The cerebrovascular response to norepinephrine: A scoping systematic review of the animal and human literature

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Abstract

Intravenous norepinephrine (NE) is utilized commonly in critical care for cardiovascular support. NE’s impact on cerebrovasculature is unclear and may carry important implications during states of critical neurological illness. The aim of the study was to perform a scoping review of the literature on the cerebrovascular/cerebral blood flow (CBF) effects of NE. A search of MEDLINE, BIOSIS, EMBASE, Global Health, SCOPUS, and Cochrane Library from inception to December 2019 was performed. All manuscripts pertaining to the administration of NE, in which the impact on CBF/cerebral vasculature was recorded, were included. We identified 62 animal studies and 26 human studies. Overall, there was a trend to a direct vasoconstriction effect of NE on the cerebral vasculature, with conflicting studies having demonstrated both increases and decreases in regional CBF (rCBF) or global CBF. Healthy animals and those undergoing cardiopulmonary resuscitation demonstrated a dose-dependent increase in CBF with NE administration. However, animal models and human patients with acquired brain injury had varied responses in CBF to NE administration. The animal models indicate an increase in cerebral vasoconstriction with NE administration through the alpha receptors in vessels. Global and rCBF during the injection of NE displays a wide variation depending on treatment and model/patient.

KEYWORDS
cerebral blood flow, cerebrovascular response, norepinephrine

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INTRODUCTION

L-1-(3,4-Dihydroxyphenyl)-2-aminoethanol or norepinephrine (NE) is an adrenergic drug that is used in a variety of medical care and treatment. It has emerged as one of the most commonly utilized vasopressor agents for general cardiovascular support in the management of critically ill patients, through modulation of adrenergic receptors. Systemically, NE is well known to cause vasoconstriction and in high sustained doses it may lead to limb or end-organ ischemia.

Despite these concerns regarding systemic vasoconstriction related to NE, it is widely employed, including in those patients with critical neurological illness, such as traumatic brain injury (TBI). However, it remains unclear if detrimental vasoconstrictive responses are seen in the cerebral vasculature with NE administration in human TBI patients. Given that many secondary injury mechanisms in the setting of TBI and other critical neurological illness, resulting in altered or reduced cerebral blood flow (CBF) or impaired cerebrovascular reactivity, understanding the impact of exogenously administered NE on cerebrovascular reactivity and CBF is crucial. Such understanding may impact our choice of vasopressor agent in specific neuropathologic states. Similarly, knowledge here will allow us to anticipate potential cerebral physiologic responses related to NE, as we begin to transition to personalized physiologic targets, particularly in TBI care, based on cerebrovascular reactivity monitoring.

Human studies evaluating vaso pressors and cerebrovascular response in critical neurological illness are inherently confounded by ongoing active treatments for intracranial pressure (ICP), cerebral perfusion pressure (CPP), and other physiologic metrics. As such, focusing on past experimental studies may shed light on the overall impact of NE on cerebrovascular reactivity and CBF, providing a basic understanding of potential expected responses in humans. This will aid the design of future prospective human and large animal model studies on the impact of vasopressor agents on the cerebral vasculature.

The goal of this study was to perform a systematically conducted scoping review of all available literature on the impact of NE on cerebrovascular responsiveness/CBF response, including animal and human studies.

MATERIALS AND METHODS

A systematic review of the available literature was conducted using the methodology outlined in the Cochrane Handbook for Systematic Reviewers. The data were reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Appendix A of the Supplementary Materials provides the PRISMA checklist. The review questions and search strategy were decided upon by the supervisor (FAZ) and primary author (LF).

Search question, population, and inclusion and exclusion criteria

The question posed for systematic review was: What is the effect of exogenous systemically administered NE on the cerebrovascular response/cerebral blood flow? All studies, prospective and retrospective, animal or human subject, of any size were included. The reason for an all-inclusive search was the small number of studies of any type identified by the primary author during a preliminary search of MEDLINE.

The primary outcome measure was the impact on CBF or the cerebrovascular responsiveness as documented by autoradiographic diffusable tracer technique, electromagnetic flow probe, freely diffusible tracers, thermal diffusion probe, clearance method, laser-Doppler flow probe, radioactive gas elimination, radioactive microsphere, flow transducer and flow meter, visual recording software, or any other objective means of CBF determination. Secondary outcomes included adverse effects of NE administration.

All studies, whether prospective or retrospective, of all sizes or of any age category, and with the use of NE with formal documentation of cerebrovascular response/CBF during administration were eligible for inclusion in this review. Exclusion criteria were the following: being a non-English study or CBF mediation with substance other than NE.

Search strategy

MEDLINE, BIOSIS, EMBASE, Global Health, SCOPUS, and Cochrane Library from inception to December 2019 were searched using individualized search strategies for each database. The search strategy for MEDLINE can be seen in Appendix B of the Supplementary Materials, with a similar search strategy used for the other databases. Finally, the reference lists of reviewed articles on the cerebral blood vessels/CBF response to NE were examined to ensure no references were left out.

Study selection

Using two reviewers (LF and JD), a two-step review of all articles returned by our search strategies was performed. First, the reviewers independently screened all titles and abstracts of the returned articles to decide whether they met the inclusion criteria. Second, full text of the chosen articles was assessed to confirm whether they met the inclusion criteria and that the primary outcome of CBF/cerebrovascular response to NE was documented. Any discrepancies between the two reviewers were resolved by a third party (FAZ).

Data collection

Data were extracted from the selected articles and stored in multiple electronic databases to ensure data integrity.

Animal studies

Data fields included the following: number of animals, type of study, animal model characteristics, the goal of the study, dose of...
2.6 | Human studies

Data fields included the following: number of patients, type of study, patient characteristics, the goal of the study, dose of vasopressors administered, type of vasopressors administered, technique of CBF/vasculature assessment, ventilator parameters (including pCO₂ and pO₂—if documented), sedation regimen administered, CBF/cerebral vasculature response to NE, other outcomes and general conclusions.

2.7 | Bias assessment

Given the goal of this review was to provide a comprehensive scoping overview of the available preclinical literature, a formal bias assessment was not conducted.

2.8 | Statistical analysis

A meta-analysis was not performed in this study because of the heterogeneity of model types, study designs, and data.

3 | RESULTS

3.1 | Search results and study characteristics

The results of the search strategy across all databases and reference sections of articles are summarized in Figure 1. Overall, a total of 2463 articles were identified, all from the databases searched. A total of 635 were removed because of duplication of references, leaving 1825 to review. By applying the inclusion/exclusion criteria to the title and abstract of these articles, we identified 288 articles that fit these criteria. Six articles were added from reference sections of pertinent review articles, leaving a total of 294 papers to review. The portable document formats (PDFs) of these 294 were then gathered. Applying the inclusion/exclusion criteria to these PDFs, only 88 articles were found eligible for inclusion in the systematic review. Articles were excluded because they either: did not report

![FIGURE 1 PRISMA flow diagram](image-url)
details around the CBF/cerebrovascular response to NE administration or were nonrelevant. One article was a retrospective study focused on CBF and brain function during hypotension and shock.  

3.2 | Animal models

Within the 62 animal studies identified, the majority of cases measured CBF response to NE and other agents, utilizing: autoradiographic diffusible tracer technique, electromagnetic flow probe, freely diffusible tracers, thermal diffusion probe, clearance method, laser-Doppler flow velocity, radioactive gas elimination, radioactive microsphere, flow transducer and flow meter, visual recording software, and two other methods. The animal models studied included baboons (3), 17-19 cats (8), 20-27 dogs (11), 28-38 goats (3), 39-41 pigs (12), 42-53 sheep (1), 44 mice (1), 55 rabbits (5), 56-60 rats (17) 61-77 and one retrospective study 16 with dogs, cats, rats, and humans. The characteristics of the animal studies can be seen in Tables 1 and 2. The majority of the models was heavily anesthetized, with only two studies where the animals were lightly sedated 40,42 and four studies where animals had no sedation or anesthesia. 39,41,55,60 A further four articles 27,38,44,70 had NE injected with another vasoactive substance, seven articles 20,23,27,52-54,70 where the models had cranioectomy, five articles 34,36,37,73,77 where models had explanted brains for the evaluation of vessel response, four articles 44-47 where models were administered cardiopulmonary resuscitation (CPR) during NE injection, four articles 48,50,51,74 where models had a TBI, three articles 21,35,66 where some models had hypothermia, two articles 43,54 where models had a superior cervical sympathetic ganglionectomy, one article where models had bile duct ligations. 19 and one article where models had induced endotoxin shock. 43 Seventeen studies had NE administered at varying dose levels on healthy models. 17,20,26,29,36,39,40,52-54,59,63-65,69,71,72 In 23 of the studies the partial pressure of oxygen and carbon dioxide were either controlled through ventilation, 21,25,29,31,35,43,49,51,53,56,57,60-62,66,67,70,71,73 or taken to be constant throughout the study in 28 17,19,22-24,28,30,32-34,36-39,50,52,54,55,58,59,63-65,68,72,74,75 Ten studies did not mention accounting for the pCO₂ or pO₂. 20,26,27,40-42,67,69,76,77

3.3 | NE impact on objectively measured CBF

The following subsections provide a narrative summary of the impact of NE administration on objectively measured cerebrovascular response/CBF, looking first at overall increase/decrease in CBF, followed by measured models pathology-specific responses to NE. Table S2 of the Supplementary Materials provides a detailed tabulation of medication dosing, measurement technique, and results.

3.4 | Increase in CBF

Twenty-six studies demonstrated an increase in global or rCBF with the administration of NE. 17,18,22,24,26,29-33,49,57-69,71,72,75,76 Five showed a nonsignificant response in CBF to NE administration. 25,31,57,60,66 In the remaining studies there were conflicting responses seen, with NE leading to both increasing 17,18,22,25,33,62-64,69,71,72,75,76 and decreasing CBF. 22,24,29-31,58,60,61,65 Despite these conflicting responses, there were some study design specifics to take note of. First, the influence of coadministered substances on the effects of NE demonstrated some findings of interest. Such substances include: hypertonic saline, 18,62 phentolamine, 24,33,59,61 phenoxybenzamine, 32,64 and propranolol 31,32,49,62 Hypertonic saline injected with NE significantly increased CBF and cerebral metabolic rate of oxygen consumption (CMRO₂) as compared to NE alone. 18,62 Similarly, when NE was allowed to pass the blood-brain barrier (BBB) after osmotic opening with urea, an increased regional flow was obtained. 62 Phentolamine inhibited or completely mitigated the CBF increase ranged from not significant, to changes on the order of 500% of the initial CBF value. 45 In studies which measured rCBF, all areas increased in blood flow except the auditory cortex 45 and mesencephalon. 62 Six studies had a dose-dependent increase in CBF, 40,45,46,70-72 with one study showing a peak CBF at a NE dose of 0.16 mg/kg. 45 The variation within the data between the individual animal models and pathologies limits the ability to draw any clear conclusions within species or technique.

3.5 | Decrease in CBF

Twenty-two studies demonstrated a decrease in CBF or rCBF by the administration of NE. 19,21,22,24,28-30,32-34,39,42-44,51,55,57,58,60,61,73,74 The CBF decrease had a wide range in variation from not significant, to a max reduction of 70%. 38 In the single study that both monitored rCBF and CBF, an overall decrease in rCBF was seen in all areas except the brain stem. 43

3.6 | Direct vascular response

Of the seven studies that evaluated direct cerebrovascular response to NE, 20,26,27,52,53,59,77 all had some form of constriction to the cerebral vessels. This cerebral vessel change ranged from nonsignificant up to 20% constriction as compared to baseline values. 52,53,59 However, models that had a significant constrictive response to NE were either injected with another solution (a hypertonic saline solution or Wahl solution 45) or had NE locally applied to cerebral vessels. 52,53,59

3.7 | Model-specific responses

3.7.1 | Healthy models

There were 29 studies that used healthy fully anesthetized models, without a cranioectomy, and assessed CBF. 17,18,22,24,26-29,33,49,57-69,71,72,75,76 Five showed a nonsignificant response in CBF to NE administration. 25,31,57,60,66 In the remaining studies there were conflicting responses seen, with NE leading to both increasing 17,18,22,25,33,62-64,69,71,72,75,76 and decreasing CBF. 22,24,29-31,58,60,61,65 Despite these conflicting responses, there were some study design specifics to take note of. First, the influence of coadministered substances on the effects of NE demonstrated some findings of interest. Such substances include: hypertonic saline, 18,62 phentolamine, 24,33,59,61 phenoxybenzamine, 32,64 and propranolol 31,32,49,62 Hypertonic saline injected with NE significantly increased CBF and cerebral metabolic rate of oxygen consumption (CMRO₂) as compared to NE alone. 18,62 Similarly, when NE was allowed to pass the blood-brain barrier (BBB) after osmotic opening with urea, an increased regional flow was obtained. 62 Phentolamine inhibited or completely mitigated the CBF
| Reference                        | Number of animals | Study type   | Model characteristics                                | Primary and secondary goals of study                                                                 |
|---------------------------------|-------------------|--------------|------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Healthy heavily anesthetized animal models |                    |              |                                                      |                                                                                                         |
| McCalden et al, 197917          | 15 baboons        | Three-arm study | Healthy baboons anesthetized with ketamine hydrochloride and sodium pentobarbital | Primary: Role of catecholamine degradative enzymes and the adrenergic innervation in determining the cerebrovascular response to infused NE |
| MacKenzie et al, 197618         | 18 baboons        | Two-arm study | Healthy baboons anesthetized with thiopentone sodium, phencyclidine, and suxamethonium | Primary: Test the effects of NE on cerebrovascular activity                                             |
| Chandra et al, 197220           | Not specified     | Four-arm study | Healthy cats were anesthetized with pentobarbital sodium | Secondary: Effect of hypertonic urea                                                                   |
| Muravchick et al, 197621        | 26 cats           | Eight-arm study | Healthy mongrel cats anesthetized with pentobarbital   | Primary: Choroidal blood flow and the effects of autonomic agents                                       |
| Lobato et al, 198022            | Not specified     | Nonrandomized control study | Healthy cats intraperitoneally anesthetized with sodium pentobarbital with vessel change measured in removed brains | Primary: Cerebrovascular reactivity to NE and serotonin following experimental subarachnoid hemorrhage |
| Tomita et al, 197923            | 23 cats           | Four-arm study | Healthy and cranial hypertensive cats anesthetized with urethane and chloralose | Secondary: Distensibility of cerebral vessels in response to acute hypertension                          |
| Haggendal et al, 196628         | 11 dogs           | Three-arm study | Healthy mongrel dogs anesthetized with pentobarbital   | Primary: Effects of some vasoactive drugs on the vessels of cerebral grey matter in the dog            |
|                                 |                   |              |                                                      | Secondary: In a few dogs, similar procedures were performed under the influence of induced slight hypoxia and/ or hypercapnia. |
| Gabrielyan et al, 197029        | Not mentioned     | Nonrandomized control trial | Healthy dogs that were bleed anesthetized with nitrous oxide and oxygen | Primary: Effect of NE on rCBF depending on initial MAP                                                      |
| MacDonnell et al, 197130        | 4 dogs            | Three-arm study | Healthy mongrel dogs anesthetized with sodium pentobarbitalonal | Primary: Factors affecting response of CBF and cerebral metabolism to NE infusion                       |
| James et al, 197531             | 37 dogs           | Seven-arm study | Healthy mongrel dogs were anesthetized with sodium pentobarbitalonal | Primary: Evaluate factors affecting the cerebrovascular response to NE in the dog                         |
| Ekstrom-Jodal et al, 197432     | 21 dogs           | Two-arm study | Healthy mongrel dogs anesthetized with thiopental and nitrous oxide | Primary: Effects of NE on CBF in dogs                                                                 |
| Rogers et al, 198942            | 21 pigs           | Four-arm study | Healthy piglets anesthetized with halothane and with right common carotid artery ligated | Secondary: Effect of alpha-adrenergic blockers on NE and CBF                                            |
| Reynier-Rebuffel et al, 198654  | 29 rabbits        | Nonrandomized control study | Healthy rabbits—some anesthetized                    | Primary: Possible mediation of CBF response to systemic NE                                              |
| Patel et al, 199057             | Not mentioned     | Three-arm study | Healthy rabbits anesthetized with 1.0 MAC isoflurane  | Primary: CBF and cerebral blood pressure during 1.0 MAC isoflurane anesthesia                           |
| Gannushkina et al, 197458       | 22 rabbits        | Two-arm study | Renal hypertension in healthy rabbits                | Primary: Effect of high blood pressure on CBF in renal hypertension                                    |

(Continues)
| Reference             | Number of animals | Study type    | Model characteristics                                                                 | Primary and secondary goals of study                                                                 |
|-----------------------|-------------------|---------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Tomomatsu et al, 1981 | 62 rabbits        | Two-arm study | Healthy rabbits of either sex anesthetized with urethane                                | Primary: Increased activity of carotid sinus baroreceptors by sympathetic stimulation and NE           |
| Edvinsson et al, 1979 | 49 rats           | Six-arm study | Healthy adult male Sprague-Dawley rats anesthetized with halothane                      | Primary: Quantitative changes in rCBF of rats induced by alpha and beta-adrenergic stimulants          |
| Edvinsson et al, 1978 | 46 rats           | Four-arm study| Healthy Sprague-Dawley rats anesthetized with halothane                                 | Primary: Effect of exogenous NE on local CBF after osmotic opening of the blood-brain barrier in the rat |
| Lasbennes et al, 1988 | 52 rats           | Three-arm study| Healthy male Wistar rats anesthetized with halothane                                    | Primary: Effect of monoamine oxidase inhibition on rCBF                                               |
|                      |                   |               |                                                                                        | Secondary: Effect of clotryline on cerebral hemodynamics                                              |
| Edvinsson et al, 1978 | 49 rats           | Six-arm study | Healthy adult male Sprague-Dawley rats anesthetized with halothane                      | Primary: Quantitative changes in rCBF of rats induced by alpha and beta-adrenergic stimulants          |
|                      |                   |               |                                                                                        | Primary: Effect of exogenous NE on local CBF after osmotic opening of the blood-brain barrier in the rat |
|                      |                   |               |                                                                                        | Secondary: Effect of clotryline on cerebral hemodynamics                                              |
| Edvinsson et al, 1978 | 46 rats           | Four-arm study| Healthy Sprague-Dawley rats anesthetized with halothane                                 | Primary: Effect of exogenous NE on local CBF after osmotic opening of the blood-brain barrier in the rat |
|                      |                   |               |                                                                                        | Secondary: Effect of clotryline on cerebral hemodynamics                                              |
| Lasbennes et al, 1988 | 52 rats           | Three-arm study| Healthy male Wistar rats anesthetized with halothane                                    | Primary: Effect of monoamine oxidase inhibition on rCBF                                               |
|                      |                   |               |                                                                                        | Secondary: Effect of clotryline on cerebral hemodynamics                                              |
| Sato et al, 1987      | 4-6 rats per 4 studies | Four-arm study | Healthy Sprague-Dawley rats anesthetized with urethane                                | Primary: Effect of L-DOPS vs NE on CBF                                                             |
| Mascia et al, 1999    | 10 rats           | Nonrandomized control study | Healthy Sprague-Dawley rats anesthetized with halothane                                  | Primary: To investigate the role of the endothelin system in pressure autoregulation of CBF in rats |
| Stromberg et al, 1992 | 24 rats           | Nonrandomized control study | Healthy Sprague-Dawley rats anesthetized with ketamine and acepromazine                | Primary: Angiotensin in receptors regulate CBF in rats                                               |
| Zhang et al, 1991     | 16 rats           | Three-arm study | Healthy male Sprague-Dawley rats anesthetized with inactin                              | Primary: Superoxide dismutase decreases mortality, blood pressure, and CBF responses                 |
| Gozzi et al, 2007     | 35 rats           | Four-arm study | Healthy male Sprague-Dawley rats anesthetized with halothane and nitrous oxide         | Primary: Cerebral hemodynamics and autoregulation in pharmacological MRI                              |
| Kuschinsky et al, 1983| 17 rats           | Three-arm study | Healthy male Sprague-Dawley rats anesthetized with halothane with final values attend from removed brain | Primary: The effects of intravenous NE on the local coupling between glucose utilization and blood flow in the rat brain |
| Kraut et al, 2004     | 9 rats            | Three-arm study | Healthy male Wistar rats anesthetized with equithesin                                    | Primary: The effect of NE on tissue areas                                                            |

**Healthy Lightly Anesthetized Animal Models**

| Reference             | Number of animals | Study type    | Model characteristics                                                                 | Primary and secondary goals of study                                                                 |
|-----------------------|-------------------|---------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Artru et al, 1981     | 18 dogs           | Four-arm study | Unmedicated fasting mongrel dogs with succinylcholine infusion followed by endotracheal intubation (anesthetized with nitrous oxide, halothane, pentobarbital, or ketamine) | Primary: Anesthetics affect the cerebral metabolic response to circulatory catecholamines             |

(Continues)
**TABLE 1 (Continued)**

| Reference              | Number of animals | Study type       | Model characteristics                                                                 | Primary and secondary goals of study                                                                 |
|------------------------|-------------------|------------------|----------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| Lluch et al, 1973       | 15 goats          | Five-arm study   | Unanesthetized healthy female goats with thrombosis                                      | Primary: Evidence for effects of adrenergic drugs on CVR                                           |
|                        |                   |                  |                                                                                        | Secondary: The effect of amines on CBF                                                               |
| Perales et al, 1997     | 14 goats          | Three-arm study  | Conscious female goats sedated with ketamine                                           | Primary: Effects of magnesium sulfate on the NE-induced cerebral vasoconstrictor and pressor responses in the goat |
| Von Essen et al, 1972   | No Specified      | Three-arm study  | Healthy dogs lightly anesthetized                                                      | Primary: Effects of dopamine, NE, and 5-hydroxytryptamine on the CBF in the dog                      |
|                        |                   |                  |                                                                                        | Secondary: The effect of dopamine in the presence of pimozide or haloperidol                        |
| Edvinsson et al, 1972   | 124 mice          | Two-arm study    | Unanesthetized sympathectomy male albino mice                                          | Primary: Sympathetic neural influence on NE vasoconstriction in brain vessels                         |
| Animal models with ganglionectomy |             |                  |                                                                                        |                                                                                                      |
| Alborch et al, 1977     | 11 goats          | Two-arm study    | Unanesthetized female goats with removed cervical ganglion                              | Primary: Effect of blood flow after removal of cervical ganglion                                      |
|                        |                   |                  |                                                                                        | Secondary: The effect of NE, tyramine, phentolamine, and propranolol on CBF                           |
| Aubineau et al, 1985    | 7 rabbits         | Three-arm study  | Ganglionectomy on rabbit anesthetized by diazepam-pentobarbital                        | Primary: Long-term effects of superior cervical ganglionectomy on cortical blood flow of nonanesthetized rabbits in resting and hypertensive conditions |
|                        |                   |                  |                                                                                        | Secondary: Effect of NE and Angiotensin II on blood flow                                           |
| Animal models with bile duct removed |             |                  |                                                                                        |                                                                                                      |
| Bloom et al, 1975       | 16 baboons        | Nonrandomized control study | Bile duct removed in baboon anesthetized with ketamine hydrochloride and portion of them had their bile duct removed | Primary: Modification of the cerebrovascular response to NE by bile duct ligation                     |
| Healthy heavily anesthetized animal models with craniotomy |             |                  |                                                                                        |                                                                                                      |
| Shalit et al, 1974      | 32 cats           | Nonrandomized control study | Craniotomy on healthy adult cats anesthetized with pentobarbital and balloon-induced hypertension | Primary: Interrelationship between blood pressure and rCBF in experimental intracranial hypertension |
| Ulrich et al, 1985      | 21 cats           | Four-arm study   | Craniotomy on adult cats immobilized with pancuronium bromide and anesthetized with glucocorticose | Primary: In vivo effects of alpha-adrenoceptor agonists and antagonists on pial veins of cats          |
| Wei et al, 1975         | 47 cats           | Six-arm study    | Craniotomy on anesthetized cats with sodium pentobarbital or urethane                   | Primary: Determinants of response of pial arteries to NE and sympathetic nerve stimulation             |
| Busija et al, 1987      | 16 pigs           | Prospective randomized animal study | Craniotomy on newborn pigs of either sex 1-5 days of age were anesthetized with ketamine hydrochloride and acepromazine | Primary: Eicosanoid synthesis elicited by NE in piglet parietal cortex                                |
|                        |                   |                  |                                                                                        | Secondary: NE and Isoproterenol effect on cerebral vessels                                           |
| Leffler et al, 1989     | 19 piglets        | Prospective randomized animal study | Craniotomy on piglets anesthetized with ketamine hydrochloride and acepromazine         | Primary: Postischemic cerebral microvascular responses to NE and hypotension in newborn pigs         |
| Myburgh et al, 1998     | 5 sheep           | Three-arm study  | Craniotomy on female sheep, anesthetized                                              | Primary: Comparison of the effect of NE, E, and Dopamine on CBF and COU                              |
| Muir et al, 1993        | 17 rats           | Nonrandomized control study | Craniotomy on male Sprague rats anesthetized with sodium pentobarbital                  | Primary: Cocaine effect on blood pressure and CoBF (cortical) response to NE in rats                 |

(Continues)
| Reference                  | Number of animals | Study type               | Model characteristics                                                                 | Primary and secondary goals of study                                                                 |
|----------------------------|------------------|--------------------------|---------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| Oberdorster et al, 1973    | 14 dogs          | Three-arm study          | Dissected canine brains anesthetia with a mixture of allobarbital, urethane, and etheylene urea, coagulation prevented with vetren | Primary: Direct effects of alpha and beta-sympathomimetic amines on the cerebral circulation of the dog |
| Lowe et al, 1971           | 12 dogs          | Four-arm study           | Brains from mongrel dogs premedicated with morphine sulfate and anesthetic with methoxyflurane | Primary: Demonstration of alpha and beta-adrenergic receptors in canine cerebral vasculature          |
| Zimmer et al, 1974         | 6 dogs           | Three-arm study          | Isolated perfused dogs brains which were intravenously anesthetized with a mixture of amobarbital and urethane | Primary: The effect of catecholamine on CBF and oxygen consumption in isolated perfused dog's brain   |
| Omar et al, 2010           | About 23 rats for each study | Pharmacological study    | Brains of Wistar rats juvenile, mature, and old                                       | Primary: Age-related changes in the sympathetic innervation of cerebral vessels and in carotid vascular responses to NE in the rat in vitro and in vivo studies |
| Takahashi et al, 2000      | 7 rats           | Two-arm study            | Brains from male Wistar rats anesthetized with pentobarbital sodium                   | Primary: The vasoconstrictive action of NE and serotonin in deep arterioles in rat cerebral gray matter |
| Mori et al, 1999           | 34 cats          | Three-arm study          | Hypothermia induced in adult cats of both sexes anesthetized with halothane and continuous infusion of ketamine and pancuronium bromide | Primary: Misery perfusion caused by cerebral hypothermia Secondary: Effects of vasopressor administration on misery perfusion |
| Panther et al, 1985        | 8 dogs           | Three-arm study          | Brain cancer dogs anesthetized with sodium pentobarbital                                | Primary: Vasoactive drugs produce selective changes to blood flow                                     |
| Nakagawa et al, 1977       | 21 dogs          | Nonrandomized control study | Stereotaxic lesions made on hypothermic dogs anesthetized with thiamylal sodium and lesion | Primary: Role of posterior hypothalamus in the development of acute brain swelling Secondary: Lesion effect on ICP |
| Miller et al, 1984         | 17 pigs          | Three-arm study          | Endotoxin shock induced in healthy pigs anesthetized with ketamine and pentobarbital   | Primary: Vasopressors do not increase cerebral cortical blood flow in endotoxin shock                |
| Anesthetized animal models given CPR |                   |                          |                                                                                       |                                                                                                       |
| Prengel et al, 2005        | 21 pigs          | Prospective-randomized animal study | CPR in domestic pigs anesthetized with pentobarbital                                   | Primary: Effects of combined administration of vasopressin, E, and NE during cardiopulmonary resuscitation in pigs |
| Hoekstra et al 1990        | 14 piglets       | Two-arm study            | CPR on pigs anesthetized with halothane and alpha-chloralose                          | Primary: The effect of NE vs E on CBF and myocardial blood flow during CPR                            |
| Brown et al, 1989          | 5 pigs           | Three-arm study          | CPR on pigs anesthetized with halothane                                              | Primary: The effect of NE vs E on rCBF during CPR Secondary: CBF effect of NE and E in the presence of adrenergic antagonist |
| Lindner et al, 1990        | 21 pigs          | Three-arm study          | CPR on pigs anesthetized with metomidate and buprenorphine                           | Primary: The effects of E and NE on cerebral oxygen delivery and consumption during open-chest CPR Secondary: The effects of E and NE on CBF during open-chest CPR |
TABLE 1 (Continued)

| Reference                        | Number of animals | Study type                  | Model characteristics                                      | Primary and secondary goals of study                                                                 |
|----------------------------------|-------------------|-----------------------------|-------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| TBI anesthetized animal models   |                   |                             |                                                             |                                                       |
| Armstead et al, 201653           | 40 pigs           | Three-arm study             | TBI juvenile pigs anesthetized with fentanyl, midazolam,    | Primary: NE’s cerebral autoregulation effects TBI in juvenile pigs                                    |
|                                  |                   |                             | dexmedetomidine, and propofol                               | Secondary: How NE protects cerebral autoregulation                                                  |
| Friess et al, 201252             | 16 piglets        | Three-arm studies           | TBI 4-week-old piglets anesthetized with fentanyl and isoflurane | Primary: PE vs NE after noninvasive brain trauma                                                    |
|                                  |                   |                             |                                                             | Secondary: The effects of PE and NE in the young                                                    |
| Daley et al 200453               | 6 piglets         | Prospective-randomized     | TBI in healthy piglets anesthetized with ketamine and acepromazine | Primary: Assessment of cerebrovascular autoregulation in uninjured and brain-injured pigs         |
|                                  |                   | animal study                |                                                             |                                                       |
| Ract et al, 200177               | 14 rats           | Three-arm study             | TBI in Sprague-Dawley rats anesthetized with pentobarbital  | Primary: Comparison of dopamine and NE after TBI and hypoxic-hypotensive insult                   |
| Review article                   |                   |                             |                                                             |                                                       |
| Kovach et al, 197616             | Not applicable    | Systematic literature review | Dogs, cats, rats, and humans                                | Primary: CBF and brain function during hypotension and shock                                        |

Abbreviations: AT, Angiotensin II; CBF, cerebral blood flow; CBV, cerebral blood volume; ChBF, choroidal blood flow; CMOT, Catechol-O-methyltransferase; CMRO₂, cerebral oxygen consumption; CoBF, corticoid blood flow; COU, cerebral oxygen utilization; CO₂, carbon dioxide; CP, cerebral perfusion; CPR, cardiopulmonary resuscitation; CPP, cerebral perfusion pressure; CSF, cerebral spinal fluid; CVR, cerebrovascular resistance; E, epinephrine; ERK, extracellular signal-regulated kinase; FPI, fluid percussion injury; HMF, highest modal frequency; ICP, intracranial pressure; IL-6, interleukin-6; l-keto-PGFα, 1-keto-prostaglandin; L-DOPS, l-threo-3,4-dihydroxyphenylserine; L-NMMA, methylarginine; MAP, mean arterial blood pressure; MAO, Monoamine oxidases; MAP, mean arterial pressure; MAPK, mitogen-activated protein kinase; MBF, mean blood flow; MDo, myocardial oxygen delivery; MRI, magnetic resonance imaging; MVO, myocardial oxygen consumption; NE, norepinephrine; PE, phenylephrine; PGE2, Prostaglandin E2; PO₂, partial pressure of oxygen; rCBF, regional cerebral blood flow; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury; TXB2, Thromboxane B2; 5-HT, 5-hydroxytryptamine;

Effects of NE.24,33,59,61 Likewise, phenoxybenzamine22,64 injected with NE demonstrated that the CBF and CMRO₂ effects of NE were decreased.32,64 Propranolol demonstrated a decrease to CBF, when this was followed by an injection of NE CBF then increased.31,32,49,62

One study testing endothelin-1 compared hypertension with/without endothelin-1. NE was used to induce this hypertension which caused a slight increase in CBF, with a significant CPP increase in controls. Where NE and endothelin-1 caused the CBF and CPP to both increase significantly.68 NE with or without experimental renal hypertension had a similar drop in CBF from 100 to 38 mL/100 g/min. However during renal hypotension with blood loss, there was an increase in CBF followed by a return to low levels of CBF.58

Furthermore, a cerebral vascular resistance (CVR) increase was seen during induced hypotension (bleeding) models with NE administration (mean arterial blood pressure (MABP) of 151 mmHg in controls vs MABP of 113 mmHg in the hypotension group), which caused a slight decrease in CBF by 10%.30 An increase in CVR was a universal result in all the studies that evaluated CVR in healthy models.22,24,30,64

3.7.2 | Models with craniotomy or explanted brains

In the seven studies20,23,27,52-54,70 that had an in vivo craniotomy, or five studies34,36,37,73,77 with explanted brains (to analyze cerebral vessel response), the majority of them measured cerebral vessel diameter or contraction response directly. All models demonstrated that NE either caused a constriction of cerebral vessels,27,52,53,70,77 or rarely they remained unaffected.20 In line with this, when CVR was measured there was an increase in CVR in response to NE,34,36,37 with varied response in CBF.

Using an extradural balloon to modulate ICP, one study indicated that NE had no CBF effect if the ICP was above 70 mmHg, otherwise there was a direct short-term increase to CBF.23 Another study observed the pressure-flow relationship (measured using a photoelectric drop recorder) in the brain for 30 minutes after the application of catecholamines. Based on the pressure-flow relationship tested in each brain, the indirect effects of catecholamines on CVR caused by autoregulatory influences were calculated. This calculation was determined mathematically and then accounted for in subsequent physiological experiments, which enable the study to focus purely on the catecholamine effects in the absence of autoregulatory influences. After the autoregulatory influences were removed, NE was seen to decrease CVR by 50% and demonstrate a slight decrease in CBF.24

Finally, in one study, the constriction of large arterioles was induced through NE, with pial vessels remaining unchanged.20 While in rats, the carotid blood flow was decreased by 0.5 mL/min in all ages of animals with the injection of NE. This study also found the
| Reference                  | Dose of vasopressor administered | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response | Adverse effects to norepinephrine | Conclusions                                                                 |
|----------------------------|----------------------------------|---------------------|-----------------------------------------------|--------------------------|-----------------------------------|--------------------------------------------------------------------------------|
| McCalden et al., 197917    | NE: 0.55 µg/kg/min               | 60 mins             | CBF: Radioactive microspheres with injections of Xenon133 | PCO₂ and PO₂ remained constant throughout all groups |
|                            | 1.1 µg/kg/min                    |                     |                                               | All values in mL/min/100 g and are the alteration from baseline value |
|                            | COMT blockade, MAO blockade, Denervation |         |                                               | NE 0.55 µg: CBF during: | None mentioned |
|                            |                                  |                     |                                               | Control: +9.7 ± 3.6 COMT: -3.3 ± 6.1 MAO: +1.8 ± 4.0 (P < .05) Denerv: -9.0 ± 7.2 (P < .05) | The cerebrovascular uptake and degradation mechanisms may be efficient, this remains to be demonstrated by established in vitro technique. The extraneuronal COMT enzyme is important in limiting the access of blood-borne NE to cerebrovascular constrictor receptors |
|                            |                                  |                     |                                               | CBF after 10 mins Control: +11.5 ± 2.2 COMT: -4.6 ± 2.2 (P < .05) MAO: +2.1 ± 2.7 (P < .05) Denerv: -0.6 ± 4.6 (P < .05) |
|                            |                                  |                     |                                               | NE 1.10 µg: CBF during: |                                      |
|                            |                                  |                     |                                               | Control: +15.5 ± 4.8 COMT: -10.6 ± 0.9 (P < .05) MAO: +0.1 ± 2.2 (P < .05) Denerv: -6.8 ± 8.2 (P < .05) |                                      |
|                            |                                  |                     |                                               | CBF after 10 mins: Control: +14.1 ± 3.2 COMT: -7.3 ± 1.6 (P < .05) MAO: +0.6 ± 2.3 (P < .05) Denerv: -0.5 ± 4.5 (P < .05) |
|                            |                                  |                     |                                               | CMRO₂: Control: +0.2 ± 0.3 COMT: -0.7 ± 0.5 MAO: -0.7 ± 0.2 (P < .05) Denerv: +0.1 ± 0.7 |                                      |

(Continues)
**TABLE 2** (Continued)

| Reference             | Dose of vasopressor administered | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response                                                                 | Adverse effects to norepinephrine | Conclusions                                                                 |
|-----------------------|----------------------------------|---------------------|----------------------------------------------|------------------------------------------------------------------------------------------|----------------------------------|-----------------------------------------------------------------------------|
| MacKenzie et al., 1976 | NE: 40 µg/kg dissolved in 0.1 m CSF 50 µg/kg/min after hypertonic urea | 10 x every 20 mins or 15 s | CBF: Freely diffusible method with Xenon133 CMRO₂: Standard enzymatic assay Cerebral glucose uptake (CMRglc): Calculated by CBF * arteriovenous blood glucose difference | PCO₂ and PO₂ remained constant throughout all groups NE 40 µg kg: CBF: Increased by 1 ± 2 mL/100 g/min (P, NS) CMRO₂: Increased from 2.78 ± 0.10 to 3.44 ± 0.42 mL/100 g/min (P < .05) CMRglc: Increased from 4.21 ± 0.42 to 10.65 ± 2.96 mg/100 g/min (P, NS) No significant changes in CMRO₂, CMRglc, CBF, or MAP | None mentioned | In two studies there was not any decrease in cerebral blood flow associated with the administration of NE. Once NE gains access to the cerebral interstitial fluid it would appear that the dominant circulatory response is vasodilation, this being accompanied by increased oxygen and glucose utilization by the brain |
| Reference       | Dose of vasopressor administered | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response | Adverse effects to norepinephrine | Conclusions                                                                 |
|-----------------|----------------------------------|----------------------|-----------------------------------------------|--------------------------|-----------------------------------|-----------------------------------------------------------------------------|
| Chandra et al, 1972 | Levarterenol: 0.1-10 µg E: 0.5-1 µg Acetylcholine: 1-10 µg Isoproterenol: 0.01-1 µg | Not specified | Choroidal blood flow (ChBF): Krypton\textsuperscript{85}\ Clearnes | PCO\textsubscript{2} and PO\textsubscript{2} assumed to be constant throughout all groups | None mentioned | Autonomic agents have significant effects on CVR and ChBF indicating the presence of alpha and gamma receptors. In this respect, the choroidal vascular bed resembles that of other tissues except for the brain and retina. In contrast, isoproterenol does not seem to have an appreciable effect on CVR indicating the absence of beta receptors |

**TABLE 2 (Continued)**

(Continues)
| Reference | Dose of vasopressor administered | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response | Adverse effects to norepinephrine | Conclusions |
|-----------|----------------------------------|---------------------|---------------------------------------------|-------------------------|----------------------------------|-------------|
| Muravchick et al., 1976<sup>21</sup> | NE: 0.5 µg/kg E: 1.0 µg/kg Isoproterenol: 2.0 µg/kg Histamine: 3.0 µg/kg | 10-15 sec | CBF: Electromagnetic flow transducer and flow meter CVR: Calculated by net driving perfusion pressure/observed perfusate flow rate | PCO<sub>2</sub> and PO<sub>2</sub> remained constant throughout all groups NE no blockade: CBF: -21.2 ± 2.0 (-25%) mL/min/100 g CVR: +1.4 ± 0.9 (+82%) mmHg/mL/min/100 g NE alpha blockade: CBF: -8.8 ± 2.0 (-8%) mL/min/100 g CVR: +0.1 ± 0.0 (+10%) mmHg/mL/min/100 g Isoproterenol no blockade: CBF: +16.0 ± 1.2 (+21%) mL/min/100 g CVR: -0.4 ± 0.1 (-22%) mmHg/mL/min/100 g Isoproterenol beta blockade: CBF: 0.0 ± 3.6 (0%) mL/min/100 g CVR: 0.0 ± 0.1 (0%) mmHg/mL/min/100 g E no blockade: CBF: -24.8 ± 2.0 (-29%) mL/min/100 g CVR: +1.0 ± 0.2 (+62%) mmHg/mL/min/100 g E alpha blockade: CBF: -6.8 ± 1.6 (-7%) mL/min/100 g CVR: +0.2 ± 0.1 (+14%) mmHg/mL/min/100 g Histamine no blockade: CBF: 35.7 ± 10.6 (49%) mL/min/100 g CVR: -0.6 ± 0.2 (-30%) mmHg/mL/min/100 g Histamine beta blockade: CBF: 27.8 ± 2.9 (36%) mL/min/100 g CVR: -0.5 ± 0.0 (-28%) mmHg/mL/min/100 g Histamine alpha block: CBF: 10.0 ± 2.4 (13%) mL/min/100 g CVR: 0.0 ± 0.1 (-11%) mmHg/mL/min/100 g | None mentioned | The wide variation in absolute values of initial CVR presented in the data obtained with this preparation reflects the great sensitivity of the cerebral vasculature to the quality of the immediate biochemical and physical environment. The vasoconstrictor or vasodilator substance is a function of the initial vascular resistance NE demonstrated a general increase in CVR with a subsequent decrease in CBF |
| Lobato et al., 1980<sup>32</sup> | NE: 10<sup>-8</sup> to 10<sup>-4</sup> (mol/L) 5-HT: 10<sup>-8</sup> to 10<sup>-5</sup> (2.5 mol/L) | Readjusted every 15 mins during an equilibration period of 90 to 120 mins | Isometric vascular responses: Grass force-displacement transducer | NE induced a dose-dependent contractile response of the posterior communicating arteries of normal cats. This response was significantly reduced (P < .02) in a competitive manner by phentolamine (10<sup>-6</sup> mol/L), an alpha-adrenergic blocker For both NE the increase in the developed tension increases on a 0-300 mg tension, for all except SAH 3 days and ganglionectomy which both increase at the same rate from 100 mg to 500 mg or 140 to 500 mg For both 5-HT the increase in the developed tension increases on a 0-200 mg to 300-700 mg tension, for all except SAH 3 days and ganglionectomy which both increase at the same rate from 300-1400 mg or 200-500 mg | None mentioned | Super sensitivity to NE and serotonin induced by subarachnoid hemorrhage (SAH) may be involved in the production of chronic cerebral vasospasm |
| Reference          | Dose of vasopressor administered | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response                                                                 | Adverse effects to norepinephrine | Conclusions                                                                 |
|--------------------|----------------------------------|----------------------|---------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------|-----------------------------------------------------------------------------|
| Tomita et al. 1979  | Papaverine hydrochloride:         |                      | CBF: Calculated from CBV*density of brain   | PCO₂ and PO₂ were kept constant throughout all groups                                   | None mentioned                  | Intravenous administration of NE to papaverine-pretreated cats produced almost maximal distension of the cerebral vessels, together with simultaneous vasoconstriction in the peripheral vessels, giving rise to an uneven redistribution of blood between the brain and other nonessential organs of the body. NE has an indication to constrict the brain vessels though this does not translate to a direct increase in CBF or ICP. |
|                    | 10 mg/kg (n = 6)                 | To raise MABP to 150 mmHg | tissue                                      | Papaverine hydrochloride:                                                                 |                                 |                                                                             |
|                    | NE:10 µg/kg (n = 9)              |                      | CBV: Photodiode and polygraph               | ICP: Slight increase                                                                    |                                 |                                                                             |
|                    | NE and acute brain swelling:     |                      | ICP: Strain gauge transducer                | CBV: Increased by 1.4%                                                                  |                                 |                                                                             |
|                    | 10 µg/kg (n = 8)                 |                      |                                              | NE: Decrease in CBV in a cat without any premeditation, indicating that NE constricted the 'inexperienced' cerebral vessels (P < 0) |                                 |                                                                             |
|                    |                                  |                      |                                              | NE and acute brain swelling:                                                             |                                 |                                                                             |
|                    |                                  |                      |                                              | CBV: Increased by 0.8 ± 0.3%                                                            |                                 |                                                                             |
|                    |                                  |                      |                                              | ICP: Increased by 15.3 ± 3.3 mmHg                                                       |                                 |                                                                             |
|                    |                                  |                      |                                              | CBF: 91 to 101 mL/100g.min                                                              |                                 |                                                                             |

(Continues)
TABLE 2 (Continued)

| Reference            | Dose of vasopressor administered | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response | Adverse effects to norepinephrine | Conclusions                                                                 |
|----------------------|----------------------------------|----------------------|-----------------------------------------------|--------------------------|----------------------------------|-----------------------------------------------------------------------------|
| Haggendal et al, 1966 | Papaverine: 20-80 mg (n = 6)     | 1-10 mg/kg/body weight | MAP: kept at 200 mmHg                           | PCO₂ and PO₂ were kept constant throughout all groups             | None mentioned                  | Aramine and NE, given as intravenous infusions in previous doses, had qualitatively similar actions on the cerebral circulation in dogs although NE consistently seemed to have a more potent vasoconstrictor effect. The cerebral vasoconstrictor effect of the pressor drugs were observed during slight hypoxia and hypercapnia. Papaverine was found to cause a marked vasodilatation of the cerebral vessels which also was obvious although less pronounced with Aramine. |
|                      | Aramine: 2 mg/kg and 30 µg/kg/min (n = 4) | Aramine: 200-500 µg/mL (n = 8) infused at 1.5-40 µg/kg/body weight/min | Aramine: CBF: Reduced to 11 mL/100 g/min MAP: Increased CVR: MAP/CBF | Aramine flow doubled: CBF: Reduce by 70% CVR: 160% of control MAP: Increased by 50% Papaverine and Aramine: CBF: Increased to 160 mL/100 g/min CVR: Decreased to 1 mmHg*100 g*min/mL MAP: Constant at 180 mmHg NE 4 µg/kg: CBF: Decrease by about 40% CVR: 3 x increase NE 1 µg/kg: CBF: Decrease by about 40% CVR: 3 x increase Hypotensive state: CBF was unchanged compared with Aramine and NE thus indicating dilatation of the cerebral vessels as response to the decreased perfusion pressure. Papaverine 2 mg/kg: CBF: Decrease by 10% CVR: Decreased by 0.4x Aramine provoked increase of CVR also existed when papaverine was given, although to a reduced extent. |
|                      | NE: 10-50 µg/mL (n = 3) infused at 0.2-3 µg/kg/bodyweight/min |                          |                                               |                          |                                  |                                                                                           |
| Reference                | Dose of vasopressor administered | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response | Adverse effects to norepinephrine | Conclusions                                                                 |
|--------------------------|----------------------------------|---------------------|---------------------------------------------|--------------------------|----------------------------------|----------------------------------------------------------------------------|
| Gabrielyan et al, 1970   | NE: 24 µg/min                    | Not specified       | rCBF: Freely diffusible tracer Krypton\textsuperscript{85} infusion and correlated with PCO\textsubscript{2} | PCO\textsubscript{2} and PO\textsubscript{2} were constant throughout all groups | None mentioned                  | NE on the rCBF is largely dependent on the initial value of the mean arterial pressure. Whereas in normotension, in response to injection of NE the CBF remains almost unchanged, in moderate hypotension it is considerably reduced |
| MacDonnell et al, 1971   | NE 0.4 and 1 µg/kg/min Propranolol: 5 mg NE 1 µg and Propranolol 5 mg | Several hrs         | CBF: Freely diffusible tracer injection of Krypton\textsuperscript{85} | PCO\textsubscript{2} and PO\textsubscript{2} were kept constant throughout all groups | None mentioned                  | NE slightly decreased CBF. NE with propranolol caused a more prominent fall in CBF then just NE |

(Continues)
## Table 2 (Continued)

| Reference               | Dose of vasopressor administered | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response | Adverse effects to norepinephrine | Conclusions                                                                 |
|-------------------------|---------------------------------|---------------------|-----------------------------------------------|--------------------------|-----------------------------------|-----------------------------------------------------------------------------|
| James et al, 1975<sup>31</sup> | NE: 0.1-1 µg/kg/min Propranolol: 0.4 µg/kg/min Phenoxybenzamine: 1-10 mg/kg | 15 to 60 mins | Cortical blood flow (CoBF): Freely diffusible tracer injection of Krypton CMRO<sub>2</sub>: Product flow and the arteriovenous difference | PCO<sub>2</sub> and PO<sub>2</sub> were constant throughout all groups except CO<sub>2</sub> modulated | None mentioned | Cerebral vasodilatation observed following intravenous NE is relaxed and is triggered by chemoreceptors activity. Antagonism of the cortical dilatory effects if intravenous NE by raised PaCO<sub>2</sub> is the intact animal must be at a site different from the peripheral chemoreceptors |
| Ekstrom-Jodal et al, 1974<sup>32</sup> | NE: 0.03 to 7.5 µg/kg/min Phentolamine: 0.3-15 mg/kg/min | NE dissolved into 50 µg/mL Dopamine dissolved in 10 mg/mL | CBF: Radioactive gass elimination method Krypton<sup>85</sup> 1.5 hrs was waited till first measure was taken | PCO<sub>2</sub> was low in most models with some having a high value 80 mmHg NE: | None mentioned | NE induced a flow reduction which seemed to be already maximal at a fairly low infusion rate of below 2 µg/kg.min. The blood flow reduction was practically the same in normo- and hypercapnia |
| Rogers et al, 1989<sup>42</sup> | NE: 100 ng/min (n = 11) Propanol: 1 mg/kg (n = 5) Prazosin: 1 mg/kg and Yohimbine: 1 mg/kg (n = 5) | Two 5 mins infusions | CBF: Radiolabeled microsphere technique CMRO<sub>2</sub>: Blood gas analyzer | PCO<sub>2</sub> and PO<sub>2</sub> were kept constant throughout all groups NE: | None mentioned | Circulating NE may increase CBF via beta-adrenergic-mediated stimulation of cerebral oxygen consumption during severe stress |

<sup>Continues</sup>
| Reference                  | Dose of vasopressor administered | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response                                                                 | Adverse effects to norepinephrine | Conclusions                                                                                     |
|----------------------------|----------------------------------|----------------------|-----------------------------------------------|------------------------------------------------------------------------------------------|----------------------------------|-----------------------------------------------------------------------------------------------|
| Reynier-Rebuffel et al., 1986<sup>16</sup> | NE: 1 µg/kg/min                   | 35 sec               | CBF: Autoradiographic diffusible tracer technique with C-14 ethanol | PCO<sub>2</sub> and PO<sub>2</sub> were kept constant throughout all groups NE unanesthetized: CBF: No significant change in cortical regions but the flow decrease 6 to 22% in other structures which were significant in nucleus, hypothalamus, colliculus, and reticular NE anesthetized group 1: Same as unanesthetized but in superior colliculus the response was inverted leading to significant increase in blood flow NE anesthetized group 2: General increase in CBF except caudate nucleus | None mentioned | Showed that caudate nucleus but not thalamic or cortical regions reaction to circulating NE which can be specifically differentiated from the classical autoregulatory response to BP. Under anesthetized these changes in cerebrovascular reactivity appear to be linked to moderate change in systemic reactivity |
| Patel et al., 1990<sup>17</sup> | Angiotensin II (AT): 20 µg/mL NE: IV 32 µg/mL PE: 120 µg/mL | Used to increase MAP to 20%, 40%, 60% and 80% | CBF: Radiolabeled microsphere technique | PCO<sub>2</sub> and PO<sub>2</sub> were kept constant throughout all groups All values in mL/g/min AT: CBF: 0.78 ± 0.07 Hemispherical CBF: 0.75 ± 0.07 Posterior Fossa CBF: 0.86 ± 0.06 NE: CBF: 0.67 ± 0.04 Hemispherical CBF: 0.65 ± 0.04 Posterior Fossa CBF: 0.75 ± 0.05 PE: CBF: 0.73 ± 0.06 Hemispherical CBF: 0.70 ± 0.05 Posterior Fossa CBF: 0.82 ± 0.07 | None mentioned | NE and PE may indirectly result in cerebrovascular vasodilation or AT has intrinsic cerebral vasoconstrictive effects during isoflurane anesthesia and therefore the cerebrovascular autoregulation should affect selected vasopressor |
| Gannushkina et al., 1974<sup>18</sup> | NE: 10 mL of a 0.02% solution | 2-3 mins            | CBF: Hydrogen clearance method | PCO<sub>2</sub> and PO<sub>2</sub> were assumed to be constant throughout all groups NE: CBF: Dropped from 108 to 32 mL/100 g/min then remained stable NE and Renal Hypertension: CBF had a slight increase at injection (182 mL/100 g/min; P < .01), which then fell sharply to 40%-50% of its initial value (32 mL/100 g/min P < .01) In two animals there was the same rise as control | None mentioned | Raising the pressure in control rabbits above 160-180 mmHg led to an increase in the CBF; in the rabbits with experimental renal hypertension this increase in blood flow began at higher levels of the arterial pressure and was quickly followed by a decrease to 40%-50% of the initial blood flow |
| Reference                              | Dose of vasopressor administered | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response | Adverse effects to norepinephrine | Conclusions                                                                 |
|---------------------------------------|----------------------------------|----------------------|-----------------------------------------------|--------------------------|----------------------------------|----------------------------------------------------------------------------|
| Tomomatsu et al, 1981                 | NE: $10^{-9}$ to $10^{-3}$ g/mL | 10 mins              | Tension: Isometer transducer Pressure: Electrode manometer | PCO₂ and PO₂ remained constant throughout all groups | None mentioned | In the presence of $10^{-9}$ g/mL NE, discharge frequency of all units significantly increased at a given pressure step when compared with the control, whereas NE at a high concentration ($10^{-6}$ g/mL) did not produce significant changes in the discharge frequency. It is concluded that NE released by sympathetic nerve endings most likely acts directly on the baroreceptor nerve endings and sensitizes them. |
| Edvinsson et al, 1979                 | L-arterenol hydrochloride: 1 µg/kg/min | 01 mL/min at 10 mins | rCBF: Autoradiographic diffusable tracer technique with C-14 | PCO₂ and PO₂ were kept constant throughout all groups | None mentioned | The presence and heterogeneous distribution in the cerebrovascular bed of alpha- and beta-adrenoreceptors that can be activated by sympathomimetics given systemically. If NE was allowed to pass the blood-brain barrier after osmotic opening with urea, an increased regional flow was obtained, probably due to a mechanism where the vasodilator effect secondary to activation of cerebral metabolism predominated over the direct vasoconstrictor effect of the amine. |

**TABLE 2** (Continued)
Edvinsson et al., 1978
NE: 5 µg/kg/min
Propranolol: 25 µg/kg/min

10 mins
CBF: Autoradiographic diffusible tracer technique with C-14-ethanol

PCO₂ and PO₂ were kept constant throughout all groups
Brain region: (Baseline, After urea) mL/100 g/min
Parietal cortex: 4.7 ± 0.4, 16.6 ± 3.0 (P < .01)
Occipital cortex: 4.5 ± 0.5, 17.5 ± 3.6 (P < .01)
Caudate nucleus: 2.8 ± 0.4, 12.5 ± 3.0 (P < .01)
Thalamus: 2.7 ± 0.4, 10.9 ± 2.6 (P < .05)
Mesencephalon: 39 ± 0.5, 3.9 ± 0.5 (P > .05)
NE and hypertonic urea:
CBF: Significant increase over 10 mL/100 g/min in every area but mesencephalon on injection side as compared to noninjection

Conclusions
The normally low penetration of NE into the brain was enhanced fourfold in those brain regions that showed Evans blue extravasation following the administration of hypertonic urea. In the same regions, the systemic administration of NE markedly increased local CBF, compared to the contralateral hemisphere that was unaffected by the injection of urea. This effect on rCBF was blocked by the beta-receptor antagonist, propranolol.

Lasbennes et al, 1988
NE: 10 µg/mL (N = 20)
Clorgyline: 1 mg/kg (n = 9)
Clorgyline and NE: 1.9 mg/kg and 1.5 µg/kg/min (n = 8)

To achieve MAP of 121 and 171 mmHg
rCBF: Autoradiographic diffusible tracer technique with iodo-antipyrine

PCO₂ and PO₂ were constant throughout all groups
Only Clorgyline with NE had statistically significant rCBF:
Frontal Cortex: 18 ± 5 (P < .05)
Parietal Cortex: 15 ± 5 (P < .05)
Thalamus: 14 ± 5 (P < .05)
Mesencephalon: 15 ± 5 (P < .05)
Pons: 16 ± 5 (P < .05)
NE: rCBF and MAP showed linear relationship at large infusions produced substantial increase in CBF
Clorgyline: No significant effect to CBF or blood-brain barrier perfusion at any injection amount

Conclusions
Clorgyline administration alone did not significantly modify rCBF, but the subsequent infusion of NE induced an increase in rCBF in all structures investigated.
| Reference                     | Dose of vasopressor administered | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response                                                                 | Adverse effects to norepinephrine                                                                 | Conclusions                                                                                     |
|-------------------------------|----------------------------------|---------------------|----------------------------------------------|--------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Szabo et al. 1983            | NE: 10 µg/kg/min 2 hrs (n = 8)   | 1-2 hrs             | CBF: Autoradiographic diffusible tracer technique with C-14 labeled iodo-antipyrine CVR = MAP/CBF | PCO₂ and PO₂ were constant throughout all groups Control: CBF: 0.86 ± 0.03 mL/min/kg CVR:1.70 ± 0.06 mmHg min⁻¹ g/mL NE 10 µg: CBF: 1.18 ± 0.05 (P < .001) CVR: 1.49 ± 0.07 (P < .05) NE 20 µg for 1 hrs: CBF: 0.91 ± 0.04 CVR: 2.39 ± 0.12 (P < .001) NE 20 µg for 2 hrs: CBF: 0.66 ± 0.05 (P < .001) CVR: 1.8 ± 0.11 Phenoxybenzamine and NE: CBF: 1.48 ± 0.07 (P < .001) CVR: 0.94 ± 0.05 (P < .001) | Lethal outcome of shock with sustained NE blood concentrations and for infusions over 20 µg/kg/min longer than 2 hrs effectively prevent cerebral autoregulation | Supports the hypothesis that high concentrations of NE in cerebral blood vessels produced by activity might be an important factor in etiology of blood flow deficiencies |
| Tuor et al. 1986             | L-NA: 1-15 µg/kg, Dopamine: 75-300 µg/kg/min | ABP maintained at 35 mmHg | CBF: Autoradiographic diffusible tracer technique with C14 iodo-antipyrine | PCO₂ and PO₂ were constant throughout all groups NE 5 µg: CBF auditory cortex: Decreased by 18 ± 5% CBF cerebellar vermis: Increased by 66 ± 29% CBF pontine reticular: Increased by 38 ± 13% CBF median: 15% (P < .05) Dopamine: CBF in rostral cerebral cortex, posterior parietal cortex and white matter: Greater than 65% (P < .05) CBF Nuclei of lower brain stem: Less than 40% (P < .05) CBF median: 44% | None mentioned                                                                                   | The cerebrovascular response to hypertension appears to be dependent upon the catecholamine which is employed to elicit the elevation in arterial blood pressure. The present data provide clear evidence that hypertension induced by NE and that induced by dopamine have distinctly different influences on the cerebrovasculature |
| Reference          | Dose of vasopressor administered                          | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response | Adverse effects to norepinephrine | Conclusions                                                                 |
|--------------------|-----------------------------------------------------------|---------------------|-----------------------------------------------|--------------------------|-----------------------------------|-----------------------------------------------------------------------------|
| Nemoto et al, 1996 | NE: 0.269 µg/min and 0.195 µg/min (n = 9) Donor Blood Transfusion: 5-10 mL (n = 10) | 5 to 10 mL dose    | CBF: Hydrogen clearance technique             | PCO₂ and PO₂ were kept constant throughout all groups | None Mentioned               | NE infusion during hypothermia could nullify the beneficial effects of mild hypothermia in cerebral protection; NE slightly decreases CBF in both situations |
|                    |                                                           |                     | CMRO₂: Divisible into that associated with electroencephalographic | NE 38°C 0.269 µg/min: CBF: 132 ± 27 mL/100 g/min CMRO₂: 7.48 ± 2.49 mL/100 g/min |                    | | |
|                    |                                                           |                     |                                               | NE 34°C 0.195 µg/min: CBF: 121 ± 24 mL/100 g/min CMRO₂: 5.41 ± 2.02 mL/100 g/min (P < .001) |                    | | |
|                    |                                                           |                     |                                               | Donor Blood 38°C: CBF: 98 ± 28 mL/100 g/min (P < .05) CMRO₂: 7.41 ± 1.78 mL/100 g/min |                    | | |
|                    |                                                           |                     |                                               | Donor Blood 34°C: CBF: 101 ± 32 mL/100 g/min CMRO₂: 6.31 ± 1.41 mL/100 g/min (P < .001) |                    | | |
| Sato et al, 1987   | L-threo-3,4-Dihydroxyphenylserine (L-DOPS): 3 mg/kg and 1 mg/kg L-DOPS and benserazide: 3 mg/kg and 3 mg/kg/hr L-DOPS and propranolol: 3 mg/kg and 3 mg/kg/hr NE: 100 µg/kg/hr | 3 mins             | CBF: Hydrogen clearance method                | L-DOPS 3 m/kg CBF: Increase in striatal blood flow (SBF) | None mentioned               | The effects of L-DOPS may be attributed to the action of NE formed from L-DOPS, and the action may be mediated by stimulation of beta-adrenoceptor; NE increase CBF maybe due to cardiac output increase |
|                    |                                                           |                     |                                               | L-DOPS 1 mg/kg CBF: NS effect |                    | | |
|                    |                                                           |                     |                                               | L-DOPS and benserazide: CBF increase was inhibited by benserazide |                    | | |
|                    |                                                           |                     |                                               | L-DOPS and propranolol: CBF increase was inhibited by propranolol |                    | | |
|                    |                                                           |                     |                                               | NE CBF: Marked increase to 40% at 20 mins then remained constant |                    | | |
| Mascia et al, 1999 | NE: 0.08 mg/kg/min                                       | 30 mins × 2         | rCBF: Hydrogen clearance technique            | PCO₂ and PO₂ were constant throughout all groups | None mentioned               | Endothelin-1 production is required in the CBF response to increased CPP, but is not required in the maintenance of resting CBF; NE increase CBF to a higher amount in the endothelin-1 group, indication its effect on cerebral response |
|                    |                                                           |                     | PO₂: Blood samples                            | NE: CPP: Increased by 21 ± 2 (23 ± 2%) mmHg (P < .001) CBF: 3.6 ± 3.1 (6 ± 8%) mL/100 g/min (P = .5) |                    | | |
|                    |                                                           |                     |                                               | NE + endothelin-1: CPP: Increased by 18 ± 1 (20 ± 2%) mmHg (P < .001) CBF: 15.8 ± 4.1 (46 ± 13%) mL/100 g/min (P = .004) |                    | | |
|                    |                                                           |                     |                                               | PO₂: no significant change in any group |                    | | |

(Continues)
| Reference                  | Dose of vasopressor administered | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response                                                                 | Adverse effects to norepinephrine | Conclusions                                                                 |
|---------------------------|----------------------------------|---------------------|-----------------------------------------------|----------------------------------------------------------------------------------------|----------------------------------|-----------------------------------------------------------------------------|
| Stromberg et al, 1992⁹⁹  | PD123319: 1-10 mg/kg NE: 0.1-3.2 µg/min | To increase hypertension 5 mins before PD was injected | CBF: Laser-Doppler flowmetry                  | NE: CBF increased from 110 to a max of 160% (P < .01)                                      | None mentioned                    | PD did not alter baseline CBF at normal pressures, but appears to interfere with autoregulatory mechanisms of CBF. The participations of alpha-2 receptors in the regulation of CBF confirms a physiological role for this receptor subtype and may give clues for future treatment of various cerebrovascular disorders. NE increase CBF but maybe due to cardiac output then local ICP change. |
| Zhang et al, 1991⁷⁰      | NE Increasing doses: 0.01-30 µg/kg Superoxide dismutase: 24 000 units/kg plus 1600 units/kg/min | 300-400 g          | CBF: Laser-Doppler flowmetry, PO2: Blood samples | PCO₂ and PO₂ were kept constant throughout all groups                                   | Whereas five (63%) of the eight control rats died after the 10 µg/kg norepinephrine dose, all eight rats treated with superoxide dismutase survived this dose | Blood pressure and CBF responses to submaximal pressor doses of NE and reduces mortality associated with acute hypertension in rats. |
| Gozzi et al, 2007⁷¹      | NE: 0.125 µg/kg (n = 5) 0.5 µg/kg (n = 5) 2 µg/kg (n = 5) 8 µg/kg (n = 5) NE doses refer to the salt form of the compound | Over 80 s          | MAP: MRI acquisitioner CBV: Laser-Doppler flowmetry, and MRI | PCO₂ and PO₂ remained constant throughout all groups                                       | None mentioned                    | CBF autoregulation was maintained over a BP range of 60-120 mmHg. Under these conditions, no significant central rCBV responses were observed, suggesting that microvascular rCBV responses in response to abrupt changes in perfusion pressure are negligible within the autoregulatory range. Larger BP responses were accompanied by significant changes in both CBV and CBF that might confound the interpretation of pharmacological MRI results. As the dose of NE was increased and MABP exceeded 130 mmHg, For MABP greater than 130 mmHg both LDF and microvascular rCBV showed transient but significant increases. |
TABLE 2 (Continued)

| Reference                      | Dose of vasopressor administered | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response | Adverse effects to norepinephrine | Conclusions |
|--------------------------------|----------------------------------|----------------------|-----------------------------------------------|--------------------------|-----------------------------------|-------------|
| Kuschinsky et al, 1983<sup>32</sup> | L-NE: 1 mg/100 mL saline containing 0.1% ascorbic acid at 10-100 µL/min (n = 4) 2 Deoxyglucose: 50 µCi/kg (n = 4) Iodo Antipyrine: 50 µCi/kg (n = 6) | Adjust to maintain stable heart rate | PCO<sub>2</sub> and PO<sub>2</sub> were constant throughout all groups rCBF: Diffusible tracer with 14C amino antipyrine Local rates of cerebral glucose utilization (LCGU): Calculated from the local tissue concentrations | rCBF during NE increased in most of the structures LCGU: ~10% and +74% (P < .05) in only 6 of 39 structures Despite this large variability, there was still a tight correlation between the rCBF | None mentioned | When compared to the relationship between LCGU and rCBF in a control group, the slope of the regression line was increased significantly by NE, indicating a resetting of the coupling mechanism. At a given metabolic rate, a higher blood flow is needed to perfuse a brain structure during NE infusion than during control conditions |
| Kraut et al, 2004<sup>73</sup>    | NE 5 µg/100 g 60 sec             | CBF: Laser-Doppler flowmetry | NE cerebral tissue blood flow: Increased by 270 ± 47% (P < .05) | None mentioned | The significant correlation between the hemodynamic state of the organs and its mitochondrial redox state may serve as an indicator of tissue vitality under "brain sparing" conditions |

Healthy lightly anesthetized animal models

| Reference       | E: 0.1 and 0.25 µg/kg/min NE: 0.25 µg/kg/min | 40 mins injection 3 times with 20 mins rest | CBF: Determined by weighing timed collections and assuming the specific gravity of blood to be 1.05 CMRO<sub>2</sub>: Derived from measurements of arterial-cerebral venous (sagittal sinus) blood oxygen content differences | PCO<sub>2</sub> and PO<sub>2</sub> remained constant throughout all groups Cyclopropane Control: CBF: 67 ± 7 mL/min/100 g CMRO<sub>2</sub>: 4.33 ± 0.49 mL/min/100 g 30-40 mins with E 0.1 µg/kg: CBF: 113 ± 17 mL/min/100 g (P < .05) CMRO<sub>2</sub>: 5.07 ± 0.57 mL/min/100 g (P < .05) 90-100 mins with E 0.25 µg/kg: CBF: 62 ± 12 mL/min/100 g CMRO<sub>2</sub>: 4.80 ± 0.66 mL/min/100 g (P < .05) 150-160 mins with NE 0.25 µg/kg: CBF: 63.0 ± 15 mL/min/100 g CMRO<sub>2</sub>: 5.32 ± 0.93 mL/min/100 g (P < .05) Overall increased CMRO<sub>2</sub> by 17%-23% within 10-30 mins Nitrous oxide, Halothane, Pentobarbital, or Ketamine: Regardless of anesthetic, each infusion of E or NE resulted in an immediate increase in CBF which, except with E 0.1 µg/kg/min which returned to control levels within 10 mins No change in CMRO<sub>2</sub> regardless of dose or duration of infusion | None mentioned | Cyclopropane but not the other anesthetics tested increased the permeability of the BBB and presumably allowed the passage of E or NE into the brain to increase CMRO<sub>2</sub> reversibly. Opening of the BBB may be a direct effect of cyclopropane on endothelial cells or may be mediated by central adrenergic systems. For their part, E or NE may increase CMRO<sub>2</sub> by either direct action on neuronal receptors or metabolically coupled synaptic events NE increase CMRO<sub>2</sub> and CBF in all anesthetic methods tested |

(Continues)
| Reference           | Dose of vasopressor administered                                                                 | Technique to measure cerebral response | Adverse effects to norepinephrine | Conclusions                                                                 |
|---------------------|--------------------------------------------------------------------------------------------------|---------------------------------------|-----------------------------------|-----------------------------------------------------------------------------|
| Lluch et al., 1973<sup>19</sup> | E: 0.1 to 5 µg (n = 10) NE: 0.1 to 5 µg (n = 10) Isoproterenol: 0.01 to 1 µg (n = 9) phenoxymyxazine: 200 to 400 µg propranolol: 250 µg | CBF: Radioactive gas elimination method CMRO<sub>2</sub>: Polyethylene Catheter | None Mentioned | E, NE, and isoproterenol exert powerful direct effects on the cerebral circulation of the unanesthetized goat, and these effects appear to be mediated by alpha and beta receptors. |
| Perales et al., 1997<sup>10</sup> | NE: 10 µg/min 30 µg/min Magnesium sulfate (MgSO<sub>4</sub>): Infused intravenously at 0.3 g and 3 g | CBF: Electromagnetic flow probe MAP: Catheter in femoral artery CVR: Calculated as the mean arterial blood pressure in mmHg divided by CBF | None Mentioned | Magnesium sulfate reverses the NE-induced cerebral vasoconstrictor and pressor responses by a direct inhibitory action of Mg<sup>2+</sup> on the actions of NE in the cerebral and peripheral vascular beds, which leads to a decrease in vascular resistance. |

**TABLE 2** (Continued)
| Reference                  | Dose of vasopressor administered | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response | Adverse effects to norepinephrine | Conclusions                                                                                                                                 |
|----------------------------|----------------------------------|---------------------|-----------------------------------------------|--------------------------|---------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| Von Essen et al, 1972      | NE: 0.03 to 7.5 µg/kg/min         | Not Mentioned       | CBF: Radioactive gas elimination method        | PCO₂ and PO₂ were not monitored | NE:                            | Importance for the understanding of some circulatory disturbances of the brain and also for a correct interpretation of altered concentration of different amines, and their metabolites, in brain tissue and cerebrospinal fluid after administration of certain biogenic amines or their precursors. |
|                            | 5-HT: 0.1 to 22.8 µg/kg/min       |                     |                                               |                          | CBF: Max reduction −21% (P=.01) | NE:                            |                                                                                                                                           |
|                            | Dopamine: 0.05 to 57.4 µg/kg      |                     |                                               |                          | CMRO₂: Constant                |                                                                                                                                           |
|                            |                                  |                     |                                               |                          | 5-HT:                           |                                                                                                                                           |
|                            |                                  |                     |                                               |                          | CBF: +28% (P < .01)            |                                                                                                                                           |
|                            |                                  |                     |                                               |                          | CMRO₂: Constant                |                                                                                                                                           |
|                            |                                  |                     |                                               |                          | Dopamine low dose:             |                                                                                                                                           |
|                            |                                  |                     |                                               |                          | CBF: −20%                      |                                                                                                                                           |
|                            |                                  |                     |                                               |                          | CMRO₂: Constant                |                                                                                                                                           |
|                            |                                  |                     |                                               |                          | Blocked with pimozide or haloperidol |                                                                                                                                           |
|                            |                                  |                     |                                               |                          | Dopamine high dose:            |                                                                                                                                           |
|                            |                                  |                     |                                               |                          | CBF: +30% (P < .01)            |                                                                                                                                           |
|                            |                                  |                     |                                               |                          | CMRO₂: Constant                |                                                                                                                                           |
|                            |                                  |                     |                                               |                          | Blocked by pimozide or haloperidol but not by propranolol |                                                                                                                                           |
|                            |                                  |                     |                                               |                          |                                |                                                                                                                                           |
| Edvinsson et al, 1972      | Tyramine: 0-10 mg/kg              | 2 mins              | CBV: Radioisotope dilution technique          | PCO₂ and PO₂ were kept constant throughout all groups | Tyramine: CBV: Decreased as dose increases with 12% at 0.1 mg/kg (P < .05) | None Mentioned                                                                                                                                 |
|                            | NE: 5 µg/kg                      |                     |                                               |                          | NE under 12 hrs: CBV: No significant change | That a NE induced vasoconstriction in the circulation of the brain depends on the quantitative access of the amine to the adrenergic receptor area. The vasoconstrictor response may be influenced by such features as the amount of adrenergic innervation, the types of adrenergic receptors present, and the properties of the barrier. |
TABLE 2 (Continued)

| Reference          | Dose of vasopressor administered | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response | Adverse effects to norepinephrine | Conclusions                                                                 |
|--------------------|-----------------------------------|---------------------|----------------------------------------------|--------------------------|-----------------------------------|--------------------------------------------------------------------------------|
| Alborch et al., 1977* | Tyramine: 50-500 µg Norepinephrine: 0.03-3 µg Phentolamine: 1 mg Propranolol: 1 mg | 1 mg in 1 mL of saline for 10-15 mins | CBF: Electromagnetic flow transducer | PCO₂ and PO₂ were not monitored Tyramine CBF: Decreased versus control 50 µg: 10 to 1% CBF (control vs tyramine) 100 µg: 20 to 5% CBF 250 µg: 25 to 10% CBF 500 µg: 30 to 10% CBF NE CBF: Increased versus control 0.01 µg: 10 to 15% CBF (control vs NE) 1 µg: 15 to 25% CBF 2 µg: 25 to 45% CBF 3 µg: 30 to 54% CBF %CBF is the reduction percent of the CBF Phentolamine: CBF Before Removal: Increased by 31% CBF After Removal: Increased by 2% Propranolol: CBF Before Removal: Reduced by 14% CBF After Removal: Reduced by 4% | None Mentioned | There is an active participation of the perivascular sympathetic nerve endings in the overall regulation of cerebrovascular resistance. The effects of phentolamine and propranolol on cerebral blood flow before and after removal of the superior cervical sympathetic ganglion indicate that under normal conditions both alpha and beta receptors display a tonic adrenergic activity in the cerebral blood vessels. NE decrease CBF in all doses with increase dose causing increased response |
| Aubineau et al., 1985* | NE: 1.8 to 2.2 µg/kg/min Angiotensin II (AT): 1.0 to 1.8 µg/kg/min | 30 s | CBF: Radioactive microsphere with helium and thermal clearance PO₂: Measure with probes samples | PCO₂ was kept constant throughout all groups NE: CBF: Not significantly changed PO₂: Reduce by 9% (P < .05) AT: CBF: Reduced by 10% PO₂: Reduced by 9% (P < .001) Stim: CBF: Decrease 23.6 in heterolateral hemisphere and 22.2 mL/100 g/min in homolateral PO₂: Reduced by 18% (P < .01) | None Mentioned | As in the peripheral circulation, chronic sympathectomy affects the equilibrium of the vascular smooth muscle fibers but that circulating amines play no compensatory role in the cerebral circulation because of the blood-brain barrier. NE did not significantly change CBF |

*TABLE 2 (Continued)
TABLE 2 (Continued)

| Reference                  | Dose of vasopressor administered | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response                                                                 | Adverse effects to norepinephrine | Conclusions                                                                                      |
|-----------------------------|----------------------------------|---------------------|-----------------------------------------------|-----------------------------------------------------------------------------------------|-----------------------------------|-----------------------------------------------------------------------------------------------|
| Animal models with bile duct removed |                                 |                     |                                               |                                                                                         | None Mentioned                     | Indicate that in baboons following ligation of the bile duct there is an altered cerebrovascular response to infused NE. Cerebral vasoconstriction was obtained with infusions of NE at 8 µg and 16 µg in the jaundiced animals, whereas dilatation was evident in the control animals. These findings suggest an increased cerebrovascular sensitivity to NE in the obstructive jaundice following bile duct ligation. |
| Bloom et al, 1975           | NE: 8, 16, and 32 µg/min         | 10 min              | CBF: Xenon clearance method                   | PCO₂ and PO₂ were constant throughout all groups                                          | NE 8 µg:                          |                                                                                               |
|                             |                                  |                     | Cerebrovascular Resistance (CVR): Calculated with pressure/flow | CBF: Reduction 8.4 ± 4.3 mL/100 g/min (P < .005)                                          | CBF: Reduction 9.48 ± 2.63 mL/100 g/min (P < .005)                                      |                                                                                               |
|                             |                                  |                     |                                               | CVR: Decrease 0.21 ± 0.12 mmHg/mL/min                                                    | CVR: Decrease 0.66 ± 0.28 mmHg/mL/min                                                   |                                                                                               |
|                             |                                  |                     | NE 8 µg and Jaundice:                         |                                                                                         | NE 16 µg:                          |                                                                                               |
|                             |                                  |                     |                                               |                                                                                         | CBF: Reduction 8.6 ± 6 mL/100 g/min (P < .02)                                           |                                                                                               |
|                             |                                  |                     |                                               |                                                                                         | CVR: Increase 0.001 ± 0.11 mmHg/mL/min                                                  |                                                                                               |
|                             |                                  |                     | NE 16 µg and Jaundice:                        |                                                                                         | NE 32 µg:                          |                                                                                               |
|                             |                                  |                     |                                               |                                                                                         | CBF: Reduction 1.97 ± 4.6 mL/100 g/min                                                   |                                                                                               |
|                             |                                  |                     |                                               |                                                                                         | CVR: Increase 0.425 ± 0.17 mmHg/mL/min                                                  |                                                                                               |
|                             |                                  |                     | NE 32 µg and Jaundice:                        |                                                                                         | NE 16 µg:                          |                                                                                               |
|                             |                                  |                     |                                               |                                                                                         | CBF: Reduction 5.16 ± 3.6 mL/100 g/min                                                   |                                                                                               |
|                             |                                  |                     |                                               |                                                                                         | CVR: Increase 0.71 ± 0.28 mmHg/mL/min                                                   |                                                                                               |
| Healthy heavily anesthetized animal models with craniotomy |                   |                     |                                               |                                                                                         | None Mentioned                      | An increase in blood pressure in intracranial hypertension is not a favorable compensatory mechanism designed to maintain brain function. NE had no significant results of rCBF but in high ICP NE injection did increase CBF |
| Shalit et al, 1974           | ICP balloon increase (n = 18)    | 10 to 15 min        | rCBF: Krypton clearance method                | PCO₂ and PO₂ were constant throughout all groups                                          | None Mentioned                     |                                                                                               |
|                             | Brain swelling (n = 8)            |                     | ICP: Epidural transducer                       | Balloon increase:                                                                         |                                  |                                                                                               |
|                             | NE drip was increased to make 40 to 80 mmHg blood pressure |                     | PO₂: Measured with electrode system            | NE did not significantly affect ICP below 70 mmHg but does above                           |                                  |                                                                                               |
|                             |                                  |                     |                                               | NE results in a significant spike increases for rCBF (0.7 mL/gm/min) at each dose, with less effect result at ICP above 80 mmHg |                                  |                                                                                               |
|                             |                                  |                     |                                               | Brain Swelling:                                                                           |                                  |                                                                                               |
|                             |                                  |                     |                                               | NE did not significantly affect ICP below 80 mmHg but does above                           |                                  |                                                                                               |
|                             |                                  |                     |                                               | NE did not significantly affect the CBF                                                   |                                  |                                                                                               |
| Reference          | Dose of vasopressor administered | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response | Adverse effects to norepinephrine | Conclusions                                                                 |
|--------------------|----------------------------------|----------------------|---------------------------------------------|-------------------------|----------------------------------|-----------------------------------------------------------------------------|
| Ulrich et al, 1985  | Phenylephrine: 10^{-9} to 10^{-3} mol/L (n = 19)  
Oxymetazoline: 10^{-4} to 10^{-3} mol/L (n = 21)  
Prazosin: 10^{-9} to 10^{-4} (n = 15)  
Yohimbine: 10^{-8} to 10^{-4} (n = 23)  
NE: 10^{-7} to 10^{-4} mol/L (n = 25) | Injection of full solution | Venous diameter (VD): Glass micropipette with sharpened tips were filled with the test solutions and mounted on a micromanipulator | Phenylephrine VD: 1 to -10% at 10^{-3}  
Oxymetazoline VD: 2 to -8% at 10^{-4} then slightly increased  
Prazosin VD: Venous diameter remains constant  
Prazosin and NE VD: -15% to 0  
Yohimbine VD: -15% to 0  
Yohimbine + NE VD: -23 to -1% | None Mentioned | Since both alpha and alpha-2 adrenoceptor agonists are less potent constrictors of pial veins than NE in vivo, a preferential use of alpha, or alpha-2 adrenoceptor agonists cannot be recommended, if a therapeutic reduction of ICP or blood volume is desired. |
| Wei et al, 1975     | NE: 0, 10, 20 and 100 µg/mL  
Concentration of CSF was calcium increase 10 mEq/l | Short and long periods of time | CBF: Free diffusible tracer technique  
Bulb placed for sampling and ABP | NE 0 µg/mL Small vessel diameter(µm): 44.4 ± 1.8  
NE 10 µg/mL: 43.3 ± 1.9  
NE 100 µg/mL: 44.3 ± 1.4  
Ca²⁺ and CSF:  
NE 100 µg/mL caused the only change in diameter from 43.3 ± 2.1 to 42.9 ± 2.4 µm  
Ca²⁺ and Mg²⁺ in CSF:  
NE 0 µg/mL Small vessel diameter(µm): 49.8 ± 2.3  
NE 10 µg/mL: 47.5 ± 3.1  
NE 100 µg/mL: 47.0 ± 4.6  
Wahl solution:  
NE 0 µg/mL Small vessel diameter(µm): 49.8 ± 2.3  
NE 10 µg/mL: 48.2 ± 2.2  
NE 100 µg/mL: 47.5 ± 2.0  
For all Ca²⁺ levels and Mg²⁺ levels and Wahl solution all small pail arties changes similar with changes in NE | None Mentioned | The results imply a functional role for postganglionic autonomic fibers in CBF autoregulation. NE in high concentration is capable of producing substantially greater constriction of these vessels than by sympathetic nerve stimulation suggests that the potential exists for NE-induced reductions in CBF of considerable magnitude under abnormal conditions, such as in response to brain injury. |
| Reference       | Dose of vasopressor administered | Mean administration | Technique to measure cerebral vascular response | Cerebrovascular response | Adverse effects to norepinephrine | Conclusions                                      |
|-----------------|---------------------------------|---------------------|-----------------------------------------------|-------------------------|----------------------------------|---------------------------------------------------|
| Busija et al, 1987 | NE: $10^{-6}$ to $10^{-4}$ mol/L (n = 18) | 5 mins              | Pial arteries were observed with a wild trinocular stereo microscope. | PCO$_2$ and PO$_2$ remained constant throughout all groups | None Mentioned                           | NE elicits the release of prostanoids from the cortical surface, and that these substances limit cerebral vascular constriction to NE. That sympathetic nerve stimulation and exogenous NE are able to have substantial constrictor effects on the cerebral circulation of newborn pigs, and our findings are consistent with an important role of the sympathetic nervous system in regulation of CBF in the newborn animal. |
|                 | Isoproterenol: $10^{-8}$ to $10^{-6}$ mol/L (n = 7) |                      | Pial arterial diameter was measured with a television camera mounted on the microscope, a video monitor, and a video microscale |                        |                                  |                                                   |
|                 |                                                 |                     |                                              |                        |                                  |                                                   |
| Leffler et al, 1989 | NE: $10^{-6}$ to $10^{-4}$ mol/L | 20 mins             | Catheters placed in aortae for blood withdrawal and monitoring Prelims experiments showed that blood pressure was reduced such that radiolabeled microspheres did not work Observe pial arterioles with trinocular stereo microscope | PCO$_2$ and PO$_2$ was kept constant throughout all groups | None Mentioned                           | After cerebral ischemia, autoregulatory pial arteriolar dilation in response to hypotension is absent, while vasoconstriction in response to NE is intact. |
|                 | In three groups Sham-operated control (n = 7), 2-3 hrs postischemia (n = 6) and 24 hrs postischemia (n = 6) |                     |                                              |                        |                                  |                                                   |
|                 |                                                 |                     |                                              |                        |                                  |                                                   |
**TABLE 2 (Continued)**

| Reference | Dose of vasopressor administered | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response | Adverse effects to norepinephrine | Conclusions |
|-----------|----------------------------------|---------------------|---------------------------------------------|------------------------|-----------------------------------|-------------|
| Myburgh et al, 1998<sup>34</sup> | Dopamine: 0-60 µg/kg/min | 5 mins | CBF: Ultrasonic-Doppler transducer ICP: Intraparenchymal strain gauge catheter Cerebral oxygen utilization COU: Sigma CBF an auto-venous oxygen content difference | PCO<sub>2</sub> and PO<sub>2</sub> were assumed to be constant throughout all groups Dopamine: ICP: Significant increase on does greater than 20 µg/kg/min (78.6 ± 13.1 to 97.2 ± 8.8%) CBF: Statistically significant rise in CBF after 40 µg/kg/min (13.2 ± 3.2 to 52.6 ± 24.3%) COU: Initial decrease at 20 µg/kg/min followed by increase to base line at 60 µg/kg/min E: ICP: Dose-dependent increase after 40 µg/min CBF: No significant change COU: No significant change NE: ICP: Did not increase CBF: No significant change COU: No significant change | None Mentioned | Intact cerebral autoregulation model-induced hypertension by E and NE is not associated which changes in CBF, where dopamine causes cerebral hyperemia increased ICP and increased global cerebral oxygen utilization |
| Muir et al, 1993<sup>34</sup> | Ten mins after cocaine (1 mg/kg, iv) or saline: NE: increasing from 0.01-10 µg/kg | The pressor effect of L-NMMA was controlled for by comparison with NE titrated to effect an equivalent blood pressure elevation | Cortical blood flow (CoBF): Laser-Doppler flowmetry | PCO<sub>2</sub> and PO<sub>2</sub> were kept constant throughout all groups Cocaine significantly potentiated the blood pressure and cerebral blood flow responses NE: CoBF: Increased at 10<sup>-4</sup> µg/kg to 40% and 10<sup>-3</sup> µg/kg to 150% | None Mentioned | Cocaine causes a rapid, transient increase in blood pressure and CBF and potentiates the magnitude and duration of the pressure and flow response to NE. Repetitive blood pressure elevations in cocaine abusers is one of the proposed mechanisms leading to damage of cerebral vessels |
| Reference          | Dose of vasopressor administered | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response | Adverse effects to norepinephrine | Conclusions                                                                                       |
|--------------------|----------------------------------|---------------------|-----------------------------------------------|--------------------------|-----------------------------------|-------------------------------------------------------------------------------------------------|
| Oberdorster et al., 1973³⁴ | E: 0.001-10 µg (n = 5) NE: 0.001-10 µg (n = 5) Isoproterenol: 0.001-10 µg (n = 5) | 30 sec             | CBF: Photoelectric drop recorder CVR: Calculated with CBF and internal perfusion pressure ICP: Isolated with two pressure transducers | PCO₂ and PO₂ remained constant throughout all groups E and NE: Dose-dependent increase of CVR ranging from 2% to 61% CVR: NE could be reversed by phentolamine, E were increased by propranolol CBF decreases linearly with inject from 0 to −5 mL/100 g/min | None Mentioned | These sources of contamination cannot account for the vasomotor responses and that, consequently, both alpha and beta-adrenergic activity of the cerebral vessels of the dog has been demonstrated. NE increase CVR and decrease CBF which can be mediated with phentolamine |
| Lowe et al., 1971³⁵ | Phenylephrine: 50-200 µg Isoproterenol: 15-40 µg NE: 15-100 µg E: 15-100 µg | Until dose gone   | CBF: Maintained with pump Pulsatile perfusion pressure: Recorded with servo channel of a Gilson five-channel polygraph CVR: Calculated by mean perfusion pressure/CBF | PCO₂ and PO₂ remained constant throughout all groups Phenylephrine: CVR: Increased over each dose increase Phenylephrine and Phenoxybenzamine: CVR: Less effective Isoproterenol: CVR: Decreased, no apparent correlation to dose Isoproterenol and propranolol: CVR: Reduced effectiveness NE: CVR: Increased with no apparent correlation to dose NE and phenoxybenzamine: CVR: Reduced response E: CVR: Increased with no apparent correlation to dose E and phenoxybenzamine: CVR: Decreased E and propranolol: CVR: Increased | As catecholamine blood levels in intact dogs are low in comparison to those achieved in these studies, it appears doubtful that circulating catecholamines play an important physiological role in the regulation of CVR. Possible explanations are considered for the lower response of the cerebral vasculature to catecholamines when this response is compared to that observed in other vascular beds |
### TABLE 2 (Continued)

| Reference          | Dose of vasopressor administered | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response                                                                 | Adverse effects to norepinephrine | Conclusions                                                                                     |
|--------------------|---------------------------------|---------------------|-----------------------------------------------|-----------------------------------------------------------------------------------------|---------------------------------|-----------------------------------------------------------------------------------------------|
| Zimmer et al., 1974 | NE: 2 µg/min E: 2 µg/min Isoprenaline: 0.2 µg/min | 10 mins            | CBF: Photoelectric drop recorder CVR: Calculated on pressure flow relationship CMRO₂: Changes in oxygenation in blood samples | PCO₂ and PO₂ remained constant throughout all groups In all groups the CVR and CBF effects are taken after indirect effects of drug are removed NE: CBF: Decreased by 0.2 ± 6.0% (P > .05) CVR: Reduced by 50% CMRO₂: Not changed E: CBF: Decreased 4.1 ± 3.3% CVR: Reduced by 50% CMRO₂: Not changed Isoprenaline: CBF: Increased by 9.3 ± 3.6% CVR: Reduced by 50% CMRO₂: Not changed | None Mentioned | Based on these investigations it is assumed that no pronounced vascular adjustments occur in the cerebral circulation during catecholamine infusions; however, CBF is significantly affected by catecholamine. |
| Omar et al., 2010   | NE: 2.5 µg/kg Nitro-L-arginine methyl ester (L-Name): 10 mg/kg | To maintain ABP to 180 mmHg in mature and middle-aged 150 mmHg in juveniles rat | Carotid blood flow (CoBF) and MABP: Transonic flow probe | PCO₂ and PO₂ were kept constant throughout all groups For all groups CoBF decreased after the injection of NE with a decrease of 0.5 mL/min (P < .05) in mature and 0.5 mL/min (P < .01) in middle age; the juvenile only has a minor drop and it was not significant Carotid vascular conductance (CVC) in all was significant at 0.005 mL/min (P < .01) juvenile and 0.08 mL/min (P < .001) for mature and middle age rats L-Name + NE: CoBF for juvenile and mature there was a slight decrease; in middle age there was a small increase CVC for juvenile and mature there was a slight decrease; in middle age there was a small increase | None Mentioned | The results of these two studies indicate that by middle age, aging itself has already altered several key mechanisms that regulate the carotid circulation that includes the brain. |
**TABLE 2** (Continued)

| Reference | Dose of vasopressor administered | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response | Adverse effects to norepinephrine | Conclusions |
|-----------|---------------------------------|---------------------|-----------------------------------------------|-------------------------|----------------------------------|-------------|
| Takahashi et al., 2000	n| NE: $10^{-7}$ to $10^{-5}$ mol/L | Yohimbine: $10^{-6}$ mol/L | Prazosin: $10^{-9}$ mol/L | Ketanserin: $10^{-5}$ mol/L | Methiothepin: $10^{-6}$ mol/L | 5 mins | Contractile diameter: Glass pipettes on micromanipulators monitored with video camera | NE: As dose increases contractile diameter increases | Yohimbine + NE: Significantly decrease control change (n = 5, P < .05) | Prazosin + NE: Slight decrease in contractile change (n = 5) | 5-HT: Increase in control response with dose increase | Ketanserin + 5-HT: Significantly dropped in contractile response | None Mentioned | That 5-HT plays a significant role in arteriolar contractility only from the CSF side, while NE is an important regulator or regulator of arteriolar contractility from both the CSF and blood circulation sides. NE causes dose-dependent contractions of arterioles |

### Various animal models

- **Mori et al., 1999**
  - **Group A Hypothermia:** (n = 10)
  - **Group B Hypothermia with NE:** 6-30 µg/kg (n = 6)
  - **Group C Hypothermia with Barbiturate (thiopental):** 5 mg/kg (n = 6)

- **Increase Blood Pressure to 25 mmHg**
- **Increase CBF:** Hydrogen clearance method
- **CMRO₂:** Calculated with arteriovenous oxygen difference and cerebral venous oxygen saturation taken from the superior sagittal
- **CVR:** Calculated from (MABP - ICP)/CBF
- **CBV:** Technetium-99 m-labeled human serum albumin in 12 Ca

- **PCO₂ and PO₂ were kept constant throughout all groups**
- **Group A:**
  - CBF: 51.2 ± 8.3 mL/100 g/min at 37°C and decreased with lower brain temperature (6.1 ± 2.7 at 25°C)
  - CMRO₂: 2.24 ± 0.75 mL/100 g/min at 37°C was also decreased by 0.52 ± 0.20 at 25°C
  - CBV: 5.3 ± 1.2% at 37°C decreased significantly at 29°C 3.7 ± 1.0% (P < .05)
  - CVR: 3.2 ± 0.7 mmHg·mL/100 g/min at 37°C increased significantly at 29°C 13.8 ± 5.2 (P < .01)
- **Group B:**
  - CBF: 24.2 ± 3.7 mL blood/mL O₂
  - 24.6 ± 7.4 at 33°C
  - 19.1 ± 4.3 at 25°C
  - CMRO₂: Proportional change associated with CBF
- **Group C:**
  - CBF/CMRO₂: Did not decrease

- **None Mentioned**

- **These results suggest that hypothermia may cause vasoconstriction and misery perfusion in the brain. This potential risk of relative ischemia can be avoided by combination with vasopressor administration, that cerebral hypothermia may cause cerebral vasoconstriction and relative ischemia. To avoid this misery perfusion, patients should not be cooled below 31°C. Hypothermia combined with vasopressor administration may avoid this serious cerebral metabolic disturbance.**

(Continues)
### Table 2 (Continued)

| Reference                  | Dose of vasopressor administered | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response | Adverse effects to norepinephrine | Conclusions                                                                 |
|----------------------------|----------------------------------|----------------------|-----------------------------------------------|--------------------------|----------------------------------|-----------------------------------------------------------------------------|
| Panther et al, 1985<sup>37</sup> | Adenosine: 4.94 μmol/L per kg NE:0.7 μg/kg/min | Not mentioned | CBF: Radioactive microspheres PO₂: Blood samples | PCO₂ and PO₂ were constant throughout all groups Control: Cerebrum CBF: 58 mL/min/100 g Tumor CBF: 1 mL/min/100 g PO₂: 105 mmHg Adenosine: Cerebrum CBF: 10 mL/min/100 g Tumor CBF: 100 mL/min/100 g PO₂: 121 mmHg NE: Cerebrum CBF: -1 mL/min/100 g Tumor CBF: -23 mL/min/100 g PO₂: 93 mmHg | None Mentioned | Selective effects of adenosine and NE on blood flow to brain tumors may have important implications for chemotherapeutic treatment of brain tumors. Vasodilator drugs such as adenosine that selectively increase tumor blood flow, but not brain blood flow, may increase the therapeutic advantage of lipid soluble chemotherapeutic drugs. |
| Nakagawa et al, 1977<sup>38</sup> | NE: 5 μg/kg | 1.5-3 mins | ICP: Pressure transducers PO₂: Blood samples taken | PCO₂ was kept constant throughout all groups All values in mmHg NE: Control: 125.0 ± 6.4 After needle insertion: 139.2 ± 7.1 After first coagulation: 167.7 ± 12.7(P < .01) After second coagulation: 133.8 ± 9.8 NE and Lesion: Control: 396.0 ± 25.4 After needle insertion: 346.0 ± 9.2 NS After first coagulation: 362.0 ± 17.5 NS After second coagulation: 342.2 ± 20.8 NS PO₂ remains steady throughout the experiments | None Mentioned | NE was not significant regardless of the level of the ICP, or of uni- or bilateral lesions of the hypothalamus. NE resulting no significant change to CBF found from the ICP/PO₂ relationship |
TABLE 2 (Continued)

| Reference | Dose of vasoppressor administered | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response | Adverse effects to norepinephrine | Conclusions |
|-----------|-----------------------------------|---------------------|---------------------------------------------|-------------------------|-------------------------------|-------------|
| Miller et al, 1984 | NE: Not specified (n = 6) Dopamine: Not specified (n = 5) Phenylephrine: Not specified (n = 6) | Endotoxin induced by bacteria for 40 min in Dose to raise MABP to 70-80 mmHg | CBF: Radiolabeled microsphere technique | PCO₂ and PO₂ were kept constant throughout all groups NE, Dopamine, Phenylephrine: Affected CBF similarly in all brain regions, with a decrease in brain total, cortex close to 27.1 ± 2.8 and 26.3 ± 28 mL/min/100 g where is the cerebellum slight decrease at 40.9 ± 4.9. The brain stem increased by 41.8 ± 4.7 mL/min/100 g (P < .05) for all but compared to shock for last two. | Cerebellum and brains tem did not restore to control values with dose which may indicate underlying structural heterogeneity | Decreases in regional CBF with shock are similar to those reported by other, unchanged cortical CBF after injection suggest either an inability to autoregulate or disruption of the brain-blood barrier resulting in vasopressor induced vasoconstriction which limits flow. |

Anesthetized animal models given CPR

| Prengel et al, 2005 | E: 200 µg/kg Vasopressin: 0.4 units/kg NE + E + Vasopressin: 45 µg/kg, 45 µg/kg and 0.4 units/kg | Up to 5 mins | Organ perfusion: Radiolabeled microspheres technique | PCO₂ and PO₂ were kept constant throughout all groups CBF: (mL/min/100 g) Before, 90 sec and 5 min after drug administration E: 8 ± 2, 23 ± 3, and 17 ± 3 Vasopressin: 11 ± 3, 55 ± 7, and 52 ± 7 NE + E + Vasopressin: 4, 67 ± 13, and 53 ± 12 (P < .05 at 90 sec and 5 mins vasopressin vs E and vasopressin/E/NE vs E). CPP: Increased significantly after 90 sec in all drug administrations, with a decrease in E and NE + E + Vasopressin group after 5 mins, vasopressin increased slightly after 5 mins Two of seven animals in the epinephrine group, four of seven animals in the vasopressin/epinephrine/ norepinephrine group, and seven of seven animals in the vasopressin group could be successfully resuscitated | None Mentioned | Vasopressin with or without E and NE resulted in higher myocardial and cerebral perfusion than E alone, but there was no benefit in adding NE to vasopressin and E with regard to cardiac and CBF during cardiopulmonary resuscitation. |
TABLE 2 (Continued)

| Reference          | Dose of vasopressor administered | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response                                      | Adverse effects to norepinephrine | Conclusions                                                                 |
|--------------------|----------------------------------|---------------------|---------------------------------------------|-------------------------------------------------------------|----------------------------------|----------------------------------------------------------------------------|
| Hoekstra et al 1990 | E: 0.2 mg/kg(n = 7)               | 3.5 mins            | CBF: Radiolabeled microsphere technique      | PCO<sub>2</sub> and PO<sub>2</sub> were kept constant throughout all groups |
|                    | NE: 0.20 mg/kg(n = 7)             |                     |                                             | During normal sinus rhythm: CBF: No significant differences (P ≥ 0.13) |
|                    | 0.08 mg/kg                        |                     |                                             | During CPR, LCBF, and CBF: NS differences (P ≥ 0.3)           |
|                    | 0.12 mg/kg                        |                     |                                             | NE 0.2 mg and E 0.2 mg: CBF: NE as higher by 0.2 mg/kg but NS (P ≥ 0.23) |
|                    | 0.16 mg/kg                        |                     |                                             | NE 0.08 mg/kg CBF: 3.7 ± 3 mL/min/100 g (P = NS)              |
|                    | 0.2 mg/kg                         |                     |                                             | NE 0.12 mg/kg CBF: 13.5 ± 1.4 mL/min/100 g (P = NS)          |
|                    |                                  |                     |                                             | NE 0.16 mg/kg CBF: 23.7 ± 24.5 mL/min/100 g (P = NS)         |
|                    |                                  |                     |                                             | NE 0.2 mg/kg CBF: 16.8 ± 14.6 mL/min/100 g (P = NS)          |
|                    |                                  |                     |                                             | All drug administration: CBF, MBF, MDo, and MVo, rose while ER fell in both E and NE with no significant differences between groups in CBF, ER, or intravascular pressures following drug administration (P < .07). |
|                    |                                  |                     |                                             | NE: CBF: As dose increases there was an increase in CBF that stopped and went down after 0.16 mg/kg, found in all brain areas |
|                    |                                  |                     |                                             | CPP: Significant increase at 0.12 mg/kg then an average decrease with increasing dose (P < .05) |
|                    |                                  |                     |                                             | None Mentioned                                                                 |
|                    |                                  |                     |                                             | NE 0.20 mg/kg is as effective as E 0.20 mg/kg at improving myocardial and CBF during CPR. NE 0.20 mg/kg improves MBF and MDo, over E 0.20 mg/kg, but any theoretical benefits of higher MBF and MDo, are offset by a proportional increase in MVo, in the NE-treated animals. Dose lower than 0.2 mg/kg are probably more effective in the treatment of prolonged cardiac arrest. |
| Reference            | Dose of vasopressor administered | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response | Adverse effects to norepinephrine | Conclusions                                                                 |
|----------------------|----------------------------------|---------------------|---------------------------------------------|--------------------------|----------------------------------|-------------------------------------------------------------------------------|
| Brown et al, 1989    | E: 0.20 mg/kg (n = 5)            | 30 sec              | CBF: Radiolabeled microsphere technique     | PCO₂ and PO₂ were kept constant throughout all groups | None Mentioned                  | No significant difference in rCBF between the two highest doses of NE and E, 0.20 mg/kg, but these doses were superior to NE, 0.06 mg/kg, for improving flow to lower brainstem structures. That following a prolonged cardiac arrest, large doses of NE significantly improve CBF above that measured during CPR. Adrenergic agonists that contains A and B1 agonists but lacks B2 agonist properties may prove beneficial in this setting. |
|                      | NE: 0.08 mg/kg (n = 5)           |                     |                                             |                          |                                  |                                                                                |
|                      | NE: 0.12 mg/kg (n = 5)           |                     |                                             |                          |                                  |                                                                                |
|                      | NE: 0.16 mg/kg (n = 5)           |                     |                                             |                          |                                  |                                                                                |
|                      | NE:	0.08	mg/kg	(n = 5)         |                     |                                             |                          |                                  |                                                                                |
|                      | NE:	0.12	mg/kg and 0.16 mg/kg: |                     |                                             |                          |                                  |                                                                                |
|                      | Increased regional cortical CBF by 12 mL/min/100 g |                     |                                             |                          |                                  |                                                                                |
|                      | No significant increase to left cerebral cortex |                     |                                             |                          |                                  |                                                                                |
|                      | NE 0.16 mg/kg:                  |                     |                                             |                          |                                  |                                                                                |
|                      | Increased regional cortical CBF on the average above 23 mL/min/100 g |                     |                                             |                          |                                  |                                                                                |
|                      | NE and E after a 5-min cardiac arrest and 3 mins of open-chest CPR led to the same increase in cerebral oxygen delivery more than cerebral oxygen consumption, and oxygen extraction decreased. Both are strong alpha and beta-receptor stimulators, but in contrast to E, the beta effect of NE is weak. NE demonstrated an increase in CBF and CMRO₂ |                     |                                             |                          |                                  |                                                                                |
| Lindner et al, 1990  | NE: 45 µg/kg                    | 90 sec and 5 mins   | CBF: Radiolabeled microsphere technique     | PCO₂ and PO₂ were kept constant throughout all groups | None Mentioned                  |                                                                                |
|                      | E: 45 µg/kg                     |                     | Cerebral Venous Blood and measure sagittal pressure: Catheter |                          |                                  |                                                                                |
|                      | NE (open chest CPR, 90 sec and 5 mins): CBF: 30 ± 11 to 58 ± 22 to 45 ± 21 mL/min/100 g (P < .05) |                     |                                            |                          |                                  |                                                                                |
|                      | Cerebral oxygen delivery: 3.7 ± 1.4 to 7.3 ± 2.7 to 5.8 ± 2.7 mL/min/100 g (P < .05) |                     |                                            |                          |                                  |                                                                                |
|                      | Cerebral Perfusion Gradient: 2.7 ± 0.5 to 4.4 ± 1.5 (P < .05) to 3.3 ± 1.2 kPa |                     |                                            |                          |                                  |                                                                                |
|                      | NE (open chest CPR, 90 sec and 5 mins): CBF: 30 ± 11 to 58 ± 22 to 45 ± 21 mL/min/100 g (P < .05) |                     |                                            |                          |                                  |                                                                                |
|                      | Cerebral oxygen delivery: 3.7 ± 1.4 to 7.3 ± 2.7 to 5.8 ± 2.7 mL/min/100 g (P < .05) |                     |                                            |                          |                                  |                                                                                |
|                      | Cerebral Perfusion Gradient: 2.5 ± 0.8 to 4.3 ± 1.2 to 3.9 ± 0.5 kPa (P < .05) |                     |                                            |                          |                                  |                                                                                |
| Reference                | Dose of vasopressor administered                                                                 | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response                                                                                                                                                                                                 | Adverse effects to norepinephrine                                                                 | Conclusions                                                                                       |
|-------------------------|-------------------------------------------------------------------------------------------------|---------------------|-----------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| **TBI anesthetized animal models** |                                                                                                 |                     |                                               |                                                                                                                                                                                                                         |                                                                                            |                                                                                                   |
| Armstead et al, 2016    | Fluid percussion injury (FPI) post-treated with NE 0.7-1.3 µg/kg/min                            | CPP was targeted 65-70 mmHg | CBF: Radiolabeled microsphere technique        | PO\(_2\) and PO\(_2\) was kept constant throughout all groups                                                                                                                                                    | None Mentioned                                                                                   | NE protects cerebral autoregulation and limits hippocampal neuronal cell necrosis after FPI in both male and female juvenile pigs. In contrast, NE augmented ERK MAPK upregulation in newborn males but similarly blocked it in newborn females after TBI. NE reduced CBF in male pigs with an increase in CVR in both sexes |
|                         | FPI post-treated with NE 0.7-1.3 µg/kg/min + the ERK MAPK antagonist U 0126 1 mg/kg intravenously|                     | CBF: MAP - ICP                                | SCA control:                                                                                                                                |                                                                                            |                                                                                                   |
|                         | Papaverine: 10\(^{-8}\) and 10\(^{-6}\) mol/L                                                   |                     | ICP: Integra camino monitor and laser-Doppler probe | CPP male: 70 \pm 7 mmHg                                                                                                                                   |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     | Transient hyperemic response ratio (THRR): Calculated by flow before compression/release of compression | CPP female: 71 \pm 7 mmHg                                                                                                                                  |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | CBF male: No change                                                                                                                                     |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | CBF female: No change                                                                                                                                     |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | THRR male unilateral and bilateral: 1.15 and 1.27                                                                                                        |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | THRR female unilateral and bilateral: 1.15 and 1.25                                                                                                       |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | FPI untreated:                                                                                                                                          |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | CPP male: 45 \pm 4 mmHg                                                                          |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | CPP female: 45 \pm 5 mmHg                                                                         |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | CBF male: Reduced by 20 mL/min/100 g \(P < .05\)                                                   |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | CBF female: Reduced by 15 mL/min/100 g \(P < .05\)                                                  |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | THRR male unilateral and bilateral: 1.04 and 1.10                                                                   |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | THRR female unilateral and bilateral: 1.07 and 1.14                                                   |                                                                                            |                                                                                                   |
| FPI post-treated with NE|                                                                                                 |                     |                                               | CPP males: 68 \pm 5 mmHg                                                                         |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | CPP females: 66 \pm 5 mmHg                                                                         |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | CBF male: Reduced by 10 mL/min/100 g \(P < .05\)                                                   |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | CBF female: No change \(P < .05\)                                                                  |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | THRR male unilateral and bilateral: 1.14 and 1.21                                                   |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | THRR female unilateral and bilateral: 1.15 and 1.25                                                   |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | FPI post-treated with NE + the ERK MAPK:                                                                                                               |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | CPP males: 67 \pm 5 mmHg                                                                         |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | CPP females: No change \(P < .05\)                                                                  |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | THRR male unilateral and bilateral: 1.15 and 1.25                                                   |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | THRR female unilateral and bilateral: No female data                                                  |                                                                                            |                                                                                                   |
| Friess et al, 2012      | NE and PE: 7.9 \pm 5.2 and 0.9 \pm 0.7 µg/kg/min titrated to CPP > 70 mmHg                     | For 5 hrs           | CBF: Thermal diffusion probe                    | PO\(_2\): Microdialysis                                                                                                                                  | None Mentioned                                                                                   | NE resulted in greater increase in brain tissue oxygen tension than augmentation with PE, despite similar increases in CBF |
|                         |                                                                                                 |                     | ICP: Intraparenchymal monitors                   | PO\(_2\) remained constant throughout all groups                                                                                                        |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | PE:                                                                                                                                                    |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | CBF: Improves over time with peaks and valleys ranging 20 mL/100 g/min                                                                                   |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | CPP: No significant change                                                                          |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | Greater reduction in cell injury                                                                  |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | NE:                                                                                                                                                    |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | CBF: Improves over time with peaks and valleys ranging 20 mL/100 g/min                                                                                   |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | CPP: No significant change                                                                          |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | PO\(_2\): Higher than PE                                                                             |                                                                                            |                                                                                                   |
|                         |                                                                                                 |                     |                                               | No ICP difference between groups at 70 mmHg                                                        |                                                                                            |                                                                                                   |
TABLE 2 (Continued)

| Reference       | Dose of vasopressor administered | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response                                                                 | Adverse effects to norepinephrine | Conclusions                                                                                       |
|-----------------|---------------------------------|---------------------|-----------------------------------------------|-----------------------------------------------------------------------------------------|-----------------------------------|-------------------------------------------------------------------------------------------------|
| Daley et al 2004<sup>13</sup> | NE: 1 µg/kg/min                  | 5 mins              | CBF: Laser-Doppler flow meter velocity         | \( \text{PCO}_2 \) and \( \text{PO}_2 \) were kept constant throughout all groups         | None Mentioned                    | Relating changes in HMF to changes in CPP may be of even greater value for evaluating the state of cerebrovascular regulation than evaluating changes in mean ICP induced by pressor challenge alone. However, the conclusions of this is only known to be applicable to a hypertensive challenge with NE under conditions of FPI obtained from an animal model with characteristics of diffuse axonal injury, and it might not apply to other situations or pathologies. NE appeared to increase CBF after TBI but limited effect in healthy models |
|                 |                                 |                     | Pal arteriolar: VHS recordings                  | Uninjured and NE: An inverse relationship between HMF and CPP with a mean of 0.50 ± 0.14 and 0.6 ± 0.44 Hz/mmHg |                                  |                                                                                                 |
|                 |                                 |                     | ICP: Direct pressure monitor and femoral ABP recordings | CBF velocity: Decrease that remained relatively constant                                  |                                  |                                                                                                 |
|                 |                                 |                     | CPP: ABP-ICP                                   | Injured and NE: Direct relationship between HMF and CPP with a mean 0.48 ± 0.21 and 1.13 ± 2.08 Hz/mmHg |                                  |                                                                                                 |
|                 |                                 |                     | HMF: Calculated from transfer from ABP to ICP   | CBF: Increased after injury                                                                 |                                  |                                                                                                 |
| Ract et al, 2001<sup>17</sup> | Dopamine: 5 mg/mL (average: 274 ± 110 µg/kg/min) | Started at 0.1 mL/h and increased 0.1 mL/h until CPP above 70 mmHg | CBF: Extradural laser-Doppler fiber ICP: Intraparenchymal fiber-optic device | \( \text{PCO}_2 \) and \( \text{PO}_2 \) remained constant throughout all groups | None Mentioned | NE and dopamine are not able to restore values of CPP above 70 mmHg in a model of severe brain trauma and their systemic vasopressor properties are altered. NE indicates no change to CBF |
|                 | NE: 0.1-0.2 mg/mL (average: 18 ± 4.5 µg/kg/min) |                     |                                               | Head trauma: ICP: Remained constant at 27 ± 18.5 mmHg                                   |                                  |                                                                                                 |
|                 |                                 |                     |                                               | CPP: Remained constant 28 ± 22 mmHg                                                      |                                  |                                                                                                 |
|                 |                                 |                     |                                               | CBF: Decreases significantly from time 60 to 180 mins                                   |                                  |                                                                                                 |
|                 |                                 |                     |                                               | NE: ICP: Increased to 40 mmHg at 30 mins then dropped slightly \((P < .05)\)            |                                  |                                                                                                 |
|                 |                                 |                     |                                               | CPP: Decreased over time after 15 mins to 10 mmHg \((P < .05)\)                          |                                  |                                                                                                 |
|                 |                                 |                     |                                               | CBF: Decrease significantly similar to all other groups                                  |                                  |                                                                                                 |
|                 |                                 |                     |                                               | Dopamine: ICP: Increased to 50 mmHg at 45 mins then stayed constant \((P < .05)\)       |                                  |                                                                                                 |
|                 |                                 |                     |                                               | CPP: No change                                                                          |                                  |                                                                                                 |
|                 |                                 |                     |                                               | CBF: Decrease significantly similar to all other groups                                  |                                  |                                                                                                 |
## TABLE 2 (Continued)

| Reference        | Dose of vasopressor administered | Mean administration | Technique to measure cerebrovascular response | Cerebrovascular response | Adverse effects to norepinephrine | Conclusions                                                                 |
|------------------|----------------------------------|---------------------|-----------------------------------------------|--------------------------|----------------------------------|------------------------------------------------------------------------------|
| Kovach et al, 1976 | Various studies                  | CBF: Measured with a variety of methods including autoradiograph 14C, radioactive microsphere with Xenon clearance | Microinjection of NE into the hypothalamus of the rabbit caused increased flow at low concentrations and decreased flow at higher concentrations. One study observed marked CBF reduction after NE injection in hypercapnia. Three studies resulted in no CBF increase in the baboon in hemorrhagic shock upon administration of 6% CO₂. In cross-circulation experiments in which the brain of the recipient dog was hemodynamically isolated from the trunk and perfused by a donor dog, intravenous E or NE injection into the recipient's trunk caused reflexly a significant increase in its total CBF. Intracarotid injection of both catecholamines produced a significant fall in CBF. Increased CBF could be measured during intravenous infusion of NE in hemorrhagic shock, while the cerebrovascular resistance showed no change. Increased CBF accompanied by increased cerebrovascular resistance followed NE administration during tourniquet shock. | None mentioned | The reviewed results clearly suggest that vital functions of the brain in spite of the well-developed autoregulatory mechanisms are impaired during long-lasting hypovolemic and other shock conditions. The insufficiency of the cerebrocortical and hypothalamic regulatory mechanisms can contribute to the development of the irreversible shock. In other words, failure of the body suffering from shock to restore the homeostatic equilibrium can be attributed to the inadequacy of the central nervous servo control system. |

Abbreviations: ABP, arterial blood pressure; AT, Angiotensin II; CBF, cerebral blood flow; CBV, cerebral blood volume; ChBF, choroidal blood flow; CMOT, Catechol-O-methyltransferase; CMR gluc, cerebral glucose uptake; CMRO₂, cerebral oxygen consumption; CoBF, corticoid blood flow; COU, cerebral oxygen utilization; CO₂, carbon dioxide; CP, cerebral perfusion; CPR, cardiopulmonary resuscitation; CPP, cerebral perfusion pressure; CSF, cerebral spinal fluid; CVR, cerebrovascular resistance; E, epinephrine; ERK, extracellular signal-regulated kinase; FPI, fluid percussion injury; HMF, highest modal frequency; hrs, hours; ICP, intracranial pressure; IL-6, interleukin-6; keto-PGFaa, 6-keto-prostaglandin; L-DOPS, l-threo-3,4-dihydroxyphenylserine; L-NAME, Nitro-L-arginine methyl ester; L-NMMA, methylarginine; MABP, mean arterial blood pressure; MAC, minimum alveolar concentration; MAO, Monoamine oxidases; MAP, mean arterial pressure; MAPK, mitogen-activated protein kinase; MBF, mean blood flow; MDo, myocardial oxygen delivery; min, minute; MRI, magnetic resonance imaging; MVO, myocardial oxygen consumption; NE, norepinephrine; PE, phenylephrine; PCO₂, partial pressure of carbon dioxide; PGE2, Prostaglandin E2; PO₂, partial pressure of oxygen; rCBF, regional cerebral blood flow; SAH, subarachnoid hemorrhage; sec, seconds; TBI, traumatic brain injury; THRR, transient hyperemic response ratio; TXB2, Thromboxane B2; x, multiplied by; 5-HT, 5-hydroxytryptamine.
carotid vascular conductance was different with 0.005 mL/min in juveniles, and 0.08 mL/min in mature and middle-aged rats, suggesting an age-related disparity in CBF modulation.73

3.7.3 Models given cardiopulmonary resuscitation

There were four studies in pigs that evaluated CBF while CPR was administered.44-47 During CPR, NE was given in two studies at varying doses, resulting in a dose-dependent increase to CBF.45,46 Furthermore, increases in CMRO2 and CPP were also shown with the injection of NE.47 One of these studies had NE co-injected with epinephrine and vasopressin, resulting in a more apparent increase in CBF, than compared to epinephrine or the vasopressin alone.44 In all of these studies, CBF increased with NE in comparison to control animals where NE was not given, with the NE effect on CBF observed to dissipate after 5 minutes.44,47

3.7.4 Models with traumatic brain injuries

In the four studies that had head trauma models, three of them used pigs48,50,51 and one used rats.74 In general, TBI caused a decrease in CBF, after the injury NE was given which caused an increase in CBF back to near baseline levels.50,51,74 The partial pressure of oxygen was also increased in the one study that monitored blood gases.50 One study compared the CBF effects of NE in brain-injured pigs (fluid percussion injury) vs uninjured pigs. This study showed minor changes in CBF by NE in the uninjured pigs, but a significant increase in CBF by NE in the injured.51 In the study with rat TBI models, NE administration led to an increase in ICP for 30 minutes, with a gradual decrease in CPP and slight decrease in CBF.74

3.7.5 Other studied pathologies

There were some “other” pathologic states studied, including those with sympathectomy,55 induced intracranial hypertension,23,25,58 induced hypothermia,21,35,66 brain tumors, stereotoxic induced lesions,35 and endotoxic shock.43 In the studies that had models with removed ganglion41,56 or sympathectomy,55 there was a nonsignificant change in CBF. However in models with ligated bile ducts NE both decreased CBF and increased CVR as compared to NE alone.19 Whereas, in dogs with a brain tumor (induced by avian sarcoma virus) NE decreased CBF in both hemispheres (one with tumor/one without) and a subsequent decrease in partial pressure of oxygen.28 In models with stereotoxic lesions (made in the posterior hypothalamus, unilaterally or bilaterally)35 or endotoxishock43 there was limited change in CBF or practical pressure of oxygen.35 Finally, when NE was given in induced intracranial hypertensive states, there were massive increases in CBF with each dose of NE.23,25,58

3.7.6 Anesthesia in models

In the identified literature there were six studies where the animal model was not fully anesthetized.38,42,55,60 Within these studies there was a dose-dependent change CBF seen in these models 40,41 and a constrictive force seen by NE injection.40 However no uniform results based on anesthetic regimen were documented. In the healthy anesthesia group, pentobarbital was used in 17 studies,17,20,22-24,26,28,29,31,32,43,44,56,64,70,74,77 ketamine used in 10 studies,17,19,21,38,40,43,51,53,69 as well as a variety of other substances. All displayed diverse effects of NE on CBF and CMRO2, with no clear trend toward a specific effect. Though for the 13 studies that used halothane,21,38,45,46,49,61-63,65,66,68,72,75 either a nonsignificant change or an increase in CBF was seen. To note, in the studies that had a CBF increase due to NE, NE was either given in large amounts (over 0.12 mg/kg),45,46,63,72 with hypertonic urea62 or with endothelin-1.68

3.8 Human patients

Of the remaining studies, CBF was measured with nitrous oxide,95 Kety-Schmidt technique,96-98 gas inhalation,99,100 positron emission tomography,101 or the CMRO2/AVDO2 method (as previously stated)102 All failed to document a significant CBF response to NE administration. However, in those studies assessing CVR, as measured through the comparison of CBF to MAP/CPP, there was a universal increase in CVR seen.80,84,87,93,95,97,98

Despite the multiple human studies with both healthy patients78-83,98 and patients with TBI,86-88,100-102 CBF in most patients remained relativity unchanged. Thus, no pathology-specific trends could be found in the human studies. There were three studies that had a nonsignificant decrease in CBF,86,98,100 and one with a nonsignificant increase in CBF,102 indicating a wide range of CBF response to NE. In the one study that evaluated CBF in patients with cardiac arrest through the MCAv, the flow velocity increased from 27 to 33 cm/s.86 Of the remaining studies no clear trends were demonstrated in the associate of NE to CBF.

3.9 Adverse events

No human studies document the adverse effect to NE but three animal studies included adverse events.43,64,71 Two studies reported lethal doses of NE administration.64,71 In one study, the cause of death was determined to be the inhibition of autoregulation by NE.64 This study also reported that continuous moderate doses of NE for longer than 2 hours prevented autoregulation measured through autoradiography.64 In TBI models, there appeared to be a trend toward vasoconstriction and varying global and rCBF reductions with NE administration.
4 | DISCUSSION

NE is commonly used to treat life-threatening low blood pressure situations for its direct vascular effects. The scattered literature on the cerebrovascular effects of NE has produced studies displaying both a reduction and an increase in CBF, leaving a confusing picture on the exact cerebrovascular effects of the drug. The goal of this study was to provide a comprehensive systematically conducted scoping review of animal studies on NE’s effect on the cerebrovascular response/CFB. Through our review we identified 62 animal studies and 26 human studies pertaining to the cerebrovascular/CFB effects of NE. Within the 62 animal studies, a variety of different models were used, with the majority focusing on changes in global CBF or rCBF. A minority of studies focused on the direct effects of NE on the cerebral vasculature. Overall, regardless of the model or modality of measurement, NE led to a vasoconstrictive effect in medium cerebral vessels in a dose-dependent manner, with no clear directional change to either global CBF or rCBF. Pial vessels seemed to remain unaffected. However, significant heterogeneity in study design, models, and outcome assessment limits the degree to which these results can be interpreted and translated to clinical practice. Some important points can be gleaned from this review.

First, NE administration in animals leads to a vasoconstriction of medium cerebral vessels. This is in the setting of constant pCO₂ and pO₂ during the experiments. The literature demonstrating an effect on pial vasculature was limited, with only one study which demonstrated no change to their diameter. Furthermore this constrictive effect was shown to be inhibited by alpha adrenergic blockers like phenoxybenzamine and phenolamine in animal models and in one human study. Given the relative homogeneity of the studies on NE vasoconstrictive traits and the inhibition by alpha adrenergic drugs, it can be inferred that NE stimulates alpha receptors to contract vessel within the brain, similar to NE’s effect on other systemic vessels. This general feature, found across different species of animal models, different model types from healthy to injured, and different sedation regimens, carries important implications for the application of the agent in humans with critical neurological illness. Direct cerebral vasoconstriction from NE may expose the brain to wider derangements in cerebral autoregulation/cerebrovascular reactivity, and lead to episodes of hyperemia or ischemia. Further to this, if NE administration were to abolish or eliminate cerebral autoregulatory capacity altogether, as seen on some of the animal studies identified, this could lead to catastrophic consequences. These consequences are particularly important in TBI patients, where it is well known that impaired cerebrovascular reactivity is strongly associated with outcome and is present in many patients during their ICU stay and remains refractory to treatment effects. It also carries implications for the use of vasopressor agents in the targeting of individualized physiologic targets in TBI based on continuous cerebrovascular reactivity monitoring. Though, it must be acknowledged, these results from animal models and one human study may not translate directly to all humans and requires further investigation in both large animals and humans with TBI.

Second, the data are not clear regarding the change in global and rCBF with the injection of NE and why there appears to be such a discrepancy of response between studies and models. In healthy and CPR animal models, there was a trend toward a dose-dependent increase in CBF. However, in TBI and other cerebral lesion models, the impact of NE on CBF was heterogeneous, in the setting of constantcontrolled pCO₂ and pO₂. Sedation regimen did not seem to impact these findings based on the available data in the parent manuscripts. In such acquired brain injury models, it is possible that the CBF reductions seen can be more directly associated with the alterations in CBV, and thus ICP, occurring with NE-based cerebral vasoconstriction, as opposed to any direct flow augmenting effect of NE. However, in some studies that measured CBV and CBF, the data demonstrated a positive linear connection between them during NE administration. Furthermore, such acquired brain injury states may lead to regional disparities in blood-brain barrier (BBB) functionality. Areas of impaired BBB integrity may lead to more extracellular deposition of NE, leading to direct action on both the vasculature and cellular support network, causing variability in CBF response seen. Such BBB impacts on NE effects may be important, as healthy data suggest that an intact healthy barrier prevents much of the systemic catecholamines from entering the extracellular space. Further investigation is required into the regional disparities of CBF secondary to NE in the context of acquired brain injury.

Furthermore, the injection of NE through systemic routes may have effects different than NE directly injected within the brain. NE injected with hypertonic urea or MgSO₄ solution resulted in an increase in CBF with the same dose of NE. As such it is likely that the BBB mediates the perfusion of NE throughout the brain and its effects on CBF. This point may also be enforced by the fact that during studies where animals had lesions that opened the BBB, an increase in CBF after NE injection was seen. Also in studies with impaired autoregulation there was a consistent response to NE with an increase in ICP and CBF. All these findings support a potential role for the BBB in the regulation on cerebrovascular response to NE. As mentioned above, in line with this, NE given systemically may not enter the brain parenchyma due to the BBB, though it is clear that the BBB limits the permeation of NE it may not prevent all of the NE from entering the BBB. This particular area of BBB integrity, its impact on NE-based cerebrovascular/CFB responses in acquired brain injury, is an area requiring much further investigation.

Third, six studies demonstrated that the exogenous administration of NE reaches a maximal effect on cerebrovascular response. All of these studies compared various doses of NE which resulted in a maximum change in both CBF and CVR of the animal models. Thus, a dose-dependent response to NE occurs, which again carries important implications for continuous cerebrovascular reactivity monitoring and derivation of individualized physiologic target in TBI. However, a universal max dose of NE, in
animal studies, given heterogeneity and potential species-specific responses, limits our ability to translate these results to the clinical application of NE in humans regardless of the underlying pathology. Furthermore, most human studies measured CBF through an application of NE in humans regardless of the underlying pathology. Another limitation is the lack of blood gas control in some of the studies. Cerebrovascular/CFB physiologic response is intimately linked to pCO₂ and pO₂ status, therefore due to the large number of studies that did not fully account for fluctuations in the blood gas level, leaves any conclusion linked with NE deficient. Last, although there are trends in the animal models, there is still a significant limitation to apply them in clinical practices simply based on the limited number of effect human studies.

4.2 | Future directions

Further prospective studies on the cerebrovascular/CFB effects of NE in the neurologically ill patient population need to be performed to determine the role of this medication within neuroanesthesia and the neuro-ICU. The potential CBF trends seen with NE are interesting and carry important implications in the treatment of a variety of cerebral pathologies, with TBI mentioned as exemplar given that CFB and cerebral autoregulation are key factors to improve patient outcome. When it comes to TBI, literature in the field of moderate/severe TBI has demonstrated that impaired cerebral autoregulation/cerebrovascular reactivity is directly associated with poor 6-month global outcome. 6,104,106,109,110 This has been validated in prospective multicenter data, 106 and recent retrospective data sets suggest that cerebrovascular reactivity remains unaffected by changes in guideline-based management of TBI over the last 25 years, in concert with relatively stable mortality rates.105 Such findings suggest that despite improvement in ICP and CPP targeting, cerebrovascular reactivity remains resistant to current therapeutic measures in moderate/severe TBI care, and may be a main contributor to persistently high mortality rates despite advancements in therapeutic targeting. There currently exists limited literature on the impact of commonly administered therapies in TBI, such as NE, and their impact on cerebrovascular reactivity, with most suggesting an unclear association.111 Cerebrovascular reactivity monitoring is being adopted to direct personalized physiologic targets in TBI care, this aspect of prolonged high-dose NE administration needs to be considered and investigated further.
requires substantial coordination between multiple centers of excellence/expertise, and requires multidisciplinary research teams. This is the focus of ongoing collaborative work in Europe\textsuperscript{120,121} and Canada.\textsuperscript{122}

5 | CONCLUSIONS

The animal models indicate an increase in vasoconstriction with NE administration through the alpha receptor in vessels. There appeared to be a dose-dependent increase in CBF with NE administration in healthy and CPR animal models, which was also seen in one human study. However, there was no clear trend to describe the global and rCBF changes seen during the injection of NE in models with TBI, acquired brain injury, or within any other group of human patients. Further investigation into the impact of NE on cerebrovasculature in large animal models and humans is required.

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DISCLOSURE

There is no conflict of interest by any of the authors in the work presented.

ETHICAL STATEMENT

There were no trial or experiments preformed in this systematic review as such all ethics outlined by the WMA Declaration of Helsinki or the Ethics regarding animal testing are not applicable. Further all article references are fully published and have been vetted by their respective journals.

DATA AVAILABILITY STATEMENT

Data derived from public domain resources. The data that support the findings of this study are available in MEDLINE, BIOSIS, EMBASE, Global Health, SCOPUS, or Cochrane Library.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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