac arrest outside of neuraxial anesthesia but limited information during neuraxial anesthesia. There are no randomized controlled trials of determining dose of epinephrine to administer during cardiac arrest while under neuraxial anesthesia. Limited selective studies were reviewed, systematic review was not performed, and no studies looked specifically at neuraxial induced-bradycardia or –cardiac arrest. This limitation compelled this review to search for answers by paralleling, extrapolating data and drawing inferences based on cardiac arrests outside of neuraxial anesthesia. This study has found that epinephrine may be used as a vasopressor treatment for

bradycardia and cardiac arrest. Its consideration for use in treating neuraxial induced-bradycardia or -cardiac arrest is warranted and further exploration and research is recommended.

### Conclusion

Identifying early signs and symptoms of cardiovascular compromise is a critical component to mitigate the mortality of cardiac arrest during neuraxial anesthesia. Vigilant monitoring of patients' heart rate, blood pressure, and sensory level blockade are easily identifiable clue of the patients' cardiovascular function. Prompt recognition of cardiovascular compromise allows time for early administration of epinephrine and optimizes cardiovascular function. By administering low dose epinephrine upon the initial recognition of cardiovascular compromise, epinephrine can best mitigate cardiovascular changes. Cardiac arrest during neuraxial anesthesia remains a risk. In the event of cardiac arrest, early administration of epinephrine as opposed to a less potent sympathomimetic drugs, optimizes the restoration of hemodynamics.

### References

- Arrich, J., Sterz, F., Herkner, H., Testori, C., & Behringer, W. (2012). Total epinephrine dose during asystole and pulseless electrical activity cardiac arrests is associated with unfavourable functional outcome and increased in-hospital mortality. *Resuscitation*, 83(3), 333-337. doi:10.1016/j.resuscitation.2011.10.027
- Aung, K., & Htay, T. (2005). Vasopressin for cardiac arrest: A systematic review and meta-analysis. *Archives of Internal Medicine*, 165(1), 17-24. doi:10.1001/archinte.165.1.17
- Behringer, W., Kittler, H., Sterz, F., Domanovits, H., Schoerhuber, W., Holzer, M., . . . Laggner, A. N. (1998). Cumulative epinephrine dose during cardiopulmonary resuscitation and neurologic outcome. *Annals of Internal Medicine*, 129(6), 450-456. doi:10.1059/0003-4819-129-6-199809150-00004
- Brown, C. G., Martin, D. R., Pepe, P. E., Stueven, H., Cummins, R. O., Gonzalez, E., . . . the Multicenter High-Dose Epinephrine Study Group. (1992). A comparison of standard-dose and high-dose epinephrine in cardiac arrest outside the hospital. *The New England Journal of Medicine*, 327(15), 1051-1055. doi:10.1056/NEJM199210083271503
- Callaway, C. W. (2012). Questioning the use of epinephrine to treat cardiac arrest. *Jama*, 307(11), 1198-1200. doi:10.1001/jama.2012.313
- Caplan, R. A., Ward, R. J., Posner, K., & Cheney, F. W. (1988). Unexpected cardiac arrest during spinal anesthesia: A closed claims analysis of predisposing factors. *Anesthesiology*, 68(1), 5-11. doi:10.1097/00000542-198801000-00003
- Charuluxananan, S., Thienthong, S., Rungreungvanich, M., Chanchayanon, T., Chinachoti, T., Kyokong, O., & Punjasawadwong, Y. (2008). Cardiac arrest after spinal anesthesia in

- thailand: A prospective multicenter registry of 40,271 anesthetics. *Anesthesia and Analgesia*, 107(5), 1735-1741. doi:10.1213/ane.0b013e31817bd143
- Donnino, M., Saliccioli, J., Howell, M., Cocchi, M., Giberson, B., Berg, K. . . for the American Heart Association's Get With The Guidelines-Resuscitation Investigators. (2014). 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-British Medical Journal*, 348(may20 2), g3028-g3028. doi:10.1136/bmj.g3028
- Dumas, F., Bougouin, W., Geri, G., Lamhaut, L., Bougle, A., Daviaud, F. . . Cariou, A. (2014). Is epinephrine during cardiac arrest associated with worse outcomes in resuscitated patients? *Journal of the American College of Cardiology*, 64(22), 2360-2367. doi:10.1016/j.jacc.2014.09.036
- Geffin, B., & Shapiro, L. (1998). Sinus bradycardia and asystole during spinal and epidural anesthesia: A report of 13 cases. *Journal of Clinical Anesthesia*, 10(4), 278-285. doi:10.1016/S0952-8180(98)00028-2
- Glover, B. M., Brown, S. P., Morrison, L., Davis, D., Kudenchuk, P. J., Van Ottingham, L. . . Resuscitation Outcomes Consortium. (2012). Wide variability in drug use in out-of-hospital cardiac arrest: A report from the resuscitation outcomes consortium. *Resuscitation*, 83(11), 1324-1330. doi:10.1016/j.resuscitation.2012.07.008
- Gueugniaud, P., David, J., Chanzy, E., Hubert, H., Dubien, P., Mauriaucourt, P. . . Marret, E. (2008). Vasopressin and epinephrine vs. epinephrine alone in cardiopulmonary resuscitation. *The New England Journal of Medicine*, 359(1), 21-30. doi:10.1056/NEJMoa0706873



- Jang, Y., Do, S., & Song, I. (2013). Vasovagal cardiac arrest during spinal anesthesia for cesarean section -A case report. *Korean Journal of Anesthesiology*, *64*(1), 77-81. doi:10.4097/kjae.2013.64.1.77
- Johansson, J., Hammerby, R., Oldgren, J., Rubertsson, S., Gedeberg, R., Medicinska och farmaceutiska vetenskapsområdet. . Kardiologi. (2004). Adrenaline administration during cardiopulmonary resuscitation: Poor adherence to clinical guidelines. *Acta Anaesthesiologica Scandinavica*, *48*(7), 909-913. doi:10.1111/j.1399-6576.2004.00440.x
- Kopp, S. L., Horlocker, T. T., Warner, M. E., Hebl, J. R., Vachon, C. A., Schroeder, D. R. . Sprung, J. (2005). Cardiac arrest during neuraxial anesthesia: Frequency and predisposing factors associated with survival. *Anesthesia and Analgesia*, *100*(3), 855-865. doi:10.1213/01.ANE.0000144066.72932.B1
- Larabee, T. M., Liu, K. Y., Campbell, J. A., & Little, C. M. (2012). Vasopressors in cardiac arrest: A systematic review. *Resuscitation*, *83*(8), 932-939. doi:10.1016/j.resuscitation.2012.02.029
- Layek, A., Maitra, S., Pal, S., Bhattacharjee, S., & Baidya, D. K. (2014). Efficacy of vasopressin during cardio-pulmonary resuscitation in adult patients: A meta-analysis. *Resuscitation*, *85*(7), 855-863. doi:10.1016/j.resuscitation.2014.03.303
- Limongi, J. A. G., & Lins, Rossana Sant'Anna de Melo. (2011). Cardiopulmonary arrest in spinal anesthesia. *Brazilian Journal of Anesthesiology*, *61*(1), 110-120. doi:10.1016/S0034-7094(11)70012-5
- Løvstad, R.Z., Granhus, G., & Hetland, S. (2000). Bradycardia and asystolic cardiac arrest during spinal anaesthesia: A report of five cases. *Acta Anaesthesiologica Scandinavica*, *44*(1), 48-52. doi:10.1034/j.1399-6576.2000.440109.x

- Australian Resuscitation Council, & New Zealand Resuscitation Council. (2011). Medications in adult cardiac arrest. ARC and NZRC guideline 2010. *Emergency Medicine Australasia*, 23(3), 282-285. doi:10.1111/j.1742-6723.2011.01422\_13.x
- Naguib, M., Magboul, A., Samarkandi, A. H., & Attia, M. (1998). Adverse effects and drug interactions associated with local and regional anaesthesia. *Drug Safety*, 18(4), 221-250. doi:10.2165/00002018-199818040-00001
- Neumar, R. W., Otto, C. W., Link, M. S., Kronick, S. L., Shuster, M., Callaway, C. W. . . Morrison, L. J. (2010). Part 8: Adult advanced cardiovascular life support: 2010 American heart association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*, 122(18 Suppl 3), S729-S767. doi:10.1161/CIRCULATIONAHA.110.970988
- Pollard, J. B. (2001). Cardiac arrest during spinal anesthesia: Common mechanisms and strategies for prevention. *Anesthesia and Analgesia*, 92(1), 252-256. doi:10.1097/00000539-200101000-00050
- Reese, C. (2012). *Clinical techniques of regional anesthesia: Spinal and epidural blocks* (3<sup>rd</sup> ed.). Park Ridge: American Association of Nurse Anesthetists.
- Sostaric, S., & Oremus, K. (2013). Sudden cardiorespiratory arrest following spinal anesthesia. *Periodicum Biologorum*, 115(2), 283-288.
- Steffek, M., Owczuk, R., Szlyk-Augustyn, M., Lasinska-Kowara, M., & Wujtewicz, M. (2004). Total spinal anaesthesia as a complication of local anaesthetic test-dose administration

through an epidural catheter. *Acta Anaesthesiologica Scandinavica*, 48(9), 1211-1213.

doi:10.1111/j.1399-6576.2004.00500.x

Stiell, I. G., Hebert, P. C., Weitzman, B. N., Wells, G. A., Raman, S., Stark, R. M. Dickinson, G.

E. (1992). High-dose epinephrine in adult cardiac arrest. *The New England Journal of Medicine*, 327(15), 1045-1050. doi:10.1056/NEJM199210083271502

Warren, S. A., Huszti, E., Bradley, S. M., Chan, P. S., Bryson, C. L., Fitzpatrick, A. L.. . Amer

Heart Assoc Get. (2014). Adrenaline (epinephrine) dosing period and survival after in-hospital cardiac arrest: A retrospective review of prospectively collected data.

*Resuscitation*, 85(3), 350-358. doi:10.1016/j.resuscitation.2013.10.004

Appendices*Figure 1: Critique of Literature*

Author(s)/ Date	Design	Participants	Conclusion	Strength of Evidence
Arrich et al. (2012)	Non-experimental Retrospective Cohort Study	N=946 Patients admitted to ER for cardiac arrest at Vienna General Hospital	There is a statistically significant greater risk of unfavorable patient outcomes and in-hospital mortality when accompanied with a high cumulative dose of epinephrine.	Level III = Good Quality of Evidence
Behringer et al. (1998)	Non-experimental Retrospective cohort study	N=178 Retrospective cohort study of adults who experienced cardiac arrest admitted to the University Hospital of Vienna, Austria.	During cardiac arrest, an increase in cumulative epinephrine dose was associated with unfavorable neurological outcomes after resuscitation.	Level III = Good quality of evidence
Brown et al. (1992)	Experimental - RCT	N = 1280 Cardiac arrest in out-hospital patients in six medical centers.	Unable to determine if high-dose epinephrine improved survival and ROSC compared with standard-dose epinephrine.	Level I = High Quality of Evidence
Caplan et al. (1988)	Non-experimental Retrospective study	N=14 Retrospective study of closed claims of 14 healthy young adults who experienced cardiac arrest during spinal anesthesia.	Epinephrine may have played a crucial role in stopping cardiac arrest. Early administration of epinephrine could have shorted the amount of insufficient cerebral perfusion and reduced the degree of neurological outcomes.	Level III = Good quality of evidence
Charuluxananan et al. (2008)	Non-experimental Retrospective study	N=11 Retrospective study of cardiac arrests during spinal anesthesia in 20 hospitals during a 12-month period in Thailand.	Cardiac arrest during spinal anesthesia is associated with high mortality. To decrease risk factors: increase anesthesiologist staffing, improve monitoring during spinal anesthesia, and improve CRNA training program.	Level III = Good quality of evidence
Dumas et	Non-	N= 1,556	73% of patients studied	Level III =

al. (2014)	experimental Retrospective Cohort Study	Retrospective cohort study of out-of-hospital cardiac arrest. The administration of epinephrine was categorized as (none, 1 mg, 2-5 mg, >5 mg).	received epinephrine, 17% of this group had a good outcome. Whereas, the 63% of the 422 patients who were not treated with epinephrine. The delayed administration of epinephrine was associated with worse patient outcomes. The administration of pre-hospital epinephrine was associated with lower patient survival rates.	Good quality of evidence
Geffin et al. (1997)	Non-experimental (Case Report)	N = 13 Patient that developed severe bradycardia or asystole during spinal anesthesia	Bradycardia and asystole occurred in 15 minutes or longer after the initial administration of spinal anesthesia.	Level III = Good Quality of Evidence
Gueugniard et al. (2008)	Experimental-RCT	N= 2,894 Out-of-hospital cardiac arrests were randomly assigned 1 mg of epinephrine and 40 IU of vasopressin or 1 mg or epinephrine and a saline placebo. Primary and secondary end points of survival were analyzed.	The administration of combined vasopressin and epinephrine did not improve patient outcome, when compared to the administration of epinephrine during ACLS	Level I = High Quality of Evidence
Jang et al. (2012)	Non-experimental (Case Report)	N = 1 Gravid woman under going an elective cesarean section who experienced vasovagal cardiac arrest.	The high neuraxial blockade (T3) potentiated the cardiovascular system of this patient to not be able compensate for the severity of the vasovagal response.	Level III = Good quality of evidence
Johansson et al (2004)	Non-experimental Retrospective Cohort Study	N = Patients from Uppsala University Hospital who underwent CPR during period of one year were reviewed for duration of CPR, total epinephrine dose administered, and average interval	The average interval between epinephrine was longer than the 3-5 minutes recommended by ACLS (median 6.5 minutes).	Level III = Good Quality of Evidence

		between doses.		
Kopp et al. (2005)	Non-experimental Retrospective Cohort Study	N = 26 Cardiac arrests during a 20-year period at the Mayo Clinic, comparing cardiac arrest during general and spinal anesthesia.	There is greater likelihood of survival of cardiac arrest during spinal anesthesia than compared to general anesthesia.	Level III = Good Quality of Evidence
Limongi et al. (2011)	Non-experimental Retrospective Study	N = Reviewed literature to determine the incidence, etiology, prevention types and treatment for cardiac arrest during spinal anesthesia.	Cardiac arrest during spinal anesthesia is mostly related to the reduction of preload from sympathetic blockade. The early administration of epinephrine aids to minimized damage to patient during cardiac arrest.	Level III = Good Quality of Evidence
Lovstad et al. (1999)	Non-experimental Case Series	N=5 Case series on five healthy patients who experienced bradycardia and asystolic cardiac arrest.	Significant preventative measures: limiting extent of sensory blockade, correct preoperative hypovolemic patients, and Trendelenburg position to optimize venous return.	Level III = Good quality of evidence
Sostaric et al. (2013)	Non-experimental (Case Report)	N = 1	The early administration of epinephrine is critical to restoring cardiac function.	Level III= Good Quality of Evidence
Stiell et al. (1992)	Experimental-RCT	N= 650 Randomized Controlled Trial of adults who experienced cardiac arrest inside or outside of Ottawa Civic or General Hospital.	No significant difference between the standard-dose group and the high-dose group in survival after cardiac arrest. Conclusion: The use of high-dose epinephrine did not improve the survival or neurological outcomes of adults who suffered cardiac arrest.	Level I = High quality of evidence