

REVIEW

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The effects of norepinephrine in shockable cardiac arrest, a scoping review

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Abstract

Background Out-of-hospital cardiac arrest is considered a major public health issue with an incidence of 67–170 per 100,000 inhabitants in Europe. Sufficient coronary perfusion pressure is a requisite for successful defibrillation and return of spontaneous circulation (ROSC). Although epinephrine (E) was found to increase ROSC and hospital survival when compared to placebo, its role in shockable arrest is under debate due to the absence of favorable neurological outcome.

Objective Norepinephrine (NE) increases coronary perfusion pressure and may be an alternative for epinephrine because of differences in affinity in alpha- and beta- adrenergic receptors.

Methods An extensive literature search was conducted in PreMedline, Medline, Embase and Cochrane electronic databases. All original studies (randomized controlled trials, experimental and observational studies, including case-reports) were included; guidelines, (editorial) reviews and commentaries were excluded, no date constraints were applied. Articles were included in the literature review if they described intra-arrest administration of norepinephrine and contained at least an abstract in English, French, or German.

Results A total of 3308 articles were screened after deduplication. Following initial title/ abstract screening, full-texts analysis was performed in $n=46$ studies. A total of 18 articles were included, consisting of 5 human and 13 animal studies. Norepinephrine appears to optimize macrocirculatory and myocardial hemodynamics, increased regional cerebral blood flow and might improve survival.

Conclusion Norepinephrine has shown several beneficial effects when administered during shockable cardiac arrest in animal studies, with similar signals suggested in human studies. Despite the limited evidence, norepinephrine appears to offer potential advantages over epinephrine in terms of multiple haemodynamic parameters and possible survival.

Keywords Scoping review, Cardiopulmonary resuscitation, Norepinephrine, Shockable cardiac arrest

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Introduction

Out-of-hospital cardiac arrest (OHCA) is considered a major public health issue with an incidence of 67–170 per 100.000 inhabitants in Europe [1]. With a survival rate under 10%, OHCA is currently ranked the third most common cause of death in Europe [1]. Two major sub-groups can be distinguished in cardiac arrest: shockable arrest - i.e. ventricular fibrillation and pulseless ventricular tachycardia and non-shockable arrest - i.e. pulseless electrical activity and asystole.

Sufficient coronary perfusion pressure is a requisite for successful defibrillation and return of spontaneous circulation (ROSC), particularly in the shockable arrest group [2]. Within the Advanced Life Support (ALS) guidelines, epinephrine (E) is therefore advocated every 3 to 5 min from the third shock block onwards [3]. In a mixed patient population, epinephrine was found to increase ROSC and hospital survival when compared to placebo [4, 5]. The role of epinephrine in shockable cardiac arrest is under debate [6–8], because of the absence of long-term favorable neurological outcome after its administration [5, 6, 9–11]. Furthermore, the β -adrenergic agonistic effect of epinephrine is particularly concerning as it can induce cardiac arrhythmias or recurrence of VF [3, 12, 13], increase myocardial oxygen demand, increase myocardial dysfunction after ROSC [14–16]. The α -1-adrenergic effects lead to constriction of cerebral microvasculature [4–6, 10] and activation of platelets through α -2 adrenergic effects [17].

Norepinephrine (NE), being the precursor of epinephrine, may be an alternative vasopressor. This compound could be more effective as a result of its greater α 1-receptor and less β -adrenergic affinity compared to epinephrine [18], without impeding coronary perfusion [19, 20].

This scoping review summarizes the available literature related to norepinephrine administration during shockable cardiac arrest.

Methods

A literature search was conducted in (Pre) Medline, Medline, Embase and the Cochrane electronic databases (central and reviews) on the 1st of June 2024, using a combination of free text and Medical Subject Headings (MeSH). The full search query is included in the online supplement A. The search strategy was reviewed and supervised by an experienced librarian (GF). This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR 2018) [21]. The search was updated in April 2025 before submission to screen for additional literature. Ethical approval is not applicable due to the methods of this study.

Eligibility criteria

The components of the PICOST search are summarized in Table 1. Population was defined as either animal or human trials with a shockable cardiac arrest (P) in which norepinephrine was administered *during* the arrest (I). No comparison was required (C) and all parameters (regarding arrest, vital signs, pharmacology or survival) were included (O). All original studies (randomized controlled trials, experimental and observational studies, including case-reports) were included; guidelines, (editorial) reviews and commentaries were excluded (S) no date constraints were applied (T). Articles were included in the literature review if they contained at least an abstract in English, French, or German. This multilingual approach allowed for a comprehensive screening of the literature while maintaining accessibility for the research team.

Study selection

Titles and abstracts were reviewed independently using Rayyan software application by two reviewers (SB, EB) who were blinded to each other’s decisions. Discrepancies after unblinding were discussed with a third researcher (LM) until consensus was reached. All eligible articles were retrieved and a full-text review was

Table 1 PICOST

Population	Cardiopulmonary arrest in humans or animals with ventricular fibrillation or pulseless ventricular tachycardia
Intervention	Administration of norepinephrine during cardiac arrest
Comparison	Not required
Outcomes	Any clinical outcome, such as (but not limited to): the resuscitation event (e.g. duration, return of spontaneous circulation), the clinical status (e.g. vital signs, hemodynamic endpoints, cardiac rhythm changes, laboratory results), survival (e.g. neurologic outcome, quality of life) as well as adverse effects and complications.
Study design	Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, before-and-after studies, cohort studies and case series) were eligible for inclusion. Unpublished studies (e.g. trial protocols) and narrative reviews were excluded. All languages were included as long as there was an English, German or French abstract
Timeframe	All dates
Literature search	1st of June 2024 Updated in April 2025

undertaken with the research team. Reference lists of included articles were screened for additional studies.

Collecting- and synthesizing data

No formal critical appraisal was undertaken according to the methodology of the included studies. A descriptive-analytical method was used to categorize findings, emphasizing patterns and contextual variability. Results are reported as *mean ± SD* or *median with interquartile range (IQR 25th – 75th percentile)*, depending on their distribution and original publication.

Results

The search strategy identified 3979 publications: 975 from (Pre) Medline, 2598 from Embase, and 406 from Cochrane databases. After removing duplicates ($n=671$), 3308 records remained for title and abstract screening. Articles were excluded if they did not focus on CPR ($n=1995$), if only post-resuscitation phase was analysed ($n=951$), if they did not study norepinephrine ($n=305$), or if they were published in a language other than those specified in the inclusion criteria ($n=11$). This process resulted in 46 articles for full-text review. Cross-reference checking added one additional study, see Fig. 1. An updated literature search prior to publication did not yield any new studies eligible for inclusion. Figure 2 shows the PRISMA flowchart of search and inclusion. Table 2 shows an overview of the included studies. A visual abstract of NE's effects in shockable cardiac arrest is shown in Fig. 1.

Study characteristics

The included articles published between 1961 and 2024, consisting of 5 human studies [22–26] and 13 animal studies [27–39]. Eight studies reported arrest outcomes (e.g. amount of spontaneous circulation, survival), while ten studies described intra-arrest vital signs or hemodynamic parameters. The majority of the studies ($N=15$) were randomized trials [24, 25, 27–39]. Two studies had a retrospective cohort design ($N=2$) [22, 26] and one was an observational case report [23].

The norepinephrine dosages used in the studies ranged from 10ug/kg to 11 mg intravenously. An overview of the dosing regimen for each study is provided in Tables 2 and 3. Two studies compared endobronchial administration of norepinephrine [31, 32]. One study used continuous administration of catecholamines (30ug/kg/min (nor)epinephrine intravenously) [30], all other studies described bolus administrations. Norepinephrine was compared with other vasoactive drugs in $n=16$ studies [24–39]. These drugs were: epinephrine, 1-(3,4-dihydroxyphenyl)-1,2-diaminoethane (DHPDAE) [38], methoxamine [30], sodium nitroprusside [28], isoprenaline [26] and placebo [34–36]. Table 3 shows an overview of the interventions and main findings per study.

Pharmacology

Three animal studies analyzed pharmacological aspects of norepinephrine administration [31, 32]. One study described a small sample size dose finding in pigs (1 mg vs. 3 mg IV) and found optimal dosing to be 1 mg intravenously (IV) [27].

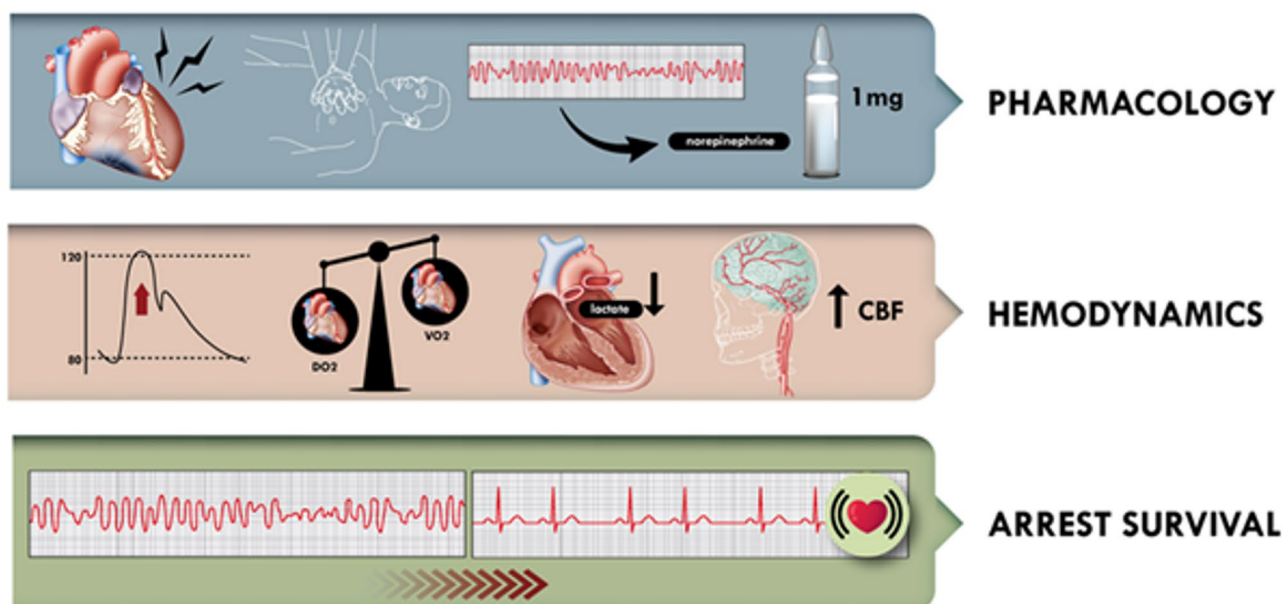


Fig. 1 Visual summary

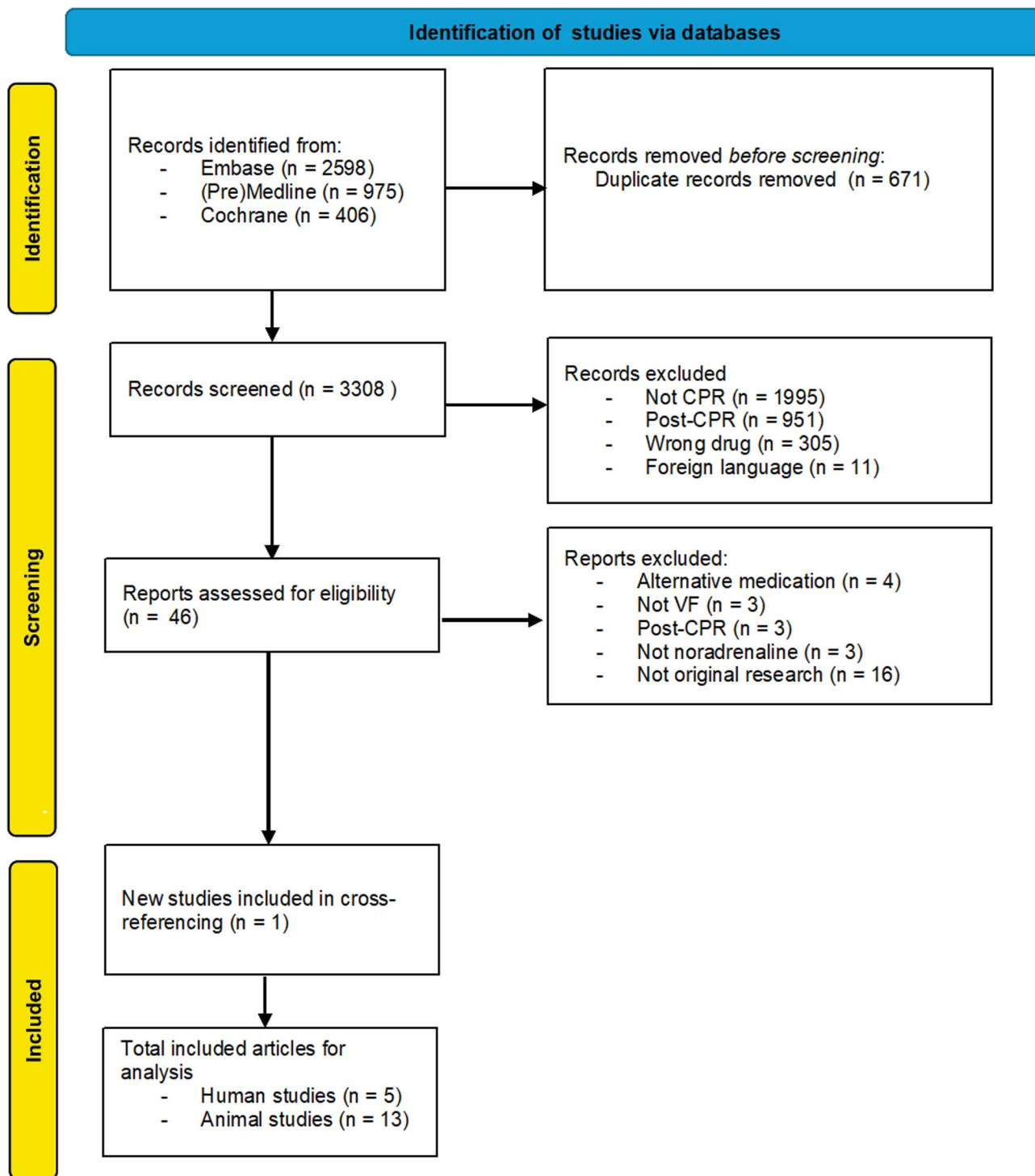


Fig. 2 PRISMA flowchart of search and inclusion

When comparing intravenous (IV) versus endobronchial (EB) administration of norepinephrine, peak plasma levels were reached more rapidly after IV administration [31]. Specifically, venous peak levels were 642 ng/mL at 3.5 min in the IV-group vs. 77 ng/mL at 5.5 min for EB administration. Similarly, arterial peak levels were

147 ng/mL at 4.2 min in the IV-group vs. 46 ng/mL at 6 min for EB administration. No difference was observed between intravenous and endobronchial administration of norepinephrine on hemodynamic parameters during cardiac arrest [32]. In a comparison dose effect study during cardiac arrest, 1 mg of norepinephrine resulted in

Table 2 Overview of included studies

First author, year	Country	Study design	Study intervention	Population	Outcome measures
Drumheller, 2021 [22]	USA	Retrospective case series	NE 1 mg IV/IO +/- REBOA	Human (n = 9)	DBP, ROSC
Mion, 2014 (23)	France	Case report	NE n/s	Human (n = 1)	ROSC
Callaham, 1992 [24]	USA	Randomized Controlled Trial	Standard Dose E (1 mg) IV vs. High dose E (15 mg) IV vs. high dose NE (11 mg) IV	Human (n = 816)	ROSC
Lindner, 1991 [25]	Germany	Randomized Trial	1 mg E IV vs. 1 mg NE IV	Human (n = 50)	ROSC
Hao-Hui, 1981 [26]	China	Retrospective cohort	Intra-cardiac injection versus no Intra-cardiac injection (1 mg E + 1 mg NE + 0,2–1 mg isoprenalin)	Human (n = 59)	ROSC
Jaeger, 2024 [27]	USA	Randomized trial	0,5 mg E IV 1,0 mg NE IV	Pigs (n = 19)	CPP, CePP
Zuercher, 2012 [28]	unknown	Randomized trial	45 ug/kg E IV 25 ug/kg NE IV 45 ug/kg E + 16,5 ug/kg sodium nitroprusside IV 16,5 ug/kg sodium nitroprusside IV	Pigs (n = 35)	ROSC
Lindberg, 2000 [29]	Sweden	Randomized trial	45 ug/kg E IV vs. 45 ug/kg NE IV	Pigs (n = 18)	EtCO ₂ , CPP, PBF
Von Planta, 1993 [30]	Switzerland	Randomized trial	300 ug/kg/min methoxamine IV vs. 30 ug/kg/min E IV vs. 30 ug/kg/min NE IV	Rats (n = 32)	60 min. survival, CPP, MAoP
Hörnchen, 1992 [31]	Germany	Randomized trial	10 ug/kg NE IV vs. 100 ug/kg NE EB	Porcs (n = 20)	Hemodynamics, plasma levels
Hörnchen, 1992 [32]	Germany	Randomized trial	10 ug/kg E IV 50 ug/kg E IV 100 ug/kg E EB 10 ug/kg NE IV 100 ug/kg NE EB	Porcs (n = n/a)	ROSC, SV, SVR
Brown, 1989 [33]	USA	Randomized Trial	80 ug/kg NE IV 120 ug/kg NE IV 160 ug/kg NE IV 200 ug/kg E IV	Pigs (n = 20)	CBF, ADP
Lindner, 1989 [36]	Germany	Randomized trial	Intervention 45 ug NE / 45 ug E / placebo	Animals (n = 21 pigs asphyxial arrest + n = 28 VF)	ROSC, MAP, MPAP, Cardiac Index
Lindner, 1989 [35]	Germany	Randomized trial	Intervention 45 ug NE / 45 ug E / placebo	Pigs (n = 21)	MDO ₂ , MVO ₂
Lindner, 1989 [34]	Germany	Randomized trial	Intervention 45 ug NE / 45 ug E / placebo	Pigs (n = 14)	CBF, Cerebral Oxygen Delivery
Hoekstra, 1989 [37]	USA	Randomized trial	200 ug/kg NE IV 200 ug/kg E IV	Pigs (n = 14)	MBF, CBF, MOER

Table 2 (continued)

First author, year	Country	Study design	Study intervention	Population	Outcome measures
Nejman, 1989 [38]	USA	Randomized trial	160 ug/kg NE IV 2,5 mg/kg DHPDAE IV	Pigs (n = 6)	CBF, MBF, Defibrillation success
Robinson, 1988 [39]	USA	Randomized trial	80 ug/kg NE IV 120 ug/kg NE IV 160 ug/kg NE IV 200 ug/kg E IV	Pigs (n = 20)	MBF, MOER, ADP, CPP

Human studies have a grey coloured background

Abbreviations: ADP: Aortic Diastolic Pressure, CBF: Cerebral Blood Flow, CPP: Coronary Perfusion Pressure, CePP: Cerebral Perfusion Pressure DBP: Diastolic Blood Pressure, EB: Endo Bronchial, etCO₂: End-Tidal CO₂, epi: epinephrin, IO: Intra Osseous, IV: Intra Venous, kg: kilograms, MAP: Mean Arterial Pressure, MAoP: Mean Aortic Pressure, MPAP: Mean Pulmonary Arterial Pressure, MDO₂: Myocardial Oxygen Delivery, MVO₂: Myocardial Oxygen Demand, MOER: Myocardial Oxygen Extraction Ratio, n/a: not applicable or not described in study, n/s: not specified, nor: norepinephrine, PBF: Pulmonary Blood Flow, ROSC: Return of Spontaneous Circulation, SV: Stroke Volume, SVR: Systemic Vascular Resistance, ug: micrograms, USA: United States of America, vs.: versus

higher Coronary Perfusion Pressure (CPP) as compared to 3 mg 14.1 mmHg and 9.3 mmHg respectively [27]. No level of statistical significance was provided in this study.

Hemodynamic parameters

Ten studies reported on hemodynamic parameters during cardiac arrest [22, 27, 29, 30, 34–39], including one human trial [22], see Tables 4 and 5. These studies primarily focused on macrocirculatory parameters ($n=8$) such as Mean Arterial Pressure (MAP) and Diastolic Blood Pressure (DBP) [22, 27, 29, 30, 35–38]. Several studies examined myocardial parameters ($n=4$), including myocardial blood flow (MBF), myocardial delivery of oxygen (MDO₂) and myocardial usage of oxygen (MVO₂) [35, 37–39]. Cerebrovascular parameters were assessed in five studies [27, 33, 34, 37, 38]. Tables 4 and 5 show an overview of the described hemodynamic parameters and norepinephrine effects.

Macrocirculatory parameters

Five studies (four animal [33, 37–39] and one human [22]) reported on DBP as a surrogate parameter for coronary perfusion pressure [22, 33, 37–39]. In animal studies, norepinephrine led to an increased DBP during CPR [33, 37–39], although these studies did not provide level of significance for baseline changes. DBP increased significantly after norepinephrine treatment in the human study, rising from 21.6 ± 8.3 to 26.1 ± 12.1 mmHg ($p < 0.025$) [22]. Statistically significant differences in mean DBP were observed between different NE dosages: a lower dose of 0.08 mg/kg resulted in a DBP of 22.4 ± 14.1 mmHg, while higher doses of 0.12 and 0.16 mg/kg yielded DBPs of 56.0 ± 8.6 mmHg and 47.6 ± 18.4 mmHg, respectively ($p = 0.07$) [33, 39].

Coronary Perfusion Pressure (CPP) was significantly higher in animals treated with norepinephrine at doses of 0.12 mg/kg ($48.4 (\pm 8.6)$ mmHg) and 0.16 mg/kg ($34.4 (\pm 18.8)$ mmHg) compared to those receiving 0.08 mg/kg

($18.8 (\pm 9.8)$ mmHg) ($p = 0.012$) [39]. Mean Arterial Pressure (MAP) was found to increase with norepinephrine treatment in several studies [27, 29, 34, 35]. However, none of the studies reported the level of significance for changes between baseline and intervention measurements with norepinephrine.

Myocardial hemodynamics

Four animal studies examined myocardial hemodynamic parameters [35, 37–39]. Administration of norepinephrine led to increased Myocardial Blood Flow (MBF) in all four studies [35, 37–39]. Additionally, norepinephrine resulted in higher myocardial delivery of Oxygen (MDO₂) and decreased myocardial oxygen usage (MVO₂) [35, 37]. There was also a decrease in the myocardial oxygen extraction rate compared to intra-arrest baseline values. Furthermore, myocardial lactate production decreased from 223 ± 240 mmol/min/100 g at baseline to 154 ± 218 mmol/min/100 g with the administration of norepinephrine [35].

Cerebral hemodynamics

Four animal studies reported on Cerebral Blood Flow (CBF) values during cardiac arrest following the administration of norepinephrine [33, 34, 37, 38]. All these studies observed an increase in CBF after norepinephrine administration compared to intra-arrest baseline values. One study found a statistically significant difference in cerebral blood flow between a lower dose of 0.08 mg/kg norepinephrine and higher doses of 0.12 mg/kg or 0.16 mg/kg across multiple brain regions [33]. The same study demonstrated that with the administration of norepinephrine, blood flow to the cervical spinal cord, cerebellum and pons reached levels comparable to those during normal sinus rhythm in spontaneous circulation [33].

Table 3 Overview of interventions and main findings

First author, year (ref)	Norepinephrine dose / route of administration	Comparison	Main findings / conclusions
Drumheller, 2021 [22]	1 mg IV/IO	+/- REBOA	a) Mean DBP 26,1 mmHg after norepinephrine administration b) 4/24 reached DBP > 40mmHg c) REBOA not beneficial
Mion, 2014 [23]	1 mg IV	n/a	Case report, describes gaining ROSC in prolonged cardiac arrest after switch from E to NE
Callaham, 1992 [24]	11 mg IV	- Standard Dose E (SDE)(1 mg) IV - High dose E (HDE) (15 mg) IV	a) Comparable ROSC-rates in all groups. b) Better survival in NE-group (not significant) c) less ventricular arrhythmia in the NE-group compared to HDE-group (not significant). This was not described for SDE
Lindner, 1991 [25]	1 mg IV	1 mg E IV	a) more successful resuscitation in the NE-group (14/25 vs. 6/25) in the E-group b) recurrent VF was seen more frequent in the E-group (14/25) versus the NE-group (5/25) c) higher successful resuscitation rates in the prolonged CPR-group (NE: 16/25, E: 8/25) d) shorter duration of resuscitation in favor of NE e) less need for anti-arrhythmic drugs in NE group compared to E (0/25 vs. 6/25).
Hao-Hui, 1981 [26]	1 mg E + 1 mg nor + 0,2–1 mg isoprenaline (intra-cardiac)	No intervention	n/a
Jaeger, 2024 [27]	1 mg IV	0,5 mg E	no statistically significant differences in CPP/MAP, carotid blood flow or coronary perfusion pressure
Zuercher, 2012 [28]	25 ug/kg IV	- 45 ug/kg E IV - 45 ug/kg E + 16,5 ug/kg sodium nitroprusside IV - 16,5 ug/kg sodium nitroprusside IV	No differences between vaso-active drugs in relation to ROSC
Lindberg, 2000 [29]	45 ug/kg IV	45 ug/kg E IV	No differences were found between norepinephrine and epinephrine
Von Planta, 1993 [30]	30 ug/kg/min IV	- 300 ug/kg/min methoxamine IV - 30 ug/kg/min E IV	a) 100% survival in NE group versus 50% survival in E-group b) Mortality in E-group due to profound hypotension and ventricular tachy-arrhythmia refractory to defibrillation
Hörnchen, 1992 [31]	10 ug/kg IV	100 ug/kg NE EB	Depot-effect with lower plasma concentrations and a later peak concentration in EB-group
Hörnchen, 1992 [32]	10 ug/kg IV 100 ug/kg nor EB	- 10 ug/kg E IV - 50 ug/kg E IV - 100 ug/kg E EB	a) 100% survival in the E-10iv-group b) 100% survival in the E-100eb-group c) 80% survival in the NE-10iv-group, d) 60% survival in the NE-100eb-group e) 50% survival in the control group f) tachycardia and progressive myocardial failure in the high-dose epinephrine group and smaller stroke volumes due to high systemic vascular resistance in the NE-groups
Brown, 1989 [33]	80 ug/kg IV 120 ug/kg IV 160 ug/kg IV	200 ug/kg E IV	a) Statistically significant increase in aortic diastolic pressure in animals receiving 120ug/kg, 160ug/kg NE or 200ug/kg E b) Higher blood flow in regions of the brain was seen in the NE 120ug/kg and 160ug/kg compared with the epinephrine group. c) Flow in the cerebellum, pons and cervical spinal cord were on average > 48mL/min/100 g in NE-groups (comparable to normal sinus rhythm in spontaneous circulation).
Lindner, 1989 [34]	45 ug IV	- 45 ug E IV - Placebo	a) comparable increase in cerebral blood flow after administration of NE and E, compared with saline. b) No differences were found between the catecholamines.
Lindner, 1989 [35]	45 ug IV	- 45 ug E - Placebo	a) similar increase in myocardial blood flow and a comparable increase in MVO2. b) E compromises myocardial metabolism more than NE. Because of higher lactate and less optimal MDO2/MVO2-ratios compared with NE. c) survival of cardiac arrest was 3/7 in the control group and E-group versus 7/7 in NE-group ($p < 0,05$). d) 6/7 animals in E-group required a second dose of medication and 2/7 in the NE-group. e) After epinephrine 4/7 animals developed resistant VF, 0/7 did in the NE-group

Table 3 (continued)

First author, year (ref)	Norepinephrine dose / route of administration	Comparison	Main findings / conclusions
Lindner, 1989 [36]	45 ug IV	- 45 ug E IV - Placebo	a) NE-group regained ROSC in a statistically significant shorter time (100 s NE vs. 700 s E, $p < 0,05$). b) Mean heart rate (HR) was higher in the E-group compared to NE c) higher cardiac index and DO ₂ -index in the NE-group than in the E-group.
Hoekstra, 1989 [37]	200 ug/kg IV	200 ug/kg E IV	a) no difference in CBF or measured pressures b) MDO ₂ , MVO ₂ and MBF was statistically significant higher in the NE-group compared to E-group. c) higher survival rate in E-treated groups (not significant)
Nejman, 1989 [38]	160 ug/kg IV	2,5 mg/kg DHP-DAE IV	(a) Cerebral blood flow increased up to 50 ml/min/100 g in pons and midbrain (b) MBF increased to 100,7 mL/min, c) MDO ₂ increased to 14,9 mL/min/100 g
Robinson, 1988 [39]	80 ug/kg IV 120 ug/kg IV 160 ug/kg IV	200 ug/kg E IV	a) Similar increase in aortic diastolic pressure and other measured pressures. b) NE increased myocardial blood flow and MDO ₂ more than E (n.s.)

Human studies have a grey coloured background

Abbreviations: ADP: Aortic Diastolic Pressure, CBF: Cerebral Blood Flow CPP: Coronary Perfusion Pressure, CePP: Cerebral Perfusion Pressure DBP: Diastolic Blood Pressure, EB: Endo Bronchial, etCO₂: End-Tidal CO₂, E: epinephrin, IO: Intra Osseous, IV: Intra Venous, kg: kilograms, MAP: Mean Arterial Pressure, MAoP: Mean Aortic Pressure, MPAP: Mean Pulmonary Arterial Pressure, MDO₂: Myocardial Oxygen Delivery, MVO₂: Myocardial Oxygen Demand, MOER: Myocardial Oxygen Extraction Ratio, n/a: not applicable, NE: norepinephrine, PBF: Pulmonary Blood Flow, ROSC: Return of Spontaneous Circulation, SV: Stroke Volume, SVR: Systemic Vascular Resistance, ug: micrograms, USA: United States of America, vs.: versus

Survival and re-arrest parameters

Ten animal [27–30, 32, 35–39] and two human studies [24, 25] reported on survival and/or re-arrest parameters. Two of these animal studies were placebo-controlled comparing norepinephrine with placebo [35, 36]. Both studies found higher survival rates in the norepinephrine treatment groups: one reported 3/7 survivors in the placebo-group versus 7/7 norepinephrine group ($p < 0.05$) [35] and the other reported 0/7 survivors in the placebo-group versus 7/7 in the norepinephrine group [36]. Tables 6 and 7 show an overview of ROSC- and re-arrest rates.

Re-arrest was reported in six studies [24, 25, 30, 36, 37, 39], including two human trials [24, 25]. Four of these studies found fewer re-arrest in the norepinephrine treatment groups [24, 25, 30, 36]. One study observed more re-arrests in the norepinephrine group [37]. Another study found that higher dosages of norepinephrine were associated with increased re-arrest rates: no re-arrest occurred in the 0.08 mg/kg group (0/5), while there were 2/5 re-arrest in the 0.12 mg/kg group and 3/5 re-arrests in the 0.16 mg/kg group [39].

Table 8 shows an overview of the distribution of included studies in relation to cardiac arrest parameters and the effects of norepinephrine or other vasopressors.

Discussion

This scoping review summarizes the findings of available research on norepinephrine administration during shockable cardiac arrest.

Pharmacology

This review highlights a significant gap in the pharmacological understanding of norepinephrine in cardiac arrest. Only two studies explored pharmacological aspects of norepinephrine administration in cardiac arrest, focusing on endobronchial administration; a route that is no longer common practice or advised. While these studies provide some insights, their relevance to current clinical practice is limited. Current resuscitation guidelines emphasizes either intra-venous or intra-osseus administration. Recent evidence suggest that IV drug administration should be preferred above intra-osseus drug administration [40, 41].

A critical limitation in existing research is the lack of studies comparing equipotent doses of norepinephrine and epinephrine. This oversight complicates the interpretation of their comparative efficacy and safety profiles. Some recent data in patients with shock indicate that norepinephrine and epinephrine may exert equipotent effects at approximately 1 mg when administered intra-venously [42, 43]. While preliminary, such observations could be relevant for the design of future studies.

Hemodynamic parameters

Norepinephrine has been shown to optimize microcirculatory- and myocardial parameters. Recent studies have highlighted the importance of optimizing these hemodynamic parameters to enhance CPP, which is directly related to ROSC rates [44, 45] and underscores the critical role of achieving optimal hemodynamic parameters to improve ROSC chances.

In studies comparing norepinephrine with epinephrine, favorable hemodynamic parameters were observed in the

Table 4 Cardiovascular hemodynamics

Parameter	Author, year (ref)	Epinephrine		Norepinephrine					
		Baseline intra-arrest	After drug dosing	Baseline intra-arrest	After drug dosing				
CPP (mmHg)	Jaeger, 2024 [27]	n/a	22,8 (9,1 ; 30,5)	n/a	25,3 (8,2 ; 26,1)				
	Lindberg, 2000 [29]	10 (± 2)	45 (± 5)	11 (± 1)	38 (± 5)				
	Von Planta, 1993 [30]	19 (± 1)	49 (± 5)	30 (± 2)	50 (± 7)				
	Robinson, 1988 [39]	9,2 (± 12,4)	42,6 (± 5,3)	NE 0,08 4,2 (± 6,5)	NE 0,12 9,2 (± 5,2)	NE 0,16 9,2 (± 12,4)	NE 0,80 18,8 (± 9,8)	NE 0,12 48,4 (± 8,6)	NE 0,16 34,4 (± 18,8)
MAP (mmHg)	Lindner, 1989 [36]	12 (± 4)	32 (± 8)	12 (± 4)	30 (± 6)				
	Hoekstra, 1989 [37]	6,1 (± 11,4)	40,0 (± 6,3)	6,8 (± 9,1)	25,9 (± 13,5)				
	Nejman, 1989 [38]	n/a	n/a	4,6 (± 9,9)	34,4 (± 18,8)				
	Jaeger, 2024 [27]	42,9 (31,2 ; 57,0)	49,9 (48,0 ; 69,5)	38,6 (30,3 ; 45,4)	50,8 (46,6 ; 64,2)				
DBP (mmHg)	Lindberg, 2000 [29]	39 (± 2)	69 (± 11)	35 (± 1)	63 (± 5)				
	Von Planta, 1993 [30]	34 (± 2)	63 (± 6)	30 (± 2)	61 (± 6)				
	Lindner, 1989 [34]	30,0 (± 1)	45,0 (± 7,5)	30,0 (± 1)	45,0 (± 7,5)				
	Lindner, 1989 [35]	30 (± 5)	48 (± 10)	30 (± 7)	48 (± 11)				
MBF (mL/min/100g)	Drumheller, 2021 [22]	n/a	n/a	21,6 (± 8,3)	26,1 (± 12,1)#				
	Robinson, 1988 [39]	12,4 (± 12,7)	48,6 (± 4,2)	NE 0,08 10 (± 9,1)	NE 0,12 15,6 (± 8,9)	NE 0,18 12,4 (± 12,7)	NE 0,08 22,4 (± 14,1) ¶	NE 0,12 56,0 (± 8,6)	NE 0,16 47,6 (± 18,4)
	Brown, 1989 [33]	12,4 (± 12,7)	48,6 (± 4,2)	NE 0,08 10,9 (± 9,1)	NE 0,12 15,6 (± 8,9)	NE 0,16 10,2 (± 7,7)	NE 0,08 22,4 (± 14,1) ¶	NE 0,12 56,0 (± 8,6)	NE 0,16 47,6 (18,4)
	Hoekstra, 1989 [37]	8,9 (± 12,0)	45,9 (± 5,8)	11,2 (± 8,4)	35,3 (± 15,2)				
MDO2 (mL/min/100g)	Nejman, 1989 [38]	n/a	n/a	10 (± 8)	48 (± 18)				
	Robinson, 1989 [39]	5,2 (± 3,4)	69,1 (± 53,1)	NE 0,08 3,1 (± 2,1)	NE 0,12 11,7 (± 12,0)	NE 0,16 5,1 (± 3,0)	NE 0,08 35,5 (± 39,0) ¶	NE 0,12 94,5 (± 15,4)	NE 0,16 100,7 (± 77,3)
	Lindner, 1989 [35]	71 (± 10)	126 (± 18)	74 (± 11)	107 (± 30)				
	Hoekstra, 1989 [37]	5,1 (± 3,0)	62,2 (± 45,3)	3,0 (± 2,5)	118,9 (± 73,1)*				
MVO2 (mL/min/100g)	Nejman, 1989 [38]	n/a	n/a	5,1 (± 3,0)	100,7 (± 77,3)				
	Robinson, 1989 [39]	0,8 (± 0,6)	10,5 (± 7,4)	NE 0,08 0,5 (± 0,4)	NE 0,12 2,0 (± 1,9)	NE 0,16 0,8 (± 0,6)	NE 0,08 5,4 (± 5,7) ¶	NE 0,12 16,7 (± 3,2)	NE 0,16 14,8 (± 9,6)
	Lindner, 1989 [35]	9,6 (± 1,7)	17,1 (± 3,2)	9,4 (± 1,8)	13,6 (± 4,2)				
	Hoekstra, 1989 [37]	0,8 (± 0,6)	9,4 (± 6,3)	0,5 (± 0,4)	19,9 (± 13,4)				
MVO2 (mL/min/100g)	Nejman, 1989 [38]	n/a	n/a	0,8 (± 0,6)	14,9 (9,6)				
	Robinson, 1989 [39]	0,8 (± 0,5)	7,6 (± 4,3)	NE 0,08 0,5 (± 0,3)	NE 0,12 1,7 (± 1,7)	NE 0,16 0,7 (± 0,5)	NE 0,08 4,8 (± 5,0) ¶	NE 0,12 11,5 (± 2,7)	NE 0,16 9,1 (± 4,2)
	Lindner, 1989 [35]	4,0 (± 1,5)	9,4 (± 3,0)	4,2 (± 0,8)	5,1 (± 3,0)				
	Hoekstra, 1989, [37]	0,7 (± 0,5)	7,0 (± 3,8)	0,4 (± 0,4)	14,2 (± 7,7)				
MVO2 (mL/min/100g)	Nejman, 1989 [38]	n/a	n/a	0,7 (± 0,5)	9,1 (± 4,2)				

Table 4 (continued)

Parameter	Author, year (ref)	Epinephrine		Norepinephrine					
		Baseline intra-arrest	After drug dosing	Baseline intra-arrest			After drug dosing		
MER (%)	Robinson, 1989 [39]	96,9 (± 3,3)	76,7 (± 11,0)	NE	NE	NE	NE	NE	NE
				0.08	0.12	0.16	0.08	0.12	0.16
				91,8 (± 10,7)	89,8 (± 4,9)	89,2 (± 7,3)	92,2 (± 3,4) ¶	69,4 (± 15,1)	65,2 (± 20)
	Lindner, 1989 [35]	42,9 (± 14,1)	51,5 (± 13,0)	46,3 (± 5,0)			37,3 (± 9,8)		
	Hoekstra, 1989 [37]	96,2 (± 2,5)	78,2 (± 13,0)	91,0 (± 6,6)			77,0 (± 13,4)		
Myocardial Lactate (mmol/min/100a)	Nejman, 1989 [38]	n/a	n/a	89,2 (± 7,3)			65,2 (20,0)		
	Lindner, 1989 [35]	285 (± 180)	523 (± 198)	223 (± 240)			154 (± 218) *		

Values listed as median (min; max) or mean ($\pm$ 1SD) Abbreviations: n/a: not applicable, not studied nor described in paper. * statistically significant between E and NE. # statistically significant between baseline and intervention. † statistically significant between lower and higher dose regimen. See text for *p*-values. Human studies have a grey coloured background

Table 5 Cerebral perfusion

Region of flow	Author, year (ref)	Epinephrine		Norepinephrine					
		Baseline intra-arrest	After drug	Baseline intra-arrest			After drug		
Left cortical (mL/min/100g)	Lindner, 1989 [34]	23 (± 5)	62(± 23)	21 (± 17)			57 (± 18)		
	Brown, 1989 [33]	0,8 (± 0,6)	11,1 (± 5,3)	NE 0.08	NE 0.12	NE 0.16	NE	NE	NE
				0,5 (± 0,5)	1,6 (± 1,9)	1,5 (± 1,4)	0.08	0.12	0.16
							4,9 (± 3,8)¶	12,2 (± 1,6)	23,4 (± 24,8)
Right cortical (mL/min/100g)	Hoekstra, 1989 [37]	1,0 (± 0,9)	10,5 (± 4,4)	1,1 (± 1,6)			17,3 (± 16,9)		
	Nejman, 1989 [38]	n/a	n/a	1,5 (± 1,4)			23,5 (± 25,1)		
	Lindner, 1989 [34]	23 (± 5)	68 (± 27)	21 (± 17)			55 (± 21)		
	Brown, 1989 [33]	0,9 (0,6)	10,3 (± 4,6)	NE 0.08	NE 0.12	NE 0.16	NE	NE	NE
0,4 (± 0,4)				1,7 (± 1,6)	2,2 (± 1,4)	0.08	0.12	0.16	
						3,7 (± 3,0)	13,5 (± 1,4)	23,7 (± 24,5)	
Cerebellum (mL/min/100g)	Hoekstra, 1989 [37]	1,1 (± 1,0)	10,2 (± 3,8)	1,1 (± 1,9)			16,8 (± 14,6)		
	Nejman, 1989 [38]	n/a	n/a	2,2 (± 1,4)			23,7 (± 24,5)		
	Lindner, 1989 [34]	39 (± 14)	60 (± 28)	34 (± 21)			68 (± 25)		
	Brown, 1989 [33]	2,0 (± 1,0)	25,9 (± 10,3)	NE 0.08	NE 0.12	NE 0.16	NE	NE	NE
0,8 (± 0,8)				2,8 (± 2,9)	3,4 (± 1,2)	0.08	0.12	0.16	
						10,7 (± 4,2)	35,1 (± 8,0)	50,5 (± 39,9)	
Medulla (mL/min/100g)	Hoekstra, 1989 [37]	2,5 (± 2,2)	23,6 (± 9,4)	2,1 (± 2,9)			37,3 (± 28,8)		
	Nejman, 1989 [38]	n/a	n/a	3,4 (± 1,2)			50,5 (± 39,9)		
	Lindner, 1989 [34]	29 (± 10)	56 (± 13)	32 (± 16)			55 (± 18)		
	Brown, 1989 [33]	4,1 (± 2,0)	58,7 (± 23,7)	NE 0.08	NE 0.12	NE 0.16	NE	NE	NE
2,7 (± 2,3)				6,8 (± 8,6)	6,9 (± 2,6)	0.08	0.12	0.16	
						22,4 (± 16,4)¶	67,9 (± 13,1)	71,4 (± 35,4)	
Midbrain (mL/min/100g)	Hoekstra, 1989 [37]	5,4 (± 4,4)	53,3 (± 21,5)	3,9 (± 4,6)			58,9 (± 32,1)		
	Nejman, 1989 [38]	n/a	n/a	6,9 (± 2,6)			71,4 (± 35,4)		
	Brown, 1989 [33]	0,8 (± 0,9)	21,9 (± 15,7)	NE 0.08	NE 0.12	NE 0.16	NE	NE	NE
				0,8 (± 0,9)	2,2 (± 2,2)	4,0 (± 2,0)	0.08	0.12	0.16
						8,8 (± 6,6) ¶	35,1 (± 4,6)	48,9 (± 34,1)	
	Hoekstra, 1989 [37]	1,4 (± 1,9)	24,2 (± 14,0))	2,2 (± 3,8)			37,7 (± 26,0)		
	Nejman, 1989 [38]	n/a	n/a	4,2 (± 2,0)			48,9 (± 34,0)		

Values listed as median (min; max) or mean ($\pm$ 1SD) Abbreviations: n/a: not applicable, not studied nor described in paper. * statistically significant between E and NE. # statistically significant between baseline and intervention. ¶ statistically significant between lower and higher dose regimen. See text for *p*-values

Table 6 ROSC rates

Author, year (ref)	E		NE		
Drumheller, 2021 [22]	n/a		3/8 (37,5%)		
Lindner, 1991 [25]	8/25 (32%)		16/25 (64%)		
Callaham, 1992 [24]	1 mg	10 mg	27/260 (10%)		
	21/270 (8%)	30/286 (10%)			
Jaeger, 2024 [27]	1/9 (11,1%)		2/10 (20%)		
Von Planta, 1993 [30]	4/8 (50%)		5/8 (62,5%)		
Robinson, 1989 [39]	4/5 (80%)		NE 0.08	NE 0.12	NE 0.16
			2/5 (40%)	5/5 (100%)	5/5 (100%)
Lindner, 1989 [35]	3/7 (42,9%)		7/7 (100%)*		
Lindner, 1989 [36]	6/7 (85,7%)		7/7 (100%)		
Hoekstra, 1989 [37]	6/7 (85,7%)		4/7 (57,1%)		
Nejman, 1989 [38]	n/a		5/5 (100%)		

Abbreviations: n/a: not applicable, not studied nor described in paper. * statistically significant between E and NE. See text for *p*-values. Human studies have a grey coloured background

Table 7 Rates of re-arrest between E and NE

Author, year (ref)	E		NE		
Lindner, 1991 [25]	14/25 (56%)		5/25 (20%)		
Callaham, 1992 [24]	1 mg	10 mg	253/260 (97,4%)		
	281/286 (98,3%)	267/270 (98,8%)			
Von Planta, 1993 [30]	4/8 (50%)		0/5 (0%)		
Robinson, 1989 [39]	n/a		NE 0.08	NE 0.12	NE 0.16
			0/5 (0%)	2/5 (40%)	3/5 (60%)
Lindner, 1989 [35]	4/7 (57,1%)		0/7 (0%)		
Hoekstra, 1989 [37]	0/7 (0%)		2/7 (28,6%)		

Abbreviations: n/a: not applicable, not studied nor described in paper

* statistically significant between E and NE. See text for *p*-values. Human studies have a grey coloured background

Table 8 Overview of distribution of studies

Parameter	Favoring NE #	NSFNE	ND	NSFO	Favoring other vasopressor#
CPP		27, 38	39*, 29, 36, 30		37
DBP		38	33, 39*	37	
MAP		27	29, 34, 35, 30		
MBF	37, 38	39*	35		
MDO2	37, 38	39*	35		
MVO2	37, 38	39*, 35			
MER	38	35	37, 39		
Myocardial lactate	35				
Cerebral blood flow	38	37, 33	34		
ROSC	35, 38	25, 36, 39*, 24	28	37, 30	
Re-arrest		25, 27, 35, 24	30	37	

Abbreviations: NE = norepinephrine, NSFNE: not significant favoring norepinephrine, ND = no difference, NSFO = not significant favoring other vasopressor, * = dose dependent, # = statistically significant. CPP = Coronary Perfusion Pressure, DBP = Diastolic Blood Pressure, MAP = Mean Arterial Pressure, MBF = Myocardial Blood Flow, MDO2 = Myocardial Delivery of Oxygen, MVO2 = Myocardial Oxygen Demand, MER = Myocardial Extraction Rate, ROSC = Return of Spontaneous Circulation. Human studies have a grey coloured background

norepinephrine treated groups. Notably, norepinephrine demonstrated potential beneficial effects over epinephrine and other catecholamines, particularly in terms of myocardial hemodynamics. These findings suggest that epinephrine might compromise myocardial metabolism more than norepinephrine during cardiac arrest.

Although none of the included studies directly assessed neurological outcomes, parallels can be drawn from the myocardial perspective. Optimizing cerebral hemodynamic values may have a positive impact on neurological outcomes post-cardiac arrest. Several studies suggest that norepinephrine administration results in improved blood flow in various brain regions [33, 34, 37, 38]. In studies comparing norepinephrine with epinephrine, more optimal cerebral hemodynamic parameters were observed in favor of norepinephrine. This aligns with recent findings, indicating that epinephrine administration does not improve neurological outcomes in cardiac arrest [5, 9]. This interpretation is further supported by *Oghifobibi et al.*, who found that epinephrine administration negatively affects cerebral microcirculatory conditions [46]. This may be due to the greater affinity for the α -2 adrenergic receptor of epinephrine compared to norepinephrine, which causes platelet activation and thereby may impair cerebral perfusion [11, 46–48].

Survival and re-arrest

The data in this review suggests that norepinephrine administration may improve ROSC-rates and survival in shockable cardiac arrest. However, the evidence comparing survival benefits between norepinephrine and epinephrine in cardiac arrest scenarios is mixed. One study favoured epinephrine [37], while the others reported equivalent results [24, 28, 29, 32, 36] or better outcomes in norepinephrine treated groups [25, 30, 35, 39]. It is important to note that these differences did not reach statistical significance, except one [35]. This is likely influenced by small sample sizes and varied dose regimens across studies.

A recent systematic review demonstrated that catecholamines remain effective in cardiac arrest, leading to increased ROSC rates and survival to hospital discharge [49]. However, this review did not consider norepinephrine, which may underrate its potential value. The broad dose regimens used in this review hinder aggregation of effects. High-dose regimens have largely been abandoned and current doses used in daily practice have shown at least similar rates of successful resuscitation in ventricular fibrillation [49, 50].

The risk of re-arrest or ventricular arrhythmias may be lower in norepinephrine treated shockable arrest when compared to epinephrine treated groups. This could be attributed to norepinephrine's influence on myocardial Adenosine-Triphosphate (ATP), pH, and lactate levels.

Studies have shown that ATP-depletion, lactate levels and pH are related to defibrillation success [51–54]. Norepinephrine appears to provide better myocardial oxygen delivery to consumption ratios (MDO₂/MVO₂) and myocardial blood flow (MBF) [35, 37–39], leading to improved energy supply and lactate washout. This may reduce myocardial hydrogen ions during cardiac arrest and enhance defibrillation success. Recent studies focusing on post-cardiac arrest shock and re-arrest have also reported favorable results with norepinephrine compared to epinephrine [20, 55].

A crucial difference between the catecholamines is that the reduced β -agonistic effects of norepinephrine, leading to reduced excitation of myocardial cells, potentially prevents the recurrence of ventricular fibrillation. A recent study found that many patients in so-called refractory ventricular fibrillation are actually experiencing recurrent episodes and epinephrine administration may contribute to this phenomenon [56].

In general, norepinephrine may confer potential benefits in patients with shockable cardiac arrest, through both cardiac and neurological mechanisms. The cardiac advantages could include a reduced incidence of arrhythmias compared with epinephrine, which may be attributable to less β -adrenergic stimulation and/or more favorable myocardial metabolism, as reflected by higher MBF, a more balanced myocardial oxygen delivery-to-consumption ratio (MDO₂/MVO₂), and lower myocardial lactate concentrations. Neurological benefits may arise either from improved intra-arrest hemodynamics—supported by findings of comparable CBF during norepinephrine administration relative to normal sinus rhythm circulation—or from attenuated platelet aggregation when compared with epinephrine.

Strengths

This study provides a comprehensive summary of the current scientific evidence regarding the administration of norepinephrine in shockable cardiac arrest. A key strength of the methodology is the thorough search of both traditional and grey literature, as well as the inclusion of animal studies and case reports. This approach resulted in a detailed overview of norepinephrine's effects on hemodynamic parameters and survival.

The inclusion of diverse study types and the broad scope of this review offer a holistic perspective on the current state of knowledge. This comprehensive approach is particularly valuable in the context of cardiac arrest research, where ethical constraints limit the feasibility of large-scale human trials. By synthesizing data from multiple sources, this review identifies important trends and potential areas for future research, contributing to a more nuanced understanding of norepinephrine's role in cardiac arrest management.

Limitations

This scoping review has several limitations. Firstly, the majority of included studies are animal-based, many of which are from historical perspectives. While these studies offer valuable insights into hemodynamic and outcome parameters in mammals, their direct applicability to human clinical practice is limited. The scarcity of human studies highlights a significant gap in the current literature. Inherent to scoping reviews are limitations such as potential biases in search term selection. To mitigate this, we involved the expertise of an experienced librarian and two researchers independently conducted blinded screening of titles and abstracts. The inclusion of only one additional study through cross-referencing supports the thoroughness of the search strategy. Lastly, the focus on shockable cardiac arrest may limit the generalizability of these findings to other types of cardiac arrest.

Future research

The data in this review underscores the need for future research to address the current gaps in understanding the role of norepinephrine in shockable cardiac arrest. Future well-designed, large-scale human studies are essential to investigate the potential benefits of norepinephrine compared to the current standard of administering epinephrine in shockable cardiac arrest.

Additionally, future research should consider investigating cerebral microcirculation during resuscitation with different vasopressors, as well as long-term follow-up and quality of life in survivors. Exploring potential synergistic effects between norepinephrine and other neuroprotective strategies during resuscitation could lead to further improvements in cardiac arrest care. Such research would not only enhance understanding norepinephrine's role but also contribute to optimizing treatment protocols for cardiac arrest.

Conclusion

This scoping review provides a comprehensive overview of the available evidence on the use of norepinephrine during shockable cardiac arrest. While norepinephrine appears to offer potential advantages - such as improved myocardial and cerebral blood flow and a reduced risk of re-arrest in animal studies, with similar signals suggested in humans - significant limitations prevent definitive conclusions. Further research is therefore required to validate these findings.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

Conceptualisation (SB, EB, CS, LM), methodology (SB, EB, GF), investigation and formal analysis (SB, EB), writing original draft (SB), visualization (SB, EB), writing – reviewing and editing (CS, LM), supervision (GJvG, JB, CS, LM),

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Data availability

All data generated or analysed during this study are included in this published article. Data can be traced using the references.

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