VILNIUS UNIVERSITY

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The Final thesis

Cardiac Resuscitation: Still A Place For Epinephrine

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Abbreviation	
CPR	Cardio-Pulmonary Resuscitation
ROSC	Return Of Spontaneous Circulation

1. I N T R O D U C T I O N

1.1. Motivation Behind The Thesis

My motivation behind my master thesis journey is based on the profound understanding of the criticality of Cardiopulmonary Resuscitation (CPR) in saving lives. CPR stands as a piece of hope in the face of sudden cardiac arrest, a medical emergency that can strike anyone not only medical professionals, anywhere, at any time and will most likely occur in the course of once medical career. This realization serves as the cornerstone of my thesis, pushing me towards a topic that addresses a broad spectrum of individuals, for whom adequate CPR knowledge could make a difference.

In today's rapidly evolving world of medicine, where advancements are made every day, it becomes crucial to ensure that our response to emergencies is keeping up with these advancements. The time and precision with which CPR is initiated can significantly impact patient outcomes. Clear and evidence-based guidelines play an important role in directing healthcare practitioners through the important moments of resuscitation.

A central goal of my thesis revolves around the examination of current guidelines and proposals. While the urge to attempt rescue in moments of crisis is understandable, proof suggests that patients benefit more from a structured, evidence-based treatment plan rather than from impulsive rescue actions. Furthermore, it is essential to acknowledge that CPR scenarios are inherently stressful for everyone involved, particularly for individuals and new medical professionals who have never encountered such situations before. By following the established standardized protocols, we empower healthcare professionals to react and initiate an effective treatment promptly, to maximize the chances of survival.

By reevaluating and comparing given guidelines and studies I aim to check their timeliness as well as provide an insight on the basis that they were established on.

1.2. Objectives and Study Format

In this study, we aim to explore the details of epinephrine usage in cardiopulmonary resuscitation (CPR), shedding light on its pharmacodynamics and pharmacokinetics. Our research makes an effort to address key goals and research questions important for understanding the role of epinephrine in resuscitative efforts and its impact on patient outcomes.

Firstly, we will establish a foundational understanding of the basics of pharmacodynamics and pharmacokinetics of epinephrine. By examining how this medication functions within the body, we can examine the physiological mechanisms upon which its efficacy in CPR scenarios is built.

Moreover, we will take a look to encompass other critical aspects that must be considered during CPR interventions. Factors such as timing and dosage will be taken into account for the comprehensive understanding of resuscitative efforts. Another point of our investigation involves assessing the impact of epinephrine on long-term survival and patient outcomes. By reviewing existing literature and clinical studies, we aim to take a closer look at the effects of epinephrine administration which go beyond the acute resuscitative phase. By highlighting adverse reactions and complications, we aim to provide insights into the safety profile of this medication.

An important point of our discourse will be the PARAMEDIC2 study which has as well as other studies sparked a debate regarding the utility of epinephrine in CPR. We will critically evaluate the findings of this study as well as others, assessing their relevance and implications for clinical practice.

In conclusion, our study focuses on providing a comprehensive analysis of epinephrine in CPR, bridging the gap between pharmacological principles and clinical practice. Through a detailed analysis of its origin, efficacy, and implications for patient outcomes, we seek to explore the resuscitative strategies in cardiopulmonary resuscitation.

Starting on a narrative literature review, my aim was to offer a comprehensive overview of the current standards surrounding the usage of epinephrine in cardiopulmonary resuscitation (CPR), providing insights from recent research findings and clinical guidelines. Our

methodology involved a search strategy and precise filtering process to ensure relevance and applicability to our investigation.

To initiate our review, we conducted a wide search utilizing key search terms such as "Cardiopulmonary Resuscitation guidelines", "Cardiopulmonary Resuscitation and Epinephrine," and "Cardiopulmonary Resuscitation, Epinephrine, and Survival", " timing of epinephrine administration in cardiopulmonary resuscitation". These search terms were carefully chosen to focus on the most relevant literature including guidelines, research studies, and outcomes related to epinephrine administration in CPR scenarios.

Filtering our results based on specific criteria was crucial to refine our search and focus on literature pertinent to our objectives.

We restricted publications to those within the timeframe of 2013-2023, ensuring currency and relevance. Additionally, we limited our search to publications in the English language, targeting a wide pool of literature for review. We specifically took a closer look at studies involving human populations, with a focus on adults to narrow our research results down.

In our review, we focused these diverse sources of information to offer insights into the optimal utilization of epinephrine in resuscitative efforts. The provided search results were also reviewed if they align with today's standards of the European Society of Cardiology and the American Heart Association. (1) These guidelines serve as tools of evidence-based practice, offering recommendations and best practices for the administration of epinephrine in CPR.

Ultimately, our narrative literature review underlines the importance of synthesizing current standards, recent research, and authoritative guidelines, we aim to inform clinical decision-making, enhance patient care, and stresses the importance of the ongoing evolution of resuscitative practices.

2. B A S I C K N O W L E D G E

2.1. History of Cardiopulmonary Resuscitation

Early resuscitation methods, which would be seen as primitive by today's standards reflect the creativity and resourcefulness of medical practitioners throughout history. (2) While rudimentary attempts at resuscitation can be traced back to ancient civilizations, the evolution of modern CPR as we know it today is a relatively recent phenomenon.

In the 18th century, the Paris Academy of Sciences made a groundbreaking recommendation for mouth-to-mouth resuscitation, setting one of the earliest documented efforts at artificial respiration. This paved the way for future developments in life-saving techniques.

Throughout the 19th century, various manual resuscitation methods emerged, including the Silvester method and the Holger Nielsen technique, which incorporated chest compressions and arm movements to revive individuals in distress.

Key contributors and milestones in the development of modern CPR include Dr. Friedrich Maass's pioneering use of chest compressions in 1896, Dr. George Crile's successful application of external chest compressions in 1903, and the collaborative efforts of Drs. James Elam, Peter Safar, William Kouwenhoven, James Jude, and Guy Knickerbocker in refining and popularizing the modern CPR technique in the mid-20th century. (6) The introduction of "closed chest cardiac massage" marked an essential moment, demonstrating the efficacy of chest compressions in reviving cardiac arrest patients.

Concurrently, the use of epinephrine (adrenaline) during cardiac arrest emerged as a promising intervention. In 1895, Polish physiologist Napoleon Cybulski obtained extracts from the adrenal gland, which he called "nadnerczyna" and contained adrenaline (epinephrine) and other catecholamines. (5) Epinephrine (also known as adrenaline) was first isolated in 1901 by Japanese scientist Jōkichi Takamine, and it came into medical use in 1905. (3) However, the initial use was not for resuscitation, it was for asthma. (3)

However, it wasn't until the 1950s that the modern elements of CPR began to take shape. Additionally, James Elam and Peter Safar played instrumental roles in proving the effectiveness of mouth-to-mouth resuscitation, laying the foundation for contemporary CPR protocols. (7) Epinephrine has been used in the treatment of cardiac arrest since the 1960s, after it was found to improve survival in dog models of asphyxia.

Around the same time, in 1960, the American Heart Association formally filed for CPR being endorsed officially and initiated training programs to educate healthcare professionals in its application, marking a crucial step towards the spreading of implementation of CPR worldwide.

2.2. Current Guidelines for Cardiopulmonary Resuscitation

According to the search findings, the evolution of current CPR guidelines has been marked by significant milestones. (10)

In the year 2000, the establishment of the International Liaison Committee on Resuscitation (ILCOR) by the American Heart Association and European Resuscitation Council paved the way for the development of the first "International Guidelines 2000 for CPR & ECC (emergency cardiovascular care).” (41)

These guidelines were seen as a groundbreaking effort to unify CPR practices globally and to set a standard for emergency cardiovascular care methods worldwide.

The guidelines introduced in 2000 have since been revised three times, with the most recent version presented in 2020. Each update reflects advancements in resuscitation science and incorporates the latest evidence-based practices to enhance the effectiveness of CPR and emergency cardiovascular care techniques. Usually, these guidelines are supposed to be revised and updated every 5 years, in 2020 an unforeseeable situation occurred. While the 2020 AHA Guidelines for CPR and ECC underwent a comprehensive revision, the European Resuscitation Council (ERC) guidelines for adult resuscitation were not fully updated in 2020. Despite being based on the 2020 ILCOR Consensus of CPR Science; the ERC guidelines were not fully refreshed due to the strain placed on healthcare systems by the pandemic. (9)

The 2020 AHA guidelines represent a thorough update process, indicating that despite the challenges posed by COVID-19, the full revision was successfully completed. In contrast, the ERC guidelines for adult resuscitation remained largely unchanged, with only targeted updates incorporated based on the 2020 ILCOR consensus. (11)

The next revision is expected to be presented in 2025, this time by a united by the American Heart Association and European resuscitation council.

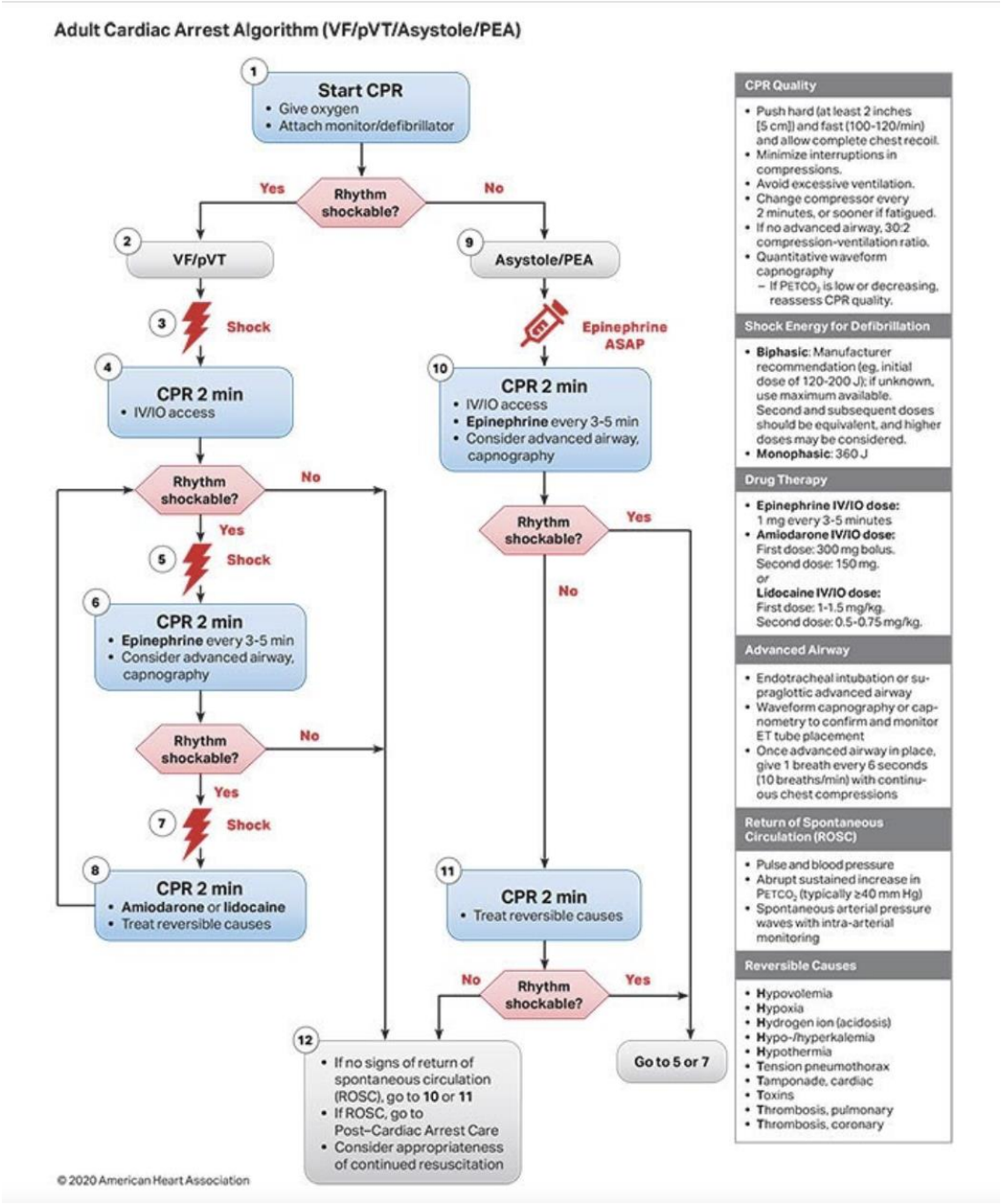

Figure 1. Algorhythm on conduction of advanced cardiac life support based on the recommendations issued in 2020 (12)

2.3. Pathophysiology of Cardiac Arrest

Cardiac arrest stands as a critical juncture of the body's physiological balance, marked by the sudden cessation of cardiac activity and progressive absence of systemic blood circulation. As the most common causes of cardiac arrest was structural heart especially ischemic coronary artery disease identified. (15)

While the term itself may seem simple and straightforward, other than that the underlying pathophysiological mechanisms driving this fatal state are rather complex. (18) When cardiac function fails, a domino effect of physiological disturbances erupts, leading to widespread tissue hypoxia and cellular damage throughout the body. (16)

The decline in adenosine triphosphate (ATP) production, the cellular powerhouse for energy, triggers a breakdown in membrane integrity. (14) This results in the efflux of potassium ions and influx of sodium ions, disrupting the balance of ion concentrations across the cell membrane (10). What follows is the accumulation of intracellular sodium which initiates a cascade of events leading to cellular edema, as water follows sodium into the cell. Excessive levels of intracellular calcium ions have toxic effects on mitochondrial function, further impairing ATP synthesis. Elevated calcium levels contribute to the generation of nitric oxide and the activation of proteases, which leads to an exacerbation of cellular injury. Abnormal ion fluxes also lead to neuronal depolarization, facilitating the release of neurotransmitters, including the excitatory neurotransmitter glutamate, which is also able to cause cellular damage. (17)

In response to cellular injury, inflammatory mediators such as interleukin-1β and tumor necrosis factor-α are released, initiating an inflammatory cascade. These mediators are promoters of microvascular thrombosis and compromise vascular integrity, supporting further cellular damage. (14)

Furthermore, certain inflammatory mediators can trigger apoptosis, a process of programmed cell death, leading to increased cellular death. Cerebral edema, a consequence of global ischemia, poses a significant threat to neurological function. The brain, limited within the skull, has restricted capacity to accommodate swelling. Consequently, cerebral edema leads to increased intracranial pressure and impairs cerebral perfusion, which leads further exacerbation of brain injuries. (14) Following successful resuscitation from cardiac arrest, a

notable number of individuals experience neurological limitations, ranging from brief cognitive impairments to long-term disabilities such as seizures and motor deficits.

In summary, the pathophysiology of cardiac arrest is characterized by multiple complex factors on cellular, inflammatory, and vascular level causing disturbances which result in widespread organ dysfunction. The brain, due to its high metabolic demands and vulnerability to ischemic injury, is particularly susceptible to the harmful effects of cardiac arrest. (15)

3. D I S C U S S I O N

3.1. Pharmacokinetics and Pharmacodynamics of Epinephrine

3.1.1. Pharmacokinetics

Epinephrine stands as the cornerstone of pharmacotherapy during cardiopulmonary resuscitation (CPR) and may be even considered as the most important drug applied in these situations.

After intravenous administration, epinephrine rapidly exits the bloodstream, facilitated by several primary clearance mechanisms. These processes are crucial for regulating epinephrine levels and reducing its effects once its therapeutic purpose has been fulfilled.

One key mechanism involves enzymatic metabolism. (20) The enzyme Monoamine oxidase (MAO), a significant player in this process, acts on epinephrine to break it down into inactive metabolites. Similarly, catechol-O-methyltransferase (COMT) also contributes to epinephrine metabolism, aiding in its transformation into metabolites that are less physiologically active.

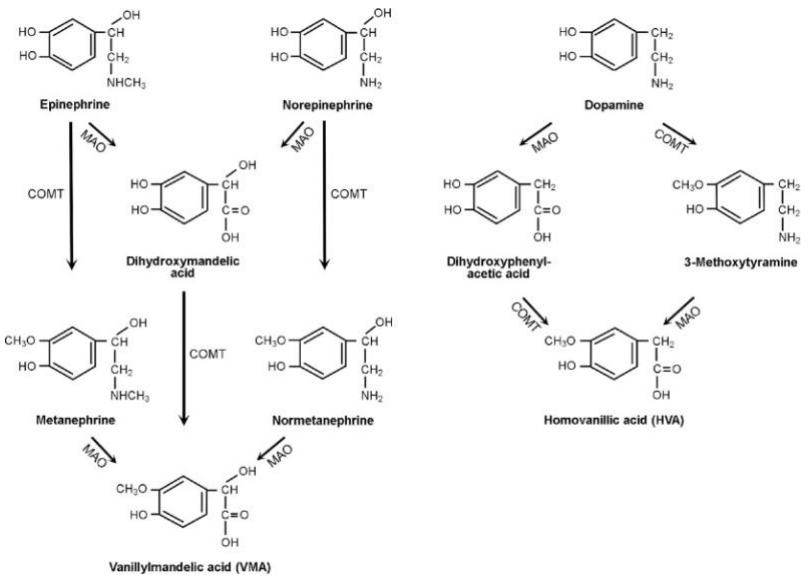

Figure 2. The breakdown of Epinephrine by the body: catecholamine metabolism (21)

Furthermore, epinephrine undergoes reuptake and recycling within the body. Adrenergic nerve terminals take up epinephrine, allowing for its reuse and recycling, in order to contribute to the efficient clearance of the drug from circulation. (21)

Additionally, a small portion of epinephrine remains unchanged and is excreted through the urinary tract, further facilitating its removal from the body.

These clearing mechanisms collaborate to ensure that epinephrine's effects are transient and that its presence in the bloodstream is regulated. This rapid clearance is essential for preventing accumulation which would lead to a prolonged or excessive stimulation of adrenergic receptors, which could lead to adverse effects or complications.

Clinical trial simulations have shed light on the relationship between intravenous (IV) dosing frequency and plasma levels of epinephrine during simulated CPR scenarios. Notably, findings reveal that a shorter dosing interval of 3 minutes provides a higher exposure to epinephrine, reflected in both area under the curve (AUC) and peak plasma concentration (Cmax), in contrast to a 5-minute dosing interval.

However, insights from a pilot study involving 8 patients unveil a nuanced aspect of epinephrine pharmacokinetics during cardiac arrest. The study indicates a prolonged elimination half-life of epinephrine, estimated at 2.6 minutes (with a range of 1.9 to 4.4 minutes). This observation suggests that the conventional practice of administering repeated doses of epinephrine every 3-5 minutes, as endorsed by guidelines, may result in the accumulation of epinephrine concentrations over time. (23)

In another study performed in 2016 by Bard E. Heradsveit and Geir Arne Sunde the pharmacokinetics of epinephrine during cardiac arrest were investigated. The focus was placed on the dynamics surrounding the administration of epinephrine during cardiac arrest resuscitation, shedding light on its pharmacokinetics and the potential connection for patient outcomes. (24)

The study discussed in the text focuses on shedding a light on the pharmacokinetic profile of epinephrine following a single dose administration during prehospital cardiac arrest treatment. By analyzing plasma concentrations of epinephrine over time, the research aimed to uncover patterns that could provide optimal dosing strategies and improve patient outcomes. Results from the study indicate that the elimination of epinephrine during cardiac arrest is prolonged, potentially leading to elevated plasma levels with repeated doses. This finding underlines the need for further investigation to determine the ideal plasma

concentration of epinephrine during resuscitation. (24) It highlights the broader implications of the study's findings, suggesting potential future treatment approaches based on the observed pharmacokinetic dynamics of epinephrine. For instance, it proposes the possibility of administering an initial bolus of epinephrine followed by a continuous infusion to maintain steady plasma levels, thereby possibly optimizing its therapeutic effects during prolonged resuscitation efforts.

However, the study was also struck by limitations, including the small sample size and the complexity of conducting research in a prehospital environment. Despite these challenges, the findings contribute valuable insights into the pharmacokinetics of epinephrine during cardiac arrest resuscitation and call for the need of larger-scale studies to validate and expand these observations.

3.1.2. Pharmacodynamics

Epinephrine, a vital pharmacological agent, operates as a potent regulator within the body, promoting a physiological response through its interaction with alpha and beta-adrenergic receptors. (25) This interaction is dependable, with epinephrine displaying varying affinities for these receptors depending on its concentration.

When engaging with alpha-1 receptors, epinephrine induces muscular contraction, leading to increased vascular tone, pupillary constriction, and intestinal sphincter tightening. Simultaneously, when binding to beta-1 receptors prompts positive chronotropic and inotropic effects, speeding up the heart rate and enhancing myocardial contractility, thus increasing cardiovascular performance. (26) Furthermore, beta-2 receptor activation by epinephrine facilitates bronchodilation and vasodilation in selected vascular beds, promoting improved oxygenation and blood flow distribution. (28) Beyond its cardiovascular effects, epinephrine modulates metabolic processes by inhibiting insulin secretion and promoting glycogenolysis, glucagon secretion and lipolysis. (27) This metabolic shift ensures the availability of essential energy substrates, such as glucose and fatty acids during periods of increased demand. In conclusion, epinephrine proves to be a flexible controller, coordinating numerous essential physiological reactions which are crucial for keeping the body in balance and reacting to stressful situations. Its detailed pharmacodynamic characteristics highlight its critical function in preparing the body for action and adjustment.

3.2. Paramedic 2 Study

3.2.1. The Study as a Broad Pilot Project

The clinical question which was the heart of this study revolves around determining whether the administration of epinephrine, as opposed to a placebo, enhances the chances of survival of adult patients who have suffered out-of-hospital cardiac arrest (OOHCA). (33)

Diving into the background of this investigation, it becomes clear that there exists a lack of clear evidence regarding the efficacy of drug interventions within the framework of Advanced Life Support (ALS) protocols. While epinephrine is believed to potentially offer beneficial effects by boosting aortic diastolic pressure and promoting coronary blood flow, concerns have also been raised regarding its adverse consequences. These include increased myocardial oxygen demand and the potential for platelet activation, which could precipitate thrombosis and compromise microvascular flow, potentially exacerbating cerebral ischemia.

Studies which has been conducted in the past were able to provide some pieces of evidence though those were still characterized by uncertainties, with conflicting reports emerging. A substantial observational study conducted in Japan indicated elevated rates of return of spontaneous circulation (ROSC) associated with epinephrine administration, although at the expense of poorer neurologic outcomes. (41)

This lack of knowledge prompted the International Liaison Committee on Resuscitation to advocate for a large-scale randomized controlled trial (RCT) to scrutinize the safety and efficacy of epinephrine in this context. (52)

Applying a randomized, double-blinded approach, treatment assignments were randomly generated using computer algorithms and allocated in a 1:1 ratio. To ensure uniformity, identical pre-prepared packs containing either 1mg epinephrine or 0.9% saline (placebo) were distributed to the participating ambulance services. An ethical approval was carefully sought and secured, while the funding was provided by the Health Technology Assessment Program of the National Institute of Health Research.

The trial's study size was wide, with a target sample size set at 8,000 participants. The determination of efficacy was based on a risk ratio for the epinephrine group, computed at 1.25 (95% CI 1.07 – 1.46), translating to a projected 30-day survival rate of 6% in the placebo arm and 7.5% in the epinephrine cohort. (29) This ratio was adjusted for various covariates,

including age, sex, interval between emergency call and ambulance arrival, initial rhythm and the circumstances surrounding the cardiac arrest event. (29)

The study was executed across five NHS ambulance services in the UK, with the trial taking place from December 2014 to October 2017. A Data Monitoring Committee (DMC) oversaw the proceedings, conducting interim reviews at three-month intervals to ensure the trial's integrity and monitor the process.

The study population was comprised on adult patients aged over 16 years who experienced out-of-hospital cardiac arrest (OHCA) and had received advanced life support (ALS) from trial-trained paramedics (30). Exclusion criteria included pregnancy, cardiac arrest caused by asthma or anaphylaxis, or prior administration of epinephrine before the arrival of trial-trained paramedics. Traumatic cardiac arrest cases were excluded in one ambulance service.

Out of 10,623 screened patients, 8,103 (76.3%) were deemed eligible, and trial packs were opened. However, during the process, additional information led to the exclusion of 87 patients, while 2 patients had unknown trial group assignments due to missing trial pack numbers. Ultimately, 8,014 patients were randomized, with 4,015 assigned to the epinephrine group and 3,999 to the control group. (29)

Both groups exhibited similar baseline characteristics, including age, gender distribution, initial cardiac rhythm, and the cause of cardiac arrest. The most common causes were medical conditions, with traumatic cases being relatively rare. Witnessing status and CPR administration by bystanders or paramedics were also comparable between the two groups.

Key time intervals between critical events, such as emergency call and ambulance arrival, and administration of trial agents were similar in both groups. The median interval between emergency call and ambulance arrival ranged from 6.6 to 6.7 minutes, while the mean interval between ambulance arrival and departure varied slightly between the epinephrine and placebo groups.

During the study the primary outcomes showed that there was no significant disparity between the epinephrine and placebo groups in terms of the proportion of patients who survived until hospital discharge with a favorable neurologic outcome. Specifically, among the patients administered epinephrine, 87 out of 4007 patients (2.2%) achieved this outcome, while in the placebo group, 74 out of 3994 patients (1.9%) did so. The unadjusted odds ratio stood at 1.18, with a 95% confidence interval ranging from 0.86 to 1.61. (30) Furthermore,

severe neurologic impairment, defined as a score of 4 or 5 on the modified Rankin scale, was more prevalent among survivors in the epinephrine group compared to those in the placebo group. (53) Specifically, 39 out of 126 patients (31.0%) in the epinephrine group experienced severe neurologic impairment, whereas only 16 out of 90 patients (17.8%) in the placebo group had such an outcome.

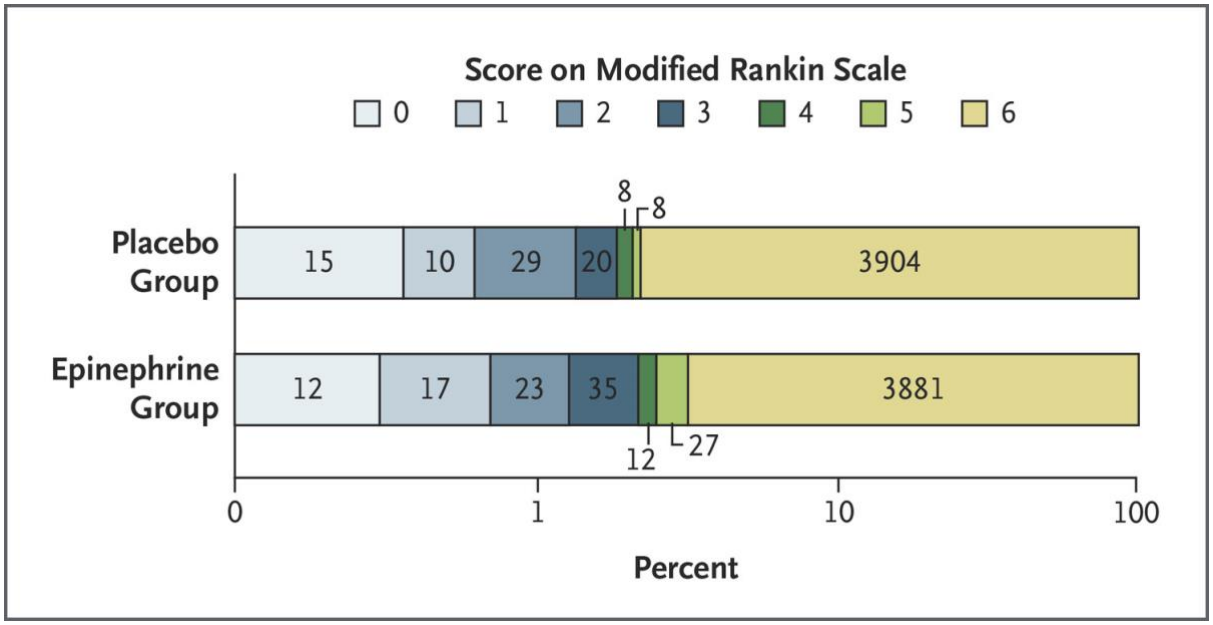

Figure 3. Scores achieved on the Rankin scale by epinephrine and placebo group (29)

Secondary outcomes, including survival rates at 3 months and neurologic outcomes at 3 months, exhibited no significant disparities between the two groups. Regarding survival with a favorable neurologic outcome at hospital discharge, the probabilities of the rate being at least 1 or 2 percentage points higher with epinephrine were 1.9% and 0%, respectively (29). Among patients admitted to the hospital screening for additional secondary outcomes showed that there were no significant disparities in the length of stay in the hospital or ICU between the two groups. Sensitivity analyses, encompassing best-case and worst-case scenarios and multiple imputation, corroborated the primary trial results. Furthermore, no additional serious adverse events were reported in either group (30).

A further point to criticize is that there was no standardized protocol on how the post-resuscitation care was delivered. It was stated that national guidelines were used, information about targeted temperature management, hemodynamic support and ventilation was not

provided. Also, neurological rehabilitation which was delivered and length of ICU stay were not taken into account.

In conclusion, the PARAMEDIC2 trial demonstrated that epinephrine significantly improved 30-day survival rates (10,5% versus 4,9%) compared to a placebo. Patients receiving epinephrine had higher rates of return of spontaneous circulation, increased frequency of hospital transport, and more intensive care unit (ICU) admissions.

Table 3. Primary and Secondary Outcomes.*

Outcome	Epinephrine	Placebo	Odds Ratio (95% CI)†	
			Unadjusted	Adjusted
Primary outcome				
Survival at 30 days — no./total no. (%)‡	130/4012 (3.2)	94/3995 (2.4)	1.39 (1.06–1.82)	1.47 (1.09–1.97)
Secondary outcomes				
Survival until hospital admission — no./total no. (%)§	947/3973 (23.8)	319/3982 (8.0)	3.59 (3.14–4.12)	3.83 (3.30–4.43)
Median length of stay in ICU (IQR) — days				
Patients who survived	7.5 (3.0–15.0)	7.0 (3.5–12.5)	NA	NA
Patients who died¶	2.0 (1.0–5.0)	3.0 (1.0–5.0)	NA	NA
Median length of hospital stay (IQR)				
Patients who survived	21.0 (10.0–41.0)	20.0 (9.0–38.0)	NA	NA
Patients who died‖	0	0	NA	NA
Survival until hospital discharge — no./total no. (%)	128/4009 (3.2)	91/3995 (2.3)	1.41 (1.08–1.86)	1.48 (1.10–2.00)
Favorable neurologic outcome at hospital discharge — no./total no. (%)	87/4007 (2.2)	74/3994 (1.9)	1.18 (0.86–1.61)	1.19 (0.85–1.68)
Survival at 3 mo — no./total no. (%)	121/4009 (3.0)	86/3991 (2.2)	1.41 (1.07–1.87)	1.47 (1.08–2.00)
Favorable neurologic outcome at 3 mo — no./total no. (%)	82/3986 (2.1)	63/3979 (1.6)	1.31 (0.94–1.82)	1.39 (0.97–2.01)

* ICU denotes intensive care unit, and NA not applicable.
† The odds ratio is for the epinephrine group as compared with the placebo group. Odds ratios were adjusted for patients' age, sex, interval between emergency call and ambulance arrival at scene, interval between ambulance arrival at scene and administration of the trial agent, initial cardiac rhythm, cause of cardiac arrest, whether the cardiac arrest was witnessed, and whether CPR was performed by a bystander.
‡ P=0.02 for the between-group comparison in the primary analysis.
§ Survival until hospital admission was defined as a sustained return of spontaneous circulation until admission and transfer of care to medical staff at the receiving hospital (also defined as "survived event").
¶ Among the patients who died, the length of stay in the ICU is for all the patients who were admitted to and died in the ICU.
‖ Among the patients who died, the length of stay in the hospital is for all the patients who died before hospital discharge.

Figure 4. Overview of Primary and secondary outcome of patients taking part in the paramedic2 study (29)

However, despite the slightly better survival rate, the trial did not find any evidence of a difference in the rate of survival with a favorable neurological outcome between the epinephrine and placebo groups. This was attributed to a higher proportion of patients in the epinephrine group surviving with severe neurological disability. (53)

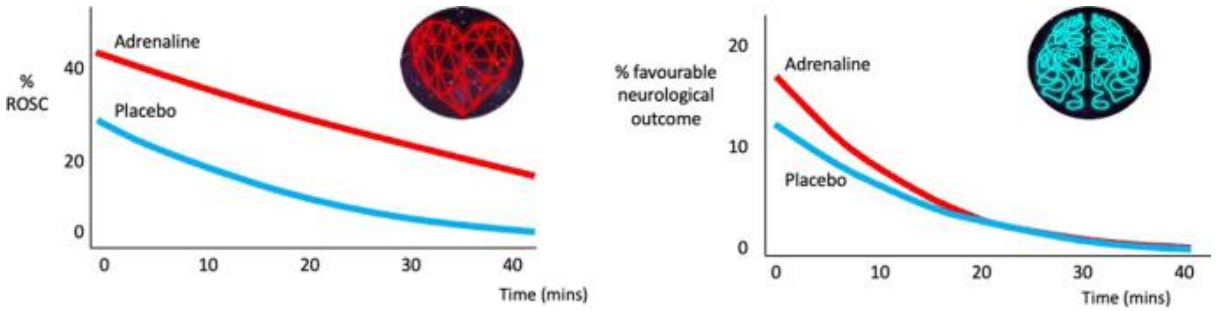

Figure 5. Comparison of placebo and epinephrine administration: Return of spontaneous circulation and favorabl neurological outcome. (29)

3.2.2. Critical Voices of the Paramedic 2 Study

In July 2019, a paper was published by E. ter Avest and H. Lameijer, they discussed the pros and cons of cardiac arrest treatment which was investigated in this study. In their opinion the focus had been put too much on the neurological outcome with the main point being that neurological recovery post-cardiac arrest depends on oxygen of microcirculatory cerebral blood flow. The main point of criticism was that all resuscitations had taken place in an out-of-hospital setting, in which the patients collapsed was in some cases not supervised and the first adrenaline bolus was administered after 21 minutes on average. (37) The possible no-flow time and delayed resuscitation efforts would have a far greater impact on the neurological outcome than the administration of adrenaline. (38) For their likeliness the focus should rather be placed on education of the public to be able to deliver bystander cardiopulmonary resuscitation and early defibrillation.

Other voices became loud commenting on the ethical dilemma that due to the time sensitive emergency situations, patients or their relatives were not able to give informed consent to be part of the study. This was seen as violation of patient autonomy and created a lack of transparency as well as emotional conflicts with families. (36) A written informed consent was obtained from the families, who also had the option to pull out of the trial, which had at that point of time already taken place. (35)

Another point was the withholding of standard care treatment, as the administration of epinephrine was delayed until the arrival at the hospital.

3.3. Epinephrine and Timing of Administration

Another question which came up while going through research and studies is the timing of epinephrine administration. (40) The study provided by Matthew Hansen and Robert H. Schmicker investigates the crucial role of early epinephrine administration in out-of-hospital cardiac arrest (OHCA) cases characterized by initial non-shockable rhythms. It emphasizes the prevalence of OHCA, affecting approximately 390,000 adults annually in North America alone. Drawing upon data from the Resuscitation Outcomes Consortium (ROC) research network, which spans 10 sites across North America, the study includes EMS-treated adult patients from June 4, 2011, to June 30, 2015, who presented with initial non-shockable rhythms. (41)A primary focus of analysis was the duration from EMS arrival to the initiation of epinephrine administration. The findings point out a compelling association: With each additional minute of delay in epinephrine administration, the odds of survival to hospital discharge decline. (39) Accounting for potential confounders, such as age, sex, witness status, initial rhythm, and others, revealed a 4% decrease in survival odds per minute of delay. Consequently, the study advocates for the prioritization of early epinephrine administration, positing its potential to enhance the likelihood of neurologically intact survival, particularly in cases of non-shockable rhythms. Despite the strength of its findings, the study confronts inherent limitations intrinsic to observational research, including potential residual confounding factors. Nonetheless, its implications reflect within the area of OHCA management, advocating for the swift initiation of epinephrine administration as a cornerstone of protocols, especially for adult patients exhibiting non-shockable rhythms such as pulseless electric activity (PEA) or asystole.

In another cohort study conducted between April 1^{sts} 2011 and June 30th 2015 it was investigated the impact of the timing of epinephrine administration on patient outcomes following out-of-hospital cardiac arrest (OHCA). (41) The study included data from 41,079 adults treated by emergency medical services (EMS) between April 1, 2011, and June 30, 2015. Among these individuals, 24.6% initially presented with shockable cardiac rhythms, while 75.4% had non-shockable rhythms. (41)

Of those with shockable rhythms, 81.5% received epinephrine, while 90.0% of those with non-shockable rhythms received it. The primary outcome measured was survival to hospital

discharge. (51) The analysis revealed that the timing of epinephrine administration significantly affected survival rates.

For patients with shockable rhythms, the risk ratio for survival to hospital discharge reached the best results between 0 and 5 minutes after EMS arrival, although this finding was not statistically significant. However, as a continuous variable, the RR for survival to hospital discharge decreased by 5.5% per minute after EMS arrival. (41)

Similarly, for patients with non-shockable rhythms, the risk ratio for the association of epinephrine administration with survival to hospital discharge was highest between 0 and 5 minutes after EMS arrival, with a decrease of 4.4% per minute after EMS arrival. (41)

In conclusion, this study also emphasizes the importance of timely epinephrine administration, as delayed administration was associated with lower survival rates for both shockable and non-shockable rhythms. These findings underline the critical role of prompt medical intervention in improving outcomes for OHCA patients. (42)

These theories are further supported by a study including numbers collected in Japan from 2011 to 2017, for which the Japanese government-led nationwide population-based registry data for out of hospital cardiac arrest who received intravenous epinephrine injections through EMS personnel was analyzed. (51) Descriptive statistics were used to summarize patient characteristics and group differences. The focus was laid on the outcomes associated with the timing of epinephrine administration which was categorized in either early (<20 minutes) or delayed (>20 minutes) and outcomes was examined using various statistical tests and multivariable logistic regression models, adjusting for factors like age, sex, CPR, and initial cardiac rhythm. (51)

During the study, 119,946 out-of-hospital cardiac arrest (OHCA) patients who received epinephrine from EMS personnel were identified. The median time to epinephrine administration was 23 minutes, with a mean of 24.4 minutes and an interquartile range (IQR) of 19 to 29 minutes. (43) The majority of patients (77,142, or 64.3%) received epinephrine more than 20 minutes after the emergency call. Additionally, most patients (75,627, or 63.1%) received multiple doses of epinephrine. (51)

After 1 month the neurological outcomes were examined by inpatient attending physician who categorized the patients according to the Glasgow-Pittsburgh cerebral performance category scores.

3.4. Potential Harm of Epinephrine Administration – The Correct Dosing

Due to the fact that in previous studies a worse neurological outcome has been linked to the application of epinephrine in cardiac arrest, the question of which harmful effects can be linked to it, especially in the long run. (38) Although epinephrine is widely known to improve return of spontaneous circulation (ROSC) after cardiac arrest, its effects on long-term outcomes remain uncertain, with potential harm during the post-resuscitation phase. In this secondary analysis, it was aimed to investigate the long-term effects of epinephrine use during cardiopulmonary resuscitation (CPR) by examining its association with neurological function three months post-cardiac arrest. (47)

The study utilized data collected by Iesu et al. (2018), comprising patients from Erasme Hospital, Brussels, Belgium, who experienced in-hospital or out-of-hospital cardiac arrest with a Glasgow Coma Scale (GCS) < 9 between January 2007 and December 2015.

The original study included patients treated with therapeutic hypothermia and collected data on demographics, comorbidities, first aid information, and clinical outcomes. Neurological function was assessed using the cerebral performance categories score (CPC) at three months post-arrest. (48)

Descriptive statistics and various tests were employed to analyze correlations between different factors and neurological status. Univariate analysis explored associations, while multivariate linear regression assessed the independent effect of epinephrine dose on neurological outcome, adjusting for covariates such as age, gender, and clinical variables.

Large observational studies and randomized clinical trials have failed to consistently demonstrate beneficial effects of epinephrine on neurological outcomes. (50)

Various confounding factors were adjusted, including baseline glucose, lactate, and comorbidities, to improve the accuracy of our analysis. Although patients with in-hospital cardiac arrest (IHCA) might receive more timely interventions, we could not detect and significant differences in outcomes between IHCA and out-of-hospital cardiac arrest (OHCA) patients, suggesting that factors beyond timing of treatment may influence outcomes. (49)

The introduction of induced hypothermia and integrated care plans has improved survival rates post-cardiac arrest, possibly mitigating the detrimental effects of epinephrine. However, the study did not find a significant association between therapeutic hypothermia and neurological outcomes at three months.

The results suggest that lower epinephrine doses may be associated with better neurological outcomes compared to higher doses, highlighting the need to reevaluate the standard 1-mg dose commonly used in CPR protocols. Additionally, prolonged resuscitation with repeated and increased doses of epinephrine may be detrimental to neurological function. (46)

Strengths of our study include analyzing patient-oriented outcomes and adjusting for potential confounders. However, as an observational study, it cannot establish causality, and there may be inherent biases such as resuscitation bias. Additionally, the study population was limited to comatose patients admitted after IHCA or OHCA, which may affect the generalizability. It was suggested that further studies need to be conducted to achieve meaningful results.

4. CONCLUSIONS

This narrative literature review, after careful consideration of the facts provided by the chosen studies and research, epinephrine is still proofed to be one of the most important tools used in cardiopulmonary resuscitation. Despite concerns regarding potential adverse neurological outcomes associated with its use, the primary objective remains achieving return of spontaneous circulation (ROSC), with neurological rehabilitation considered secondary.

The possibility of utilizing another vasopressor instead of epinephrine, unfortunately due to the lack of studies matching the criteria of actuality, no recent research points could be provided. Given the absence of alternative pharmacological agents capable of achieving comparable results with superior long-term neurological survival, epinephrine remains the preferred drug and should be administered without further delay during CPR.

To improve neurological outcome, not only further research is required, but also education of the broad public on how to perform basic life support should be on the agenda to keep the no flow time to the cerebrovascular system as short as possible, so the best possible outcome for patients can be achieved. Due to the sensitivity of the situation in CPR, studies remain entangled with an ethical debacle that is difficult to overcome. For now, there is still a place for epinephrine in cardiopulmonary resuscitation.

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