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Review Article

Resuscitation of the Penumbra Area – Lucida in the Brain of Traumatic Brain Injury

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ABSTRACT

Background: Cerebral hypoperfusion is a major cause of brain ischemia, both global and focal. In focal ischemia, there are three main zones: the ischemic core, which undergoes permanent damage; the penumbra, which remains salvageable; and the area with normal perfusion. A decrease in blood flow and disruption of cerebral autoregulation can convert the penumbra into an infarct if reperfusion is not promptly achieved. The penlucida region represents tissue capable of spontaneous recovery without intervention, whereas the penumbra requires immediate action to preserve neuronal viability. Neuronal injury in ischemia primarily results from energy production failure due to impaired oxidative phosphorylation, increased intracellular calcium, excessive glutamate release, and the formation of free radicals that lead to excitotoxicity and cell death through necrosis and apoptosis. Resuscitation of the penumbra–penlucida area aims to restore perfusion and oxygenation before irreversible damage occurs through the application of the neuroanesthetic-based ABCDE principles (airway, breathing, circulation, disability, exposure). Maintaining airway patency, oxygenation, normocapnic ventilation, and adequate cerebral perfusion pressure (CPP) are key to preserving collateral blood flow. Hypotension, hypoxia, hyperthermia, hypoglycemia and hyperglycemia must be avoided as they accelerate infarct progression. Anesthetic agents play a protective role by reducing cerebral metabolism, although careful monitoring of blood pressure is still necessary to prevent relative hypotension. Thus, the application of neuroanesthetic principles in penumbra–penlucida resuscitation aims to maintain cerebral perfusion, oxygenation, and metabolic stability to prevent the transformation of reversible tissue into a permanent infarct.

Introduction

Hypoperfusion can result in cerebral ischaemia, which may occur globally, such as after cardiac arrest, or focally, as seen in localised stroke. Although both forms share similar mechanisms of neuronal injury, they differ in distribution patterns and final outcomes. In focal ischaemia, three distinct regions are recognised: the ischaemic core, which receives no blood flow and sustains irreversible injury; the penumbra, characterised by partial perfusion and potential for recovery; and normally perfused tissue. If reperfusion is not achieved promptly, the penumbra will progress to infarction, whereas improved collateral circulation may help preserve neuronal function [1].

The progression of cerebral infarction depends on the degree of reduction in blood flow reaching the ischaemic threshold and the duration of the disturbance. Neuronal tissue may receive blood flow at a level insufficient to maintain normal function but not yet low enough to cause permanent damage. If blood flow returns to an adequate level, tissue function can recover.

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The term penumbra, initially used to describe brain tissue receiving blood flow between the functional and morphological thresholds, has now been expanded to include tissue that is ischaemic but still viable, with an uncertain potential either to progress to infarction or to recover. The term penlucida is rarely used today, although it can still be found in older literature and teaching [1-2].

Penlucida is distinguished from penumbra (literally meaning "faint shadow") to describe tissue that experiences severe ischaemia but can still recover spontaneously without immediate intervention, whereas penumbral tissue requires timely management to prevent progression to infarction [3].

The purpose of this paper is to provide an overview and management approach to resuscitation in the penumbra and penlucida regions of injured brain tissue, which may serve as a consideration for anaesthetic management in patients with brain injury.

Pathophysiology of Brain Injury

The brain is highly sensitive to ischaemia, and restricted blood supply leads to neuronal injury. The affected cerebral artery territory determines the neurological deficits observed. Energy depletion is the primary cause of neuronal damage in ischaemia [1].

Inhibition of oxidative phosphorylation results in a marked reduction in ATP production, leading to failure of energy-dependent homeostatic mechanisms. This leads to a decrease in ATP production per molecule of glucose by approximately 95%. With this markedly reduced energy production, ATP levels fall, resulting in the loss of energy-dependent homeostatic mechanisms. Furthermore, during ischaemia, the glucose supply ceases, as does the removal of metabolic by-products. The activity of ATP-dependent ion pumps decreases, leading to an increase in intracellular Na^+ and Ca^{2+} levels, while intracellular K^+ levels decline [1].

These ionic alterations cause neuronal depolarisation and the release of excitatory amino acids such as glutamate. In addition, glutamate is released due to the reversal of glutamate transporter function, which pumps glutamate into the extracellular space when the Na^+ and K^+ ion gradients are disrupted.

Elevated extracellular glutamate levels further depolarise neurons through activation of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate) and NMDA (N-methyl-D-aspartate) receptors, increasing Na^+ and K^+ conductance. NMDA receptors also permit the influx of Ca^{2+} into the cell, triggering various additional pathways of neuronal injury [1].

Glutamate also activates metabotropic receptors, which, through secondary messenger systems, can enhance the release of Ca^{2+} from intracellular stores and trigger various other biochemical processes. The damage resulting from excessive glutamate is referred to as excitotoxicity, a condition caused by glutamate receptor activation and the accompanying ionic and biochemical alterations.

In addition to increased Ca^{2+} influx through membrane channels, cytosolic Ca^{2+} levels also rise due to reduced activity of Ca^{2+} extrusion pumps and increased release of Ca^{2+} from intracellular organelles such as the endoplasmic reticulum. Elevated cytoplasmic Ca^{2+} levels initiate a cascade of events leading to ischaemic injury, including increased activity of proteases and phospholipases.

Phospholipase activity elevates the levels of free fatty acids such as arachidonic acid and promotes the formation of free radicals. Free radicals are also generated as a result of incomplete mitochondrial oxidation. One of the most destructive free radicals is peroxynitrite, which forms from the combination of nitric oxide (NO) and other free radicals [1,4].

Free radicals are known to damage proteins and lipids, while free fatty acids disrupt cell membrane function. During ischaemia, there is an accumulation of lactate and hydrogen ions (H^+), which lowers intracellular pH and promotes further free radical formation. All these processes, combined with a reduced capacity for protein and lipid synthesis, contribute to the irreversible damage that occurs as a result of ischaemia [1,4].

There are two main processes responsible for neuronal death, as described on (Figure 1 and 2). The first is necrosis, which occurs following severe injury in which mitochondrial function is lost. Necrosis is characterised by cellular disintegration and the activation of microglia and immune responses.

These immune and inflammatory responses activate and recruit neutrophils and macrophages, which then generate free radicals and damage surrounding neurons. This process results in the expansion of the lesion both in size and over time, thereby propagating and exacerbating neuronal injury [1].

The second process is apoptosis, in which cell death occurs without cellular rupture and without activation of the immune response, thus preventing excessive damage to neighbouring neurons. There are two principal pathways that can activate caspases and trigger apoptosis: the intrinsic and extrinsic pathways. Both pathways ultimately converge on the same terminal apoptotic cascade, leading to cell death [1].

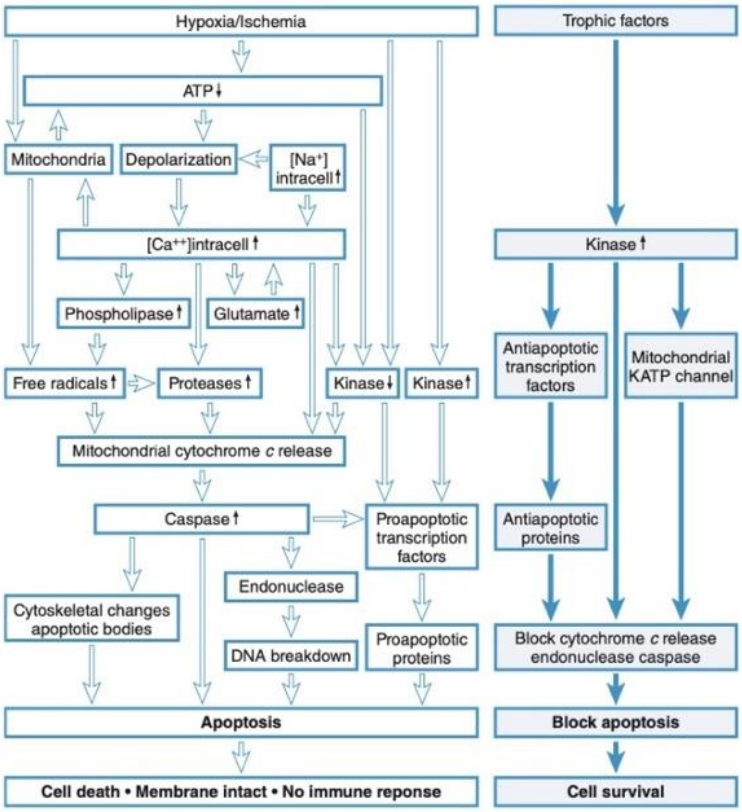

Figure 1- Pathophysiology of Apoptosis in Brain Injury [1].

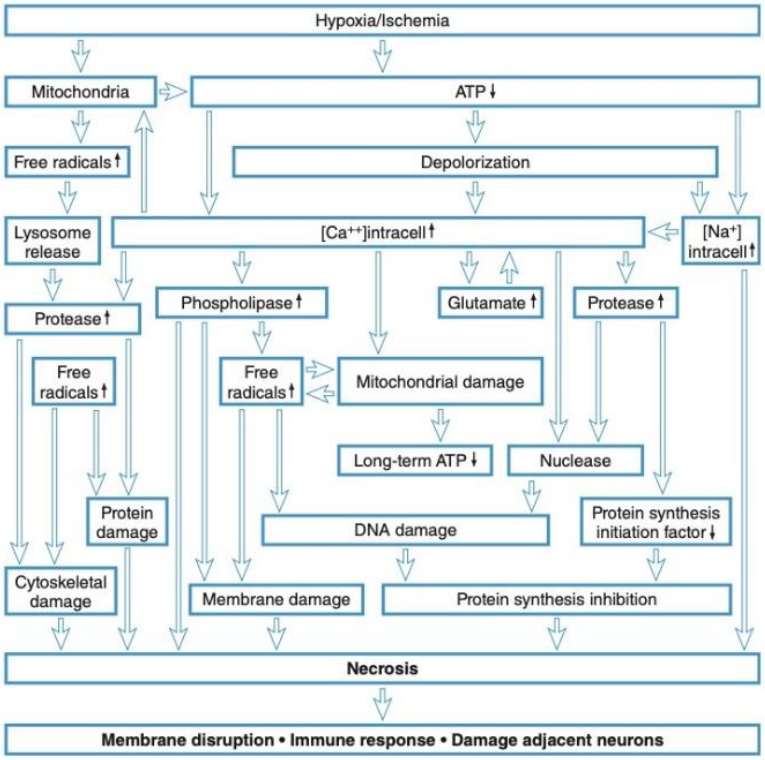

Figure 2- Pathophysiology of Necrosis in Brain Injury [1].

Cerebral Blood Flow

Cerebral autoregulation maintains stable blood flow despite fluctuations in mean arterial pressure. This mechanism may be impaired in conditions such as stroke, trauma, inflammation, neonatal asphyxia, and diabetes. Severe dysfunction may progress to vasomotor paralysis [3].

When cerebral perfusion pressure approaches the lower autoregulatory limit (~50 mmHg), arterioles dilate to maintain flow. Once compensatory capacity is exhausted, CBF declines passively. Initially, oxygen extraction increases, but eventually cerebral metabolic rate decreases, leading to synaptic failure and cytotoxic oedema [3]. If untreated, this results in infarction.

Tissue viability depends on both flow reduction severity and duration. Penlucida may recover regardless of duration, while penumbra requires timely reperfusion. In focal ischaemia, the ischaemic core, penumbra, and normally perfused regions coexist [1].

Global ischaemia allows only brief recovery windows, with selective neuronal vulnerability accounting for residual deficits [1]. Excessive CPP beyond autoregulatory limits leads to hyperperfusion, BBB disruption, oedema, and haemorrhage [1,3].

Hypoperfusion and Cerebral Ischaemia

Hypoperfusion results in cerebral ischaemia. Although cerebral blood flow (CBF) can be reduced through various mechanisms, the resulting metabolic effects on neurons are largely similar. Total and partial ischaemia produce different metabolic responses, and in local or regional ischaemia, collateral circulation from neighbouring vessels may partially sustain blood supply.

When cerebral perfusion pressure (CPP) falls toward the lower threshold of autoregulation (around 50 mmHg), arteriolar resistance vessels dilate, causing an increase in cerebral blood volume (CBV). Once this compensatory vasodilation reaches its limit, cerebral blood flow begins to decline passively as CPP continues to decrease. Initially, the brain attempts to compensate by increasing oxygen extraction; however, once this reserve is exhausted, the cerebral metabolic rate of oxygen ($CMRO_2$) falls. This leads to impaired synaptic activity and eventually complete failure (isoelectric EEG).

At this point, neurons remain structurally intact but are functionally inactive. Continued reduction in blood flow causes membrane failure, allowing sodium, calcium, and water to enter the cell while potassium exits, producing cytotoxic oedema. If not rapidly corrected, this critical reduction in CBF becomes lethal and progresses to cerebral infarction [3].

The progression of cerebral infarction depends on the degree of reduction in blood flow and the duration of ischaemia.

Neural tissue may remain viable though non-functional and can recover if blood flow is restored to normal. Two conditions may occur:

- Penlucida: tissue that can recover completely, independent of the duration of ischaemia.
- Penumbra: tissue that remains salvageable only if blood flow is restored within a limited period of time.

Ischaemia can present as either global or focal. Cardiac arrest is a typical cause of global ischaemia, while a localised stroke represents focal ischaemia. Although both forms share common pathways of neuronal injury, key differences exist in their distribution and clinical consequences.

In focal ischaemia, there are three principal regions [1]: The ischaemic core receives no blood flow and demonstrates injury patterns similar to those seen in global ischaemia. Surrounding this area is the penumbra, which receives partial perfusion through collateral vessels and remains potentially salvageable. Beyond this lies the normally perfused region, which continues to receive adequate blood supply.

- Penumbra, which is the area receiving collateral blood flow and experiencing partial ischaemia.
- Normal region, which continues to receive adequate perfusion.

If reduced perfusion persists, neurons within the penumbra undergo irreversible injury, leading to expansion of the infarcted core. Conversely, neuronal survival improves when collateral circulation increases or rapid reperfusion is achieved through recanalisation of the occluded vessel.

In complete global ischaemia, prompt restoration of circulation is essential, as only a short ischaemic duration—measured in minutes—permits recovery of neuronal and glial function. Residual neurological deficits following reperfusion are largely explained by varying vulnerability among different neuronal populations and brain regions [1].

When cerebral perfusion pressure (CPP) exceeds the upper autoregulatory limit, cerebral blood flow rises uncontrollably. Passive dilation of arterioles reduces vascular resistance, resulting in complications such as cerebral swelling, vasogenic oedema from blood–brain barrier disruption, and intracerebral haemorrhage due to vessel rupture [1,3].

Brain tissue receiving blood flow between approximately 18 and 23 mL/100 g/min becomes electrically inactive but remains viable and can recover fully if perfusion is restored; this state is termed penlucida. At lower flow levels, tissue outcome depends on the duration of ischaemia. Restoration of adequate perfusion before the critical infarction threshold allows functional recovery of the penumbra [3].

Many processes responsible for permanent neuronal damage are believed to occur during reperfusion, particularly due to reoxygenation injury. A phenomenon known as delayed hypoperfusion may develop following initial reperfusion, as illustrated in (Figure 3). The exact role of this process in neuronal injury is not fully understood. CBF generally decreases in proportion to reduced metabolic demand after ischaemia, although regional mismatches between flow and metabolism may occur, as described in (Figure 3).

Additionally, neutrophil adhesion to the vascular endothelium can obstruct microcirculatory flow and hinder reperfusion. Experimental studies in mice lacking intercellular adhesion molecules (ICAMs) demonstrate increased resistance to stroke following transient cerebral ischaemia.

Reperfusion-related injury may be attenuated with pharmacological agents such as aminoguanidine, a selective inducible nitric oxide synthase (iNOS) inhibitor, and ifenprodil, an NMDA receptor antagonist acting at the polyamine site [3].

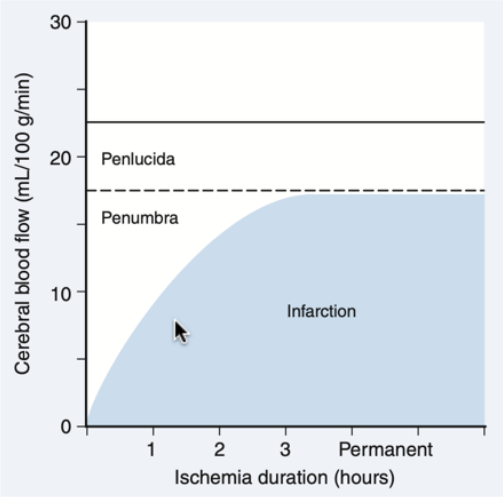

Figure 3- Interaction between the Degree and Duration of Flow Reduction on Neurological Function [3].

Cerebral Oedema and Blood–Brain Barrier Disruption

Among the various complex pathophysiological changes occurring within the traumatic penumbra, one of the most prominent is the disruption of the blood–brain barrier (BBB). Once the integrity of the BBB is compromised, foreign cells, tissue debris, and water can penetrate and infiltrate the barrier, ultimately leading to cerebral oedema. A study demonstrated that changes in BBB permeability occur earlier than the onset of cerebral oedema within the traumatic penumbra in rats. However, the exact mechanisms underlying cerebral oedema remain incompletely understood due to the complexity of the process [5].

The causes of BBB disruption include cerebral ischaemia, inflammation, and redox imbalance within the traumatic penumbra. Khan et al. found that vascular dysfunction resulting from endothelial impairment and reduced nitric oxide (NO) availability can lead to worsening oxidative stress and BBB leakage.

Decreased NO levels have been reported in both the plasma and brain tissue of stroke patients as well as in animal models, suggesting abnormalities in NO metabolism following acute injury. Therefore, reduced NO levels may contribute to BBB disruption, decreased cerebral blood flow (CBF), and cell death. In addition, the recruitment and invasion of inflammatory cells have also been shown to correlate with areas of BBB damage accompanied by neuronal degeneration [6].

Cerebral Autoregulation

Cerebral autoregulation describes the brain's capacity to preserve stable cerebral blood flow (CBF) despite fluctuations in mean arterial pressure (MAP). The term also encompasses haemodynamic responses to changes in perfusion pressure that occur independently of metabolic demand [3].

This mechanism is vital for normal neurological function, as it maintains consistent delivery of oxygen and nutrients while enabling effective removal of metabolic by-products to meet the brain's high energy requirements [7]. Autoregulation consists of two components: static and dynamic. Static autoregulation involves long-term adjustments to cerebral perfusion pressure (CPP), whereas dynamic autoregulation (dCA) responds to rapid changes in systemic blood pressure [8].

During systemic hypotension, cerebral vessels dilate to sustain blood flow, which may secondarily increase intracranial pressure (ICP). In contrast, systemic hypertension triggers vasoconstriction to maintain normal CBF and ICP. When autoregulatory mechanisms fail, cerebral circulation becomes pressure-dependent..

Several factors impair autoregulation, including elevated ICP (>25 mmHg), markedly low arterial blood pressure (ABP <75 mmHg), or excessive hypertension (ABP >125 mmHg). These limits define optimal CPP targets and may influence neurological outcomes [9].

Autoregulatory dysfunction occurs in numerous pathological conditions affecting the central nervous system. Disorders such as acute ischaemia, intracranial mass lesions, traumatic brain injury, inflammatory processes, prematurity, neonatal asphyxia, and diabetes mellitus can all compromise cerebral blood flow control..

Although the underlying mechanisms differ, severe impairment may culminate in vasomotor paralysis. This phenomenon is often attributed to tissue acidosis or

accumulation of toxic metabolites, though these explanations do not fully account for all cases.

Loss of autoregulation in areas remote from the primary injury remains poorly understood. Paulson and colleagues introduced the term dissociated vasoparalysis to describe preserved CO_2 responsiveness despite loss of pressure autoregulation [3]. Another phenomenon described after head injury is false autoregulation. In paralysed vascular regions, pressure-passive increases in CBF may generate local pressure gradients within severely damaged tissue. This may result in focal swelling that maintains constant flow despite rising systemic pressure.

Autoregulatory failure may manifest as either right-sided dysfunction (hyperperfusion) or left-sided dysfunction (hypoperfusion). While this discussion addresses general parenchymal effects, specific brain regions exhibit varying susceptibility to both ischaemia and circulatory breakthrough [3,7].

Principles of Resuscitation in the Cerebral Penumbra

The primary goal is to restore or maintain perfusion, oxygen supply, and metabolic support to the penumbral area before irreversible damage occurs. In practice, this means avoiding secondary injuries such as hypotension, hypoxia, hypercapnia, and increased intracranial pressure [10].

Rapid Reperfusion

Prompt establishment of airway, breathing, and circulation (ABC) is essential in the acute setting. The main objective in managing ischaemic stroke is to restore cerebral blood flow as quickly as possible and preserve viable brain tissue within the ischaemic penumbra. Reperfusion strategies include intravenous thrombolysis and endovascular mechanical thrombectomy.

Administration of the thrombolytic agent recombinant tissue plasminogen activator (rtPA) is recommended for all eligible patients. However, rtPA can significantly worsen outcomes if the stroke is haemorrhagic. Therefore, early identification, accurate classification, and immediate management of stroke are critical to achieving favourable outcomes. Thrombolytic therapy is contraindicated in patients with an elevated risk of bleeding, including those with head trauma, recent surgical procedures, or coagulopathies resulting from medications such as warfarin, heparin, or direct oral anticoagulants (DOACs), including direct thrombin and factor Xa inhibitors.

The most serious adverse effect of rtPA is intracerebral haemorrhage, which may be fatal. For this reason, a non-contrast CT scan—or MRI if readily available—must be performed immediately upon hospital admission to exclude haemorrhagic stroke. If appropriate, rtPA should be administered as early as possible, as shorter reperfusion times correlate with reduced brain injury. The standard therapeutic window for rtPA is within 3 hours of stroke onset.

When considering adjunctive therapies, it is important to identify patients who still have hypoperfused regions (penumbra) that have not progressed to irreversible neuronal damage. Recent research has utilised advanced imaging modalities to detect these vulnerable areas that remain salvageable with timely reperfusion. Studies have demonstrated that modern stent retriever devices are superior to earlier clot retrieval systems. Patients eligible for intravenous rtPA should receive treatment without delay, even if mechanical thrombectomy is being considered.

Candidates for mechanical thrombectomy should have confirmed occlusion of the proximal anterior intracranial circulation and no evidence of large established infarct cores. The generally accepted time window for thrombectomy is within 6 hours of symptom onset. In carefully selected patients with evidence of viable penumbra, thrombectomy may be beneficial up to 16 hours and is considered reasonable up to 24 hours after onset.

Despite advances in endovascular therapy, intravenous rtPA administered within 3 hours—extended to 4.5 hours in selected patients—remains the most widely accepted treatment for ischaemic stroke. Unfortunately, this therapy remains underutilised due to its narrow time window, multiple contraindications, and delays in hospital presentation.

Induced Hypertension

Maintaining elevated perfusion pressure, alongside optimal blood viscosity and oxygen delivery, may reduce cellular injury in threatened vascular territories. This approach improves cerebral perfusion, electrophysiological activity, and histopathological and neurological outcomes. Increasing systemic blood pressure minimises the pressure drop across stenotic vessels and collateral pathways supplying the ischaemic region.

Even a modest increase in cerebral blood flow (CBF) can convert tissue from a penumbra progressing toward infarction into a penlucida, or even restore perfusion sufficient for normal function [3].

However, induced hypertension carries risks, including worsening vasogenic oedema and haemorrhagic transformation of infarcts. These risks are reduced when blood pressure is elevated briefly during temporary carotid or intracranial artery occlusion. Pharmacologically induced hypertension accompanied by tachycardia increases the risk of myocardial ischaemia; therefore, α-adrenergic agonists are preferred.

In neurovascular surgery, temporary arterial occlusion is increasingly used during aneurysm repair. This

requires modifications to standard anaesthetic management. Systemic hypotension must be avoided, and in some cases, blood pressure elevation is necessary during occlusion.

Induced hypertension has also been employed in aneurysmal subarachnoid haemorrhage (SAH), typically combined with hypervolaemic haemodilution. This makes it difficult to isolate the independent effect of increased perfusion pressure [3].

Avoid Relative Hypotension

Preventing relative hypotension in acute ischaemic stroke is more challenging than in intraoperative or non-stroke critical care settings. Stroke often induces compensatory hypertension, which helps preserve penumbral tissue by enhancing collateral circulation. Excessive blood pressure reduction can worsen neuronal injury and impair neurological recovery [3].

In patients not eligible for rtPA or thrombectomy, blood pressure up to 220/120 mmHg should generally not be lowered within the first 24 hours unless there are compelling comorbid indications. No clear benefit has been demonstrated for reducing blood pressure below this threshold during the first 48–72 hours.

For patients receiving rtPA or undergoing thrombectomy, blood pressure should be lowered to ≤185/110 mmHg. Thereafter, systolic pressure should be maintained between 150–180 mmHg and not normalised, to preserve adequate penumbral perfusion [3].

Avoid Hypothermia

Profound hypothermia (≤27°C) is associated with significant complications that limit its clinical use. Although it markedly reduces cerebral metabolism and prolongs tolerance to ischaemia, the risks outweigh the benefits.

Experimental studies indicate that moderate hypothermia offers neuroprotection with fewer adverse effects, although myocardial depression has been observed [3]. According to the 2019 AHA/ASA guidelines, the benefit of induced hypothermia in acute ischaemic stroke remains uncertain. While infection risk increases, potential advantages cannot be entirely excluded.

It is well established that body temperatures above 38°C should be aggressively treated, as even mild hyperthermia worsens neurological outcomes. If hypothermia proves beneficial in specific stroke subtypes, optimal temperature targets, treatment duration, and rewarming rates must be defined more precisely.

In haemorrhagic stroke, mild hypothermia may be harmful because it impairs coagulation and increases bleeding risk, making haemostasis more difficult [1].

Avoid Hyperglycaemia and Hypoglycaemia

Glucose is the brain's primary energy substrate. While in vitro studies suggest hyperglycaemia may aid recovery, in vivo and clinical data show it worsens brain injury, likely due to increased acidosis and other mechanisms that remain incompletely understood.

Current guidelines recommend maintaining serum glucose within normal limits and treating hyperglycaemia >180 mg/dL. Hypoglycaemia must also be avoided, as it worsens outcomes. Strict glucose control has not improved stroke outcomes and may increase mortality. Studies show higher death rates in patients with glucose targets of 81–108 mg/dL compared with those maintained between 140–180 mg/dL.

Excessive insulin administration leading to hypoglycaemia is believed to drive these adverse outcomes. Therefore, glucose levels should be controlled below 180 mg/dL without overly aggressive regulation. Immediate correction is essential when levels fall below 60 mg/dL [1,11].

Inverse Steal

If an ischaemic region is already maximally dilated, increasing CO_2 levels will dilate surrounding normal vessels, paradoxically reducing blood flow to the ischaemic area due to decreased local perfusion pressure. Conversely, vasoconstriction in healthy tissue may divert blood toward the ischaemic region, known as inverse steal or the Robin Hood effect.

This effect may also occur with cerebral vasodilators such as volatile anaesthetics and systemic vasodilators including nitroprusside, hydralazine, and nitroglycerin [3].

Pharmacological Interventions and Anaesthetic Drugs in Brain Injury

Vasoactive agents that constrict normal cerebral vessels may favourably redistribute blood flow toward ischaemic regions. In contrast, vasodilators act similarly to hypercapnia, potentially worsening steal phenomena, as seen in (Table 1).

In cerebral vasospasm, increased CBF is often required. Initial management includes induced hypertension and euvolaemia. The previously used "Triple H therapy" (hypertension, hypervolaemia, haemodilution) has largely been abandoned.

Endovascular treatments are reserved for symptomatic vasospasm unresponsive to medical therapy. Evidence suggests proximal vasospasm responds better to angioplasty, while distal vasospasm is better managed with intra-arterial vasodilators [3].

Anaesthetic agents have been studied for neuroprotection due to their ability to reduce metabolic demand. However, each agent exerts unique effects on

ion channels, neurotransmission, intracellular signalling, and haemodynamics, explaining their variable influence on neuronal injury.

Maintaining blood pressure is critical for penumbral perfusion. Hypotension induced by general anaesthesia may worsen outcomes regardless of direct drug effects. A meta-analysis showed that patients undergoing thrombectomy under general anaesthesia had better reperfusion and functional outcomes compared with conscious sedation, concluding that general anaesthesia does not worsen clinical outcomes [11–12].

It must be noted that clinical trials often involve meticulous haemodynamic management that may not reflect routine practice. Preserving penumbral perfusion rather than merely achieving normotension is essential but challenging [1,10,12].

Currently, both conscious sedation and general anaesthesia are acceptable approaches. General anaesthesia provides patient immobility and airway protection but carries an increased risk of relative hypotension [1].

Table 1- Effects of Anesthetics on Cerebral Blood Flow (CBF) and the Cerebral Metabolic Rate for Oxygen ($CMRO_2$)

Anesthetic	CBF	$CMRO_2$	Direct Cerebral Vasodilation
Halothane	↑↑↑	↓	Yes
Enflurane	↑↑	↓↓	Yes
Isoflurane	↑	↓↓	Yes
Desflurane	↑	↓↓	Yes
Sevoflurane	↑	↓	Yes
N_2O	↑	↓	-
N_2O with volatile anesthetics	↑↑	-	-
N_2O with intravenous anesthetics	0	0	-
Thiopental	↓↓↓	↓↓↓	No
Etomidate	↓↓	↓↓	No
Propofol	↓↓	↓↓	No
Dexmedetomidine	↓	0	No
Ketamine	↑↑	↑/0	No
Fentanyl	↓/0	↓/0	No

↑, increases; ↓, decreases; 0, no effect; —, not determined. Arrows indicate relative strength of effect.

Conclusion

Cerebral hypoperfusion represents the primary mechanism underlying brain ischaemia, whether occurring globally, such as after cardiac arrest, or focally, as seen in localised stroke. In focal cerebral ischaemia, three distinct regions can be identified: the ischaemic core, which sustains irreversible injury; the penumbra, characterised by partial ischaemia and potentially reversible damage; and surrounding tissue with normal perfusion. Neuronal injury in ischaemia is mainly driven by disruption of energy metabolism due to impaired oxidative phosphorylation, intracellular calcium overload, excessive glutamate release, and increased production of free radicals. These processes collectively lead to excitotoxicity and neuronal death through necrotic and apoptotic pathways. Additional factors, including impaired cerebral autoregulation, elevated intracranial pressure, and breakdown of the blood–brain barrier (BBB), further exacerbate injury and may promote the progression of penumbral tissue to infarction if reperfusion is not promptly restored.

The primary objective in resuscitating penumbral tissue following brain injury is the timely restoration of adequate perfusion and oxygen delivery before irreversible damage develops. Key strategies include rapid reperfusion and maintenance of sufficient cerebral perfusion pressure (CPP). Relative hypotension must be avoided, as it compromises collateral circulation to the penumbra. To optimise cerebral perfusion, systolic blood pressure should generally be maintained between 150–180 mmHg. In addition, hyperthermia should be actively prevented because elevated temperature worsens neuronal injury, whereas the neuroprotective effects of moderate hypothermia remain uncertain. Glycaemic control is also essential, as both hyperglycaemia and hypoglycaemia are associated with poorer neurological outcomes. Therefore, serum glucose levels should ideally be maintained below 180 mg/dL while avoiding hypoglycaemic episodes.

Within the field of neuroanaesthesia, anaesthetic management plays a critical role in preserving penumbral perfusion. Anaesthetic agents may confer neuroprotection by suppressing neuronal activity and reducing cerebral metabolic demand, although their effects on cerebral haemodynamics differ depending on the agent used. Recent meta-analyses have demonstrated that general anaesthesia during mechanical thrombectomy does not result in inferior tissue or clinical outcomes compared with conscious sedation and may

even improve reperfusion and neurological recovery when haemodynamic parameters are carefully controlled. Nevertheless, general anaesthesia carries an inherent risk of relative hypotension, necessitating vigilant monitoring and appropriate titration of vasoactive medications.

Neuroanaesthetic principles in the resuscitation of penumbral–penlucida regions focus on sustaining cerebral perfusion, oxygenation, and metabolic stability to prevent viable tissue from progressing to irreversible infarction. Securing a patent airway and ensuring adequate ventilation are fundamental to maintaining cerebral oxygen delivery. Hypoxia accelerates neuronal death within vulnerable regions. Ventilatory parameters should be adjusted to maintain arterial carbon dioxide tension ($PaCO_2$) within an optimal range of approximately 35–40 mmHg. Excessive hypocapnia may induce cerebral vasoconstriction and reduce blood flow to penumbral and penlucida regions, whereas hypercapnia can elevate intracranial pressure. Maintenance of adequate CPP remains the cornerstone of cerebral resuscitation. Hypotension must be avoided because it expands the ischaemic area, while severe hypertension may exacerbate cerebral oedema. Vasopressor and inotropic agents should be carefully titrated to optimise cerebral blood flow without increasing intracranial pressure.

Continuous intraoperative and postoperative neurological monitoring is essential to evaluate the integrity of penumbral tissue. Early detection of neurological deterioration allows timely intervention to prevent progression of penlucida tissue to infarction. Temperature regulation and glycaemic control remain vital components of neuroprotection, as hyperthermia increases cerebral metabolic demand and accelerates neuronal injury within the penumbra.

In summary, the application of neuroanaesthetic principles provides a structured approach to the resuscitation of the injured brain by optimising perfusion, oxygenation, and metabolic conditions. This strategy is essential for preserving the penumbral–penlucida regions and preventing their progression to irreversible cerebral infarction.

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