Am J Transl Res 2026;18(3):2311-2333
www.ajtr.org /ISSN:1943-8141/AJTR0169765

Review Article

Potential neuroprotective role of dexmedetomidine in preventing postoperative cerebral hyperperfusion syndrome: from mechanisms to clinical applications

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Received November 3, 2025; Accepted February 12, 2026; Epub March 15, 2026; Published March 30, 2026

Abstract: Cerebral hyperperfusion syndrome (CHS) is an uncommon but serious problem that can occur following carotid endarterectomy, carotid artery stenting, and revascularization procedures for moyamoya disease (MMD). Clinically, CHS can lead to cerebral edema, intracerebral hemorrhage, or status epilepticus, all of which are linked to poor neurological outcomes. The syndrome is believed to be triggered by impaired autonomic regulation, endothelial dysfunction, and disruption of the blood-brain barrier (BBB), leading to oxidative stress, inflammation, ischemia-reperfusion injury, and neuronal impairment. The 24-72 hours postoperatively is a critical "amplification phase" during which BBB disruption and oxidative-inflammatory feedforward damage can gradually worsen, ultimately resulting in neurological deficits. Despite careful perioperative hemodynamic management, some patients still develop CHS; this persistent susceptibility suggests the need for specific approaches to stabilize neurovascular function. Importantly, the underlying pathophysiological mechanisms of CHS vary across surgical populations, including impaired autonomic regulation in patients with carotid stenosis and chronic vascular fragility in patients with MMD. Dexmedetomidine (DEX) is a highly selective α2-adrenergic receptor agonist that has shown neuroprotective effects in experimental models and clinical practice. Its protective mechanisms include inhibiting sympathetic activity, reducing cerebral blood flow and metabolic demands, mitigating inflammation and oxidative responses, maintaining BBB integrity, and reducing ischemia-reperfusion injury by stabilizing mitochondria. Importantly, DEX acts as a hemodynamic buffer during the acute reperfusion phase and as a molecular stabilizer during the 24-72 hour delayed phase, while simultaneously promoting cellular recovery and reducing white matter damage. However, despite promising preclinical data, clinical data on DEX specifically for the prevention of CHS remain limited. This review summarizes current experimental and clinical evidence to highlight the time-dependent and population-specific therapeutic benefits of DEX. Based on this, we propose a personalized pharmacological framework that provides targeted neurovascular protection for high-risk patients on top of systemic blood pressure control.

Keywords: Dexmedetomidine, cerebral hyperperfusion, cerebral hyperperfusion syndrome, blood-brain barrier, cognitive impairment, neuroprotection

Introduction

Cerebral hyperperfusion syndrome (CHS) is a rare yet potentially serious complication of cerebrovascular revascularization procedures, including carotid artery stenting (CAS), carotid endarterectomy (CEA), endovascular thrombectomy (EVT), intracranial angioplasty and stenting (INCS), and bypass surgery for moyamoya disease (MMD). Despite advances in surgical techniques and perioperative care, CHS remains largely unpredictable and continues to pose a significant clinical challenge [1, 2]. Current management of CHS primarily involves strict blood pressure control, adequate sedation, prevention of secondary complications, and supportive care. Clinically, CHS may still develop even with rigorous systemic blood pressure control, particularly during the 24-72 h high-risk postoperative period. This period is

https://doi.org/10.62347/NBRQ1886

often associated with impaired cerebral autoregulation, which can lead to cerebral edema or life-threatening intracranial hemorrhage (ICH). Additionally, cognitive decline related to excessive cerebral perfusion requires increased clinical attention [3, 4]. Therefore, there is an urgent clinical need for multifaceted pharmacological strategies that ensure hemodynamic stability while providing molecular-level neuroprotection.

Dexmedetomidine (DEX), a highly selective α2-adrenoceptor agonist, is widely used as an anesthetic adjunct for its sedative, anxiolytic, and sympatholytic properties, which confer cooperative sedation with minimal respiratory depression at clinical doses [5]. In neurosurgical settings, DEX offers additional benefits. It induces a readily arousable state with negligible respiratory impairment, enabling rapid transitions between wakefulness and sleep and facilitating necessary intraoperative tasks under sedation [6, 7]. Beyond its sedative effects, a growing body of evidence indicates that DEX modulates multiple pathways implicated in CHS, including inhibition of sympathetic hyperactivity, attenuation of inflammatory and oxidative stress, mitigation of ischemia-reperfusion injury, and preservation of blood-brain barrier (BBB) integrity [8-10]. Collectively, these mechanisms support DEX as a promising adjuvant for CHS prevention, conferring hemodynamic stabilization and neurovascular protection during the critical 24-72 h postoperative window.

Although several studies have postulated that DEX may decrease the incidence of CHS, a comprehensive review of the neuroprotective mechanisms underlying this potential effect is lacking. Notably, existing mechanistic discussions rarely correlate with procedure-specific phenotypes, such as chronic hypoperfusion-related vascular fragility in MMD and atherosclerotic carotid disease managed with CEA or CAS. This review synthesizes current knowledge on the pathogenesis, epidemiology, prevention, and management of CHS, and explores the potential neuroprotective effects of DEX. We discuss evidence from both clinical studies and experimental models, with a focus on DEX-mediated sympathetic inhibition, attenuation of oxidative and inflammatory stress, preservation of BBB integrity, and mitigation of ischemia-reperfusion injury. Lastly, we propose personalized pharmacological strategies for the future research and clinical translation of DEX as a perioperative management strategy for patients at high risk of CHS.

Overview of CHS

Clinical features and definition: CHS was first described by Sundt in 1981 in patients undergoing CEA [11]. It is characterized by severe, intractable headache, seizures, or intracerebral hemorrhage (ICH) and subarachnoid hemorrhage due to impaired autoregulation and excessive postoperative cerebral blood flow (CBF). The severity and timing of symptoms vary considerably. Many patients experience mild or transient symptoms, but some may develop serious neurological complications [12, 13]. Common clinical features include severe ipsilateral or generalized headache, often accompanied by visual disturbances, nausea, vomiting, facial or ocular pain, and focal neurological deficits such as hemiplegia or aphasia. Some patients may also experience seizures or altered levels of consciousness [12]. Symptoms usually appear hours to days following reperfusion, and the acute phase usually lasts 1-2 weeks. Most patients recover with appropriate management [14]. In more severe cases, cerebral edema, CH, or status epilepticus may occur, which can significantly impact postoperative outcomes [15]. Although many eventually recover, patients with edema or hemorrhage are at risk of long-term neurological impairment. Notably, even mild or asymptomatic hyperperfusion can lead to transient cognitive decline, which in some cases may persist [4].

Epidemiology and risk factors: The reported incidence of CHS varies considerably across different studies, primarily due to differences in surgical procedures and diagnostic criteria. A review of nine studies that included 4,446 patients undergoing CEA found an overall incidence of CHS of 1.16%, with incidences ranging from 0.44% to 11.7% across studies. The incidence of ICH in this cohort was 0.74% (range 0.36-4.5%) [16]. In contrast, a recent systematic review and meta-analysis of 8,731 patients who underwent CAS revealed a higher co-occurrence of CHS, at 4.6% (95% CI: 3.1-6.8%) [17]. Another large meta-analysis involv-

ing over 236,000 procedures (218,144 CEAs and 18,393 CASs) showed a higher incidence of CHS after CEA than after CAS, which may be related to differences in patient selection, surgical indications, and changes in surgical techniques over time [18].

The incidence of CHS appears to be higher in patients with MMD after revascularization compared to other cerebrovascular surgeries. In a prospective study of 121 cerebral hemispheres in 86 patients, a 21.5% incidence of CHS was reported after superficial temporal artery-middle cerebral artery (STA-MCA) bypass surgery [19]. This increased risk may be related to the unique pathophysiology of MMD relative to carotid stenosis, particularly the presence of chronic cerebral hypoperfusion and severely impaired cerebrovascular reactivity (CVR) in MMD. The disease-characteristically fragile collateral vessels are highly sensitive to even slight increases in CBF and are more prone to delayed hyperperfusion. There is also evidence that insufficient collateral circulation in chronically ischemic areas leads to decreased CVR. Therefore, patients with recurrent transient ischemic attacks due to hemodynamic disturbances or a history of stroke should be considered high-risk for CHS. In addition, individuals with radiographic features such as severe arterial stenosis, incomplete Circle of Willis, and impaired cerebral perfusion parameters are also more likely to develop CHS [1, 20].

Pathophysiological and mechanisms

Postoperative hyperperfusion and CHS is best understood as a neurovascular injury caused by the cerebral blood vessels' inability to cope with the sudden increase in local blood flow and perfusion pressure, rather than "hemodynamic overload". Clinically, this susceptibility is highest in the early postoperative period, typically within 24-72 hours, when changes in blood pressure, increased endothelial stress, and BBB impairment interact to lead to neurological deterioration. In various surgical populations, three pathobiological processes inevitably intertwine: limited autoregulatory reserves, BBB disruption, and oxidative-inflammatory amplification (**Figure 1**). Notably, the relative roles of these mechanisms differ between MMD and carotid interventional procedures (such as CEA or CAS), and this heterogeneity directly impacts specific stages and individualized prevention strategies.

Autoregulatory failure and depletion of CVR

In healthy individuals, CBF remains relatively stable within a systemic blood pressure range of approximately 60-160 mmHg through autoregulation of vascular tone. This stability is achieved through both myogenic and neurogenic mechanisms: vascular smooth muscle rapidly adapts to pressure changes, while sympathetic innervation provides secondary regulation when myogenic regulation is insufficient [21]. In chronic ischemic conditions (such as ischemia caused by carotid atherosclerosis), cerebral vessels are in a state of continuous dilation to maintain adequate perfusion. Prolonged dilation eventually leads to smooth muscle cell degeneration, causing them to lose their ability to contract or dilate in response to pressure changes [22]. The extent of this vascular damage depends on the severity and duration of ischemia. Impaired CVR is considered a marker of severely impaired autoregulation and a good predictor of CHS [23, 24]. This susceptibility is often further aggravated in individuals with chronic small vessel disease associated with long-term hypertension or diabetes, as both conditions impair autoregulation and lead to endothelial dysfunction [25].

In CAS and CEA, reopening of the carotid lumen can abruptly increase blood flow and shear stress in microvessels already at their limits of autoregulation. In CAS, stent deployment can exacerbate this mismatch by altering pulsatility and shear patterns. In CEA, blood pressure fluctuations and hemodynamic disturbances induced by vascular clips may also play a role, although this varies among patients. Crucially, once vasoconstrictive reserves are depleted, "normal" systemic blood pressure is insufficient to guarantee safe local perfusion; CBF may be excessively increased, leading to endothelial injury, BBB impairment, and vasogenic edema [12, 26-28].

In MMD, these hemodynamic disturbances are more severe and biologically specific. Chronic hypoperfusion, fragile collateral vessels, and poor CVR lead to permanent dilation of the vascularized arteries preoperatively. Following revascularization, even physiologically appropriate increases in blood flow may exceed the

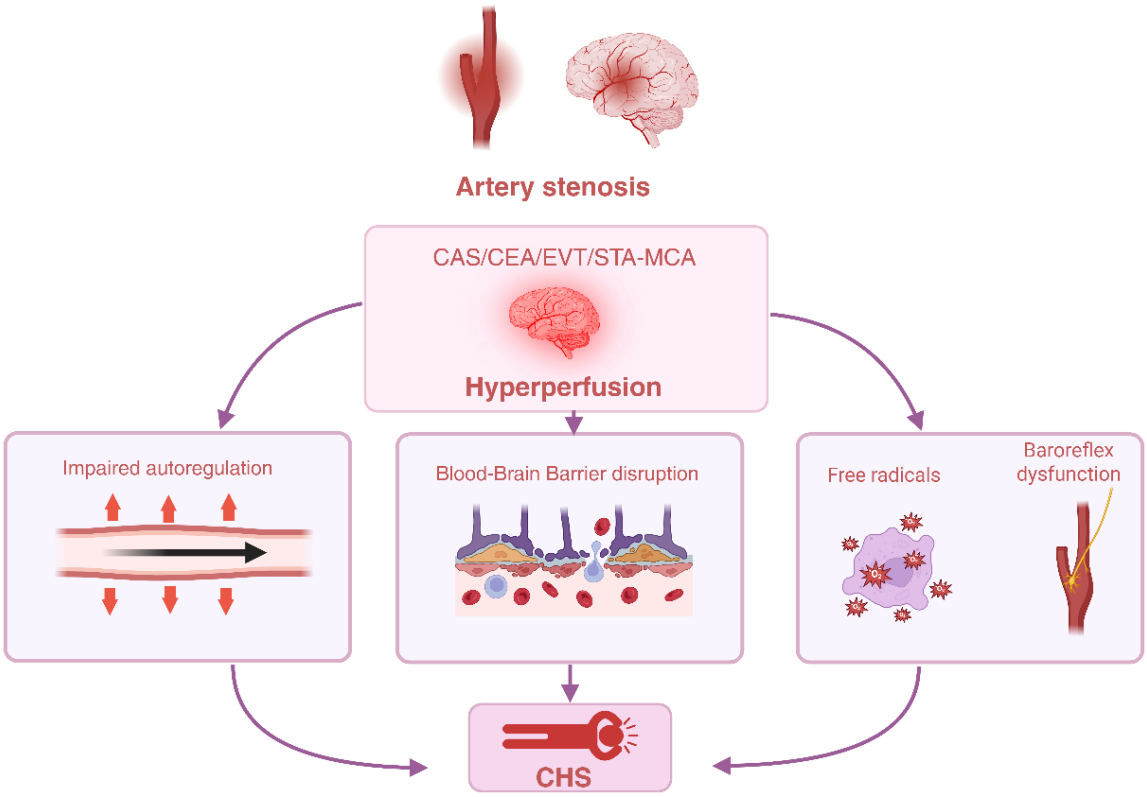

Figure 1. Pathophysiology of postoperative cerebral hyperperfusion syndrome (CHS). After revascularization procedures such as CEA, CAS, EVT, or STA-MCA bypass, postoperative hyperperfusion may occur in regions with impaired autoregulation. Excessive blood flow can disrupt the BBB, generate free radical, and cause baroreflex dysfunction, ultimately leading to CHS. Notes: BBB, blood brain barrier; CEA, carotid endarterectomy; CAS, carotid artery stenting; EVT, endovascular thrombectomy; STA-MCA, superficial temporal artery-middle cerebral artery bypass; CHS, cerebral hyperperfusion syndrome.

limited capacity of these vessels, leading to delayed or persistent hyperperfusion and capillary stress as the microvascular network takes several days to slowly adapt [29]. Simultaneously, collateral vessels in MMD are typically angiogenically driven, structurally immature, with reduced wall support, fewer smooth muscle and pericytes, and incomplete basement membrane development [30, 31]. This chronically fragile vascular bed, coupled with a lack of autoregulatory reserve, offers a mechanistic explanation for the higher incidence of CHS in MMD patients compared to those undergoing carotid revascularization.

Additionally, intraoperative cross-clamping during CEA may temporarily exacerbate autoregulatory dysfunction, although it is not a consistent predictor of postoperative hyperperfusion [32]. Similar transient effects have been observed in MMD bypass surgery, where occlusion of the vascularized vessel may further impair vascular reactivity. Overall, intraoperative hemodynamic changes are modifiers of risk, rather than primary determinants. The main susceptibility usually occurs in the early postoperative period, when blood pressure changes and gradually increasing microvascular stress repeatedly challenge the vascular bed with poor autoregulatory reserves.

BBB disruption and microvascular injury: a mechanistic hinge linking hyperperfusion to tissue damage

The exact pathogenesis of CHS remains unclear. However, increasing imaging and experimental evidence suggests that the BBB and microvascular damage are key mechanisms linking hyperperfusion, edema, epilepsy, hemorrhage, and subsequent white matter damage.

In individuals with carotid artery stenosis, coexisting systemic hypertension and chronic microangiopathy enhance endothelial cell vulnerabil-

ity and lead to BBB disruption [14]. Computed tomography perfusion studies following CAS have shown increased BBB permeability, reflecting an increased risk of microvascular and vasogenic injury [33]. Both experimental and clinical evidence indicate that hyperperfusion may induce albumin extravasation and activation of the transforming growth factor-β (TGF-β) signaling pathway following BBB disruption [34]. These events can lead to vasogenic edema, epileptiform activity, and downstream white matter damage, even without significant infarction.

In MMD, chronic hypoperfusion and fragile collateral vessels make the cerebral microvascular system particularly vulnerable. Advanced magnetic resonance imaging (MRI) and positron emission tomography (PET) studies have shown decreased cortical perfusion and increased BBB permeability in MMD patients who experience postoperative hyperperfusion [35, 36]. PET imaging has further identified delayed or persistent hyperperfusion, associated with impaired microvascular autoregulation and endothelial dysfunction [37]. These observations suggest that adverse BBB stress and adaptation responses develop gradually over several days, rather than resolving immediately postoperatively.

In summary, these results support a unified concept: CHS is a manifestation of reperfusion-induced neurovascular injury in which BBB failure leads to downstream damage, rather than simple pressure or blood flow-induced overload. Increased vascular permeability allows serum proteins and neurotoxic substances to enter the brain parenchyma, exacerbating edema and neuronal hyperexcitability [38, 39]. Notably, clinical imaging studies have shown that BBB disruption caused by hyperperfusion facilitates the leakage of neurotoxic molecules into neural tissue, leading to cerebral microbleeds and subsequent postoperative cognitive decline [40]. Therefore, BBB dysfunction should be considered a key determinant of CHS, with the 24-72 hours postoperatively being a critical period during which disruption of the BBB exacerbates secondary damage.

Oxidative-inflammatory amplification and additional contributors

Another proposed potential mechanism for CHS is oxidative stress-mediated endothelial injury. In this mechanism, the problem is not limited to increased blood flow: reactive oxygen species (ROS) generated during reperfusion exacerbate vascular damage, making short-term overperfusion potentially lead to long-term endothelial dysfunction and BBB impairment. Human studies have confirmed perioperative oxidative stress during CEA due to the detection of free radical-related signals in transcranial and jugular venous blood samples collected before and after carotid artery clipping and recanalization [41, 42]. Mechanistically, oxidative stress can activate redox-sensitive signaling pathways, leading to increased endothelial permeability, enhanced leukocyte-endothelial adhesion, and decreased barrier integrity, providing a plausible link between transient hemodynamic impairment and BBB instability [43]. Interventional studies support the role of oxidative stress in postoperative hyperperfusion. Studies have shown that preoperative use of the free radical scavenger edaravone can reduce cerebral hyperperfusion after CEA, and similar preventative strategies have been investigated in the CAS population [44, 45]. Importantly, oxidative stress may also be associated with neurocognitive risk: elevated intra-arterial oxidative stress levels are associated with cognitive impairment after carotid stenting, while preoperative use of edaravone after CEA is associated with reduced postoperative cognitive impairment [46]. Conceptually, ROS and inflammation constitute a positive feedback amplifier, exacerbating endothelial and BBB injury, and ultimately transforming transient hyperperfusion into permanent structural brain damage.

Additionally, baroreceptor reflex dysfunction may impair the ability to regulate sudden changes in systemic arterial pressure. Interventional carotid procedures (such as angioplasty, stenting, or endarterectomy) often lead to this dysfunction, and there are reports that CEA itself reduces physiological baroreceptor reserve, impairing blood pressure homeostasis [47, 48]. A less discussed mechanism is the activation of the trigeminal vasoreflex. Exposure to vasoconstrictive stimuli may trigger the release of vasoactive neuropeptides from the trigeminal pathway, leading to compensatory cerebral vasodilation and increased CBF [49].

Prevention, management, and treatment

Strict perioperative blood pressure monitoring and management are the cornerstone of the prevention and treatment of CHS. Poor postoperative blood pressure control significantly increases the risk of ICH in CHS patients [14, 50-52]. For patients at high risk of complications, continuous monitoring of postoperative CBF via transcranial Doppler (TCD) is particularly recommended [8]. For patients undergoing CAS, most studies recommend that postoperative blood pressure should be controlled below 140/90 mmHg. Patients at high risk of CHS or ICH may benefit from stricter control targets, such as blood pressure control below 120/80 mmHg [53]. In MMD bypass surgery, current guidelines recommend that systolic blood pressure should be maintained below 120 mmHg for patients with normal blood pressure and below 140 mmHg for patients with hypertension during the first week postoperatively. This approach balances the need for adequate cerebral perfusion with the risk of hyperperfusion-related complications [50]. Blood pressure should be carefully monitored during surgery and for at least 24 hours postoperatively. Currently, mixed α- and β-adrenergic antagonists are commonly used to control blood pressure, typically reducing mean arterial pressure and cerebral perfusion pressure by about 30% from baseline [54]. Centrally acting α-adrenergic agonists (such as clonidine) can also reduce sympathetic tone by stimulating baroreceptor pathways in the brainstem. This reduces arterial pressure, cardiac output, and heart rate while maintaining autoregulatory function [55].

Neurological deterioration in CHS patients is primarily caused by cerebral edema, seizures, and hemorrhage. Optimal supportive care includes sedation, hyperventilation, temperature control, and osmotic therapy such as hypertonic saline or mannitol to reduce cerebral edema [56-58]. Prophylactic anticonvulsants are often used to reduce the risk of seizures. In the event of ICH, urgent neurosurgical evaluation is crucial, and the decision to continue antiplatelet therapy should be individualized based on the patient's risk [1].

Despite strict postoperative blood pressure control with vasodilators such as beta-blockers or nitroglycerin, CHS can still occur unpredictably [14, 59]. Nevertheless, CHS can occur even when systemic hemodynamic parameters appear normal, suggesting that local vascular fragility and neurovascular unit damage (especially during the peak risk period of 24-72 hours) are key determinants. This suggests that factors other than systemic hemodynamics are involved in the pathogenesis of this disease. Therefore, additional pharmacological strategies are needed to not only stabilize circulation but also provide direct neurovascular protection.

In summary, CHS results from impaired brain autoregulation, leading to microvascular damage, BBB disruption, and subsequent cognitive impairment. These pathophysiological insights highlight the importance of effective pharmacological approaches for CHS prevention.

DEX

DEX is a highly selective α2-adrenergic receptor agonist commonly used for sedation in the operating room and intensive care unit, and there is evidence of its neuroprotective effects. Recently, it has been investigated as a potential protective agent for patients at risk of postoperative CHS. Conceptually, the benefits of DEX may extend throughout the entire course of CHS, from reperfusion stabilization to downstream neurovascular recovery. First, during reperfusion, DEX can inhibit sympathetic excitation and hemodynamic instability, which may limit shear stress on fragile microvessels and reduce hemodynamic uncoupling. Second, in the critical 24-72 hours, as BBB injury and oxidative-inflammatory amplification gradually intensify and lead to neurological deterioration, DEX may stabilize endothelial cells and the BBB, reducing the effects of these pathogenic amplifiers and thus alleviating edema and microvascular damage. Third, after the initial deterioration phase, DEX may aid cellular recovery by protecting mitochondria and inhibiting apoptotic signaling. Collectively, this multi-stage protective effect constitutes the mechanistic basis for maintaining neurocognitive function (**Figure 2**).

Importantly, the clinical application of DEX in CHS is not static; its benefits are closely related to the different pathophysiological needs of different surgical populations. Specifically, dur-

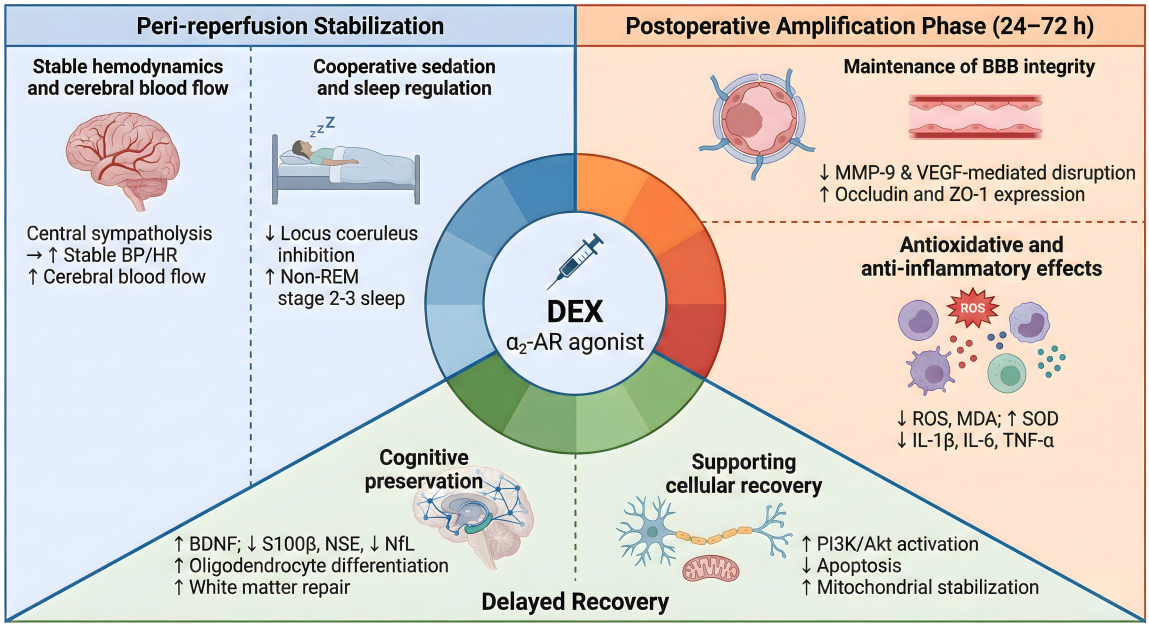

Figure 2. Schematic illustration of the neuroprotective mechanisms of dexmedetomidine (DEX) against postoperative CHS. DEX exerts multiple neuroprotection effects including cooperative sedation, hemodynamic stability, maintenance of BBB integrity, attenuation of ischemia-reperfusion injury, antioxidant and anti-inflammatory actions, reduce cognitive impairment. Together, these mechanisms contribute to improved neuroprotective and reduced risk of postoperative CHS. Notes: BDNF, brain-derived neurotrophic factor; NSE, neuron-specific enolase; S100β, S100 calcium-binding protein β; MMP-9, matrix metalloproteinase-9; VEGF, vascular endothelial growth factor; NF-κB, nuclear factor kappa-B; ROS, reactive oxygen species; SOD, superoxide dismutase; MDA, malondialdehyde; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B.

ing the acute reperfusion phase, DEX can act as a hemodynamic shield in patients undergoing CAS/CEA; while in patients with MMD, it acts as a molecular stabilizer by protecting vessels from chronic fragility during the critical 24-72 hours postoperatively.

Overall, although the evidence remains limited and somewhat inconsistent, the results indicate that DEX may have neuroprotective effects at multiple stages of CHS development, rather than through a single mechanism. This time-dependent and multi-pathway effect may be particularly beneficial for high-risk patients with CHS.

Reperfusion stability (intraoperative to early postoperative period)

In CAS and CEA, the risk of CHS is typically highest in the early postoperative period. Chronic hypertension and atherosclerotic remodeling lead to endothelial dysfunction and BBB fragility, while stent deployment or clamp release can suddenly expose a vascular bed with limited autoregulatory reserves to hemodynamic surges. Therefore, even transient increases in blood pressure can generate excessive local shear stress, triggering immediate endothelial damage and vasogenic leakage. Thus, early administration of DEX is best understood as targeted protection: DEX's sympathetic inhibitory effect and mitigation of awakening-related rebound hypertension provide a hemodynamic buffer, alleviating the initial flow-pressure mismatch that initiates the CHS cascade.

Sympathetic inhibition and synergistic sedation: reducing pressure surges and agitation-related triggers

Perioperatively, anesthesia and surgical stimulation can induce sympathetic activation and blood pressure fluctuations. These effects may be exacerbated after reperfusion, as the sudden restoration of blood flow can lead to a rapid increase in CBF and intracranial pressure, particularly in fragile or damaged vessels. Postoperative agitation or inadequate sedation may further enhance this response, increasing

the risk of immediate perioperative and early postoperative CHS. By inhibiting this early hyperdynamic response, DEX may help alleviate stress on fragile cerebral blood vessels and reduce the risk of excessive reperfusion.

DEX acts on sympathetic nerve endings, inhibiting the release of norepinephrine [60]. Its sedative effect is primarily mediated by α2A adrenergic receptors in the locus coeruleus (LC), where inhibition of norepinephrine neuronal firing reduces arousal and induces a state consistent with non-rapid eye movement (non-REM) sleep [61]. Unlike γ-aminobutyric acid-based drugs such as midazolam or propofol, DEX induces arousable, sleep-like sedation through the LC-preoptic/ventrolateral preoptic pathway, rather than directly inhibiting the medullary respiratory center, thus preserving spontaneous respiration [61, 62]. This unique mechanism produces a synergistic and easily arousable sedative effect with minimal respiratory depression. Its rapid recovery properties and maintenance of orientation make DEX particularly suitable for use in the ICU [63]. By reducing sympathetic hyperactivity and stabilizing intracranial pressure, DEX may also reduce cerebral metabolic demands, thereby lowering the risk of CHS in patients undergoing CAS, CEA, EVT, or STA-MCA bypass surgery.

Studies have shown that DEX can reduce postoperative pain and opioid use within 24-48 hours after neurosurgery, supporting its use in opioid-saving anesthesia strategies [64, 65]. This analgesic effect is partly mediated by activation of spinal α2-adrenergic receptors, which inhibit nociceptive transmission and suppress substance P release, while concomitant inhibition of LC neuronal firing enhances descending noradrenergic inhibitory pathways [66, 67]. In addition, DEX has been reported to improve sleep quality by increasing the duration of non-REM stage 2 sleep, promoting biomimetic non-REM stage 3 sleep, and reducing human REM sleep [68, 69]. These benefits may be related to mitigating microglial overactivation and protecting synaptic integrity via the complement C3 - C3aR signaling pathway [70].

In summary, the sympathetic inhibitory, analgesic, and sleep-promoting effects of DEX contribute to stabilizing systemic and cerebral hemodynamics, providing physiological support for potential prevention of CHS.

Hemodynamic control and flow-metabolism coupling: preventing a "CBF-cerebral metabolic rate of oxygen ($CMRO_2$) mismatch"

Since postoperative CHS is closely related to blood pressure, stable hemodynamics is crucial for reducing the incidence of CHS. Therefore, understanding how DEX modulates systemic and cerebral circulation is extremely important. Numerous studies have demonstrated that DEX helps stabilize hemodynamics perioperatively, reducing fluctuations in blood pressure and heart rate, which is beneficial for maintaining cardiovascular stability throughout anesthesia and recovery [71, 72].

The pharmacokinetic and pharmacodynamic properties of DEX produce dose-dependent biphasic cardiovascular effects. Initially, stimulation of α2B receptors in vascular smooth muscle induces vasoconstriction via L-type calcium channels, resulting in a transient, dose-dependent increase in blood pressure. Slow infusion can mitigate this initial increase. Subsequently, a slight decrease in blood pressure occurs due to central sympathetic inhibition (mediated by inhibition of norepinephrine release by presynaptic α2 receptors) [66, 73, 74]. Within the recommended clinical dose range, these hemodynamic effects are generally predictable, reversible, and well-tolerated, and the cardiovascular safety of DEX can be supported with appropriate monitoring [75].

Prolonged infusions of DEX (even up to 48 hours) in the ICU are generally safe for critically ill patients and do not increase in-hospital mortality. However, it is important to note that rebound increases in blood pressure and heart rate may occur after discontinuation [76]. Therefore, close hemodynamic monitoring is necessary, especially during prolonged infusions. Overall, the hemodynamically stable properties of DEX offer advantages in preventing postoperative blood pressure spikes that may lead to CHS.

In addition to stabilizing systemic hemodynamics, DEX also affects CBF and brain metabolism. In a study of 9 healthy volunteers, a loading dose of DEX followed by continuous infusion showed a significant reduction in CBF from baseline during infusion and at least 30 minutes after discontinuation [77]. Another study indicated that DEX reduces neuronal excitabili-

ty and decreases $CMRO_2$, thereby contributing to tighter hemodynamic coupling. When metabolic demand decreases in tandem with perfusion, the risk of pathological overperfusion (excessive CBF relative to $CMRO_2$) and subsequent BBB disruption is minimized [78]. However, the effect of DEX on CBF remains controversial. Some studies report that DEX has little effect on cerebral perfusion or oxygenation compared to other sedatives, or that its effect varies depending on the patient population [79]. These inconsistencies may reflect differences in depth of anesthesia, arterial carbon dioxide levels, and methods of measuring CBF, suggesting that the primary role of DEX is to maintain hemo-metabolic coupling rather than directly inducing cerebral vasoconstriction [80].

Collectively, these results indicate that in the early postoperative period, DEX can suppress sympathetic activity, has a slight effect on systemic arterial pressure, and modulates cerebral circulation and metabolism indirectly rather than directly inducing cerebral vasoconstriction.

Postoperative amplification window (24-72 hours)

The 24-72 hours postoperative period is a critical period of pathological magnification during which the first acute phase of reperfusion stress evolves into structural disruption of the BBB. Using DEX before and after reperfusion effectively mitigates this “first hit”, thereby decoupling it from the secondary peaks of matrix metalloproteinase-9 (MMP-9) and ROS which typically peak during this period.

In MMD, both the moyamoya vessels and the recipient cortical arteries exhibit chronic hypoperfusion and structural fragility, with CHS often being a delayed phenomenon. This reflects a fragile “adaptation period” during which the microvascular bed transitions from chronic ischemia to sudden hyperperfusion. DEX exerts a protective effect by stabilizing this phase; it reduces excessive activation of MMP-9 and readjusts vascular endothelial growth factor (VEGF) signaling to promote vascular maturation rather than pathological leakage, thus buffering the “second hit” of reperfusion-a phase in which systemic blood pressure control may be inadequate.

BBB/endothelium protection as a central mechanism

BBB disruption appears to be a key pathological event in the pathogenesis of CHS. CAS and revascularization surgery in MMD are known to increase BBB permeability, which is associated with postoperative cerebral edema, seizures, and ischemic injury [33, 36, 81, 82]. Growing evidence suggests that endothelial dysfunction and proteolytic degradation of the vascular basement membrane are important mediators in this process.

MMP-9 is a key molecule in the pathogenesis of CHS because it degrades extracellular matrix components and tight junction proteins, disrupting the integrity of the BBB [36, 83]. Increased MMP-9 activity is generally associated with increased vasogenic edema and increased BBB permeability. Furthermore, elevated VEGF levels in the dura mater of MMD patients further exacerbate vascular fragility. Experimental studies in ICH have demonstrated that the activation of matrix metalloproteinases (especially MMP-9) under the influence of the VEGF leads to increased vascular leakage and perivascular inflammatory damage [84]. Collectively, these findings suggest that endothelial damage induced by the activation of proteins such as VEGF and MMP-9 is a common pathological mechanism in moyamoya disease and atherosclerosis-associated cerebral hyperperfusion.

DEX offers comprehensive protection for the BBB as an antioxidant, anti-inflammatory agent, and endothelial stabilizer. In cerebral ischemia-reperfusion models, DEX suppresses MMP-9 activity and maintains the expression of tight junction proteins such as closure protein-5, occlusive protein, and ZO-1, thereby reducing Evans blue extravasation and vasogenic edema. These effects are accompanied by inhibition of the JNK/p38 MAPK signaling pathway and induction of M2 microglial polarization [85]. In hemorrhagic brain injury, DEX maintains the integrity of the BBB by inhibiting NF-κB, thereby reducing endothelial cell apoptosis and secondary inflammatory amplification [86, 87]. Similar protective effects have been observed in experimental traumatic brain injury, where DEX reduced Evans blue leakage and restored tight-junction protein expression

[88]. Beyond these models, DEX has been found in ischemic brain studies to induce microglial polarization towards the M2 type via mechanisms such as Nrf2/HO-1/NLRP3, further confirming its protective effect on the BBB [89].

Interestingly, although excessive VEGF leads to increased vascular permeability, DEX seems to modulate the expression of this growth factor in a homeostatic, pro-angiogenic yet barrier-protective manner. This regulation may involve inhibiting the activation of hypoxia-inducible factor-1α and subsequent VEGF overexpression, thereby resisting pathological angiogenesis leakage and promoting endothelial repair [90]. By balancing angiogenesis (VEGF) and endothelial stability, DEX promotes microvascular regeneration and neuronal maturation without increasing vascular permeability [91, 92]. This selective modulation offers a dual advantage in improving post-ischemic vascular recovery and preventing reperfusion-related BBB disruption.

Since the BBB is the first line of defense for the neurovascular unit, DEX's protective effect is crucial for limiting initial tissue damage. In addition to this structural stabilizing effect, DEX further inhibits the progression of CHS by mitigating the oxidative-inflammatory amplification cycle.

Oxidative-inflammatory escalation: attenuating ROS-linked endothelial damage and secondary inflammation

Oxidative stress becomes especially important in the later stages of reperfusion, peaking approximately 24-48 hours post-procedure. This surge in oxidation is closely related to core mechanisms driving CHS. Following revascularization procedures such as MMD bypass surgery or CAS, the sudden restoration of blood flow leads to an overproduction of ROS, including nitric oxide (NO) and malondialdehyde (MDA). These free radicals trigger lipid peroxidation, endothelial dysfunction, and vasodilation, ultimately resulting in BBB disruption and neuronal injury [26, 55, 93-95]. ROS are major upstream activators of the NF-κB pathway, which upregulates MMP-9 expression, thereby mediating basement membrane proteolytic degradation [96, 97]. This process further enhances the inflammatory signaling cascade, creating an oxidative-inflammatory cycle that exacerbates microvascular damage and the development of CHS.

In both experimental and clinical settings, DEX exhibits potent antioxidant activity. In microglia and neuronal models, DEX inhibits lipopolysaccharide-stimulated NO production and inducible nitric oxide synthase expression by modulating the ERK1/2 and JNK pathways [98, 99]. Additionally, in traumatic brain injury models, DEX activates the PGC-1α signaling pathway, which promotes mitochondrial biosynthesis, reduces ROS accumulation and increases intrinsic antioxidant defense [98, 100]. In vivo, DEX enhances the activity of glutathione, catalase, and superoxide dismutase, and decreases MDA and oxidized glutathione levels [101, 102]. Clinical evidence further supports these findings, showing that DEX maintains thiol/disulfide homeostasis, a sensitive indicator of systemic redox balance, suggesting a reduction in perioperative oxidative stress [103].

Excessive ROS can trigger a secondary activation of the inflammatory signaling cascade, further exacerbating endothelial injury and impairing the integrity of the BBB. DEX possesses multiple anti-inflammatory effects that can counteract this oxidative-inflammatory amplification effect. In preclinical models of ischemia-reperfusion and lipopolysaccharide, DEX inhibited the activation of NF-κB and the expression of pro-inflammatory mediators, including IL-1β, IL-6, TNF-α, intercellular adhesion molecule-1 and MMP-9 [102, 104]. In the clinic, perioperative use of DEX has been shown to reduce systemic inflammation, manifested by decreased circulating levels of IL-6 and TNF-α [105].

In summary, DEX has multi-stage neurovascular protective effects: it acts as a hemodynamic protective barrier during the acute reperfusion phase and as a molecular stabilizer during the delayed 24-72 hour phase. By neutralizing ROS and inhibiting the secondary inflammatory cascade, DEX can prevent the progression from transient physiological stress to irreversible structural damage, offering a mechanistic rationale for individualized use in high-risk populations, including those undergoing CAS, CEA and MMD.

Delayed recovery and neurocognitive sequelae

In addition to the hemodynamically unstable acute phase, the pathophysiology of CHS typically transitions from transient vasomotor dysfunction to downstream tissue damage and recovery processes, including mitochondrial stress response, white matter vulnerability, and potential neurocognitive sequelae.

Mitochondrial preservation and anti-apoptotic signaling: supporting cellular recovery after reperfusion stress

In the delayed reperfusion phase, the clinical focus shifts from hemodynamic stabilization to bioenergetic recovery; mitochondrial integrity becomes a crucial factor in determining whether early reperfusion stress is alleviated or progresses. In CEA, transient carotid artery clamping followed by reflow can induce ischemia-reperfusion-like physiological responses, and human biomarker studies have confirmed perioperative oxidative damage [106]. In contrast, CAS more often links hemodynamic stress and microembolism-related endothelial stress with oxidative injury [107], whereas MMD demonstrates a delayed, low-reserve oxidative-inflammatory amplification response in long-term damaged microvascular networks [108]. Although the initiating factors of these diseases differ, they all focus on a common determinant: mitochondrial integrity, which largely determines whether early reperfusion stress is alleviated or progresses to persistent cellular and microvascular damage. Therefore, protecting mitochondria is particularly important during the delayed recovery phase, in which mitochondrial structural repair and subsequent neurological function are established. DEX offers neuroprotection by modulating mitochondrial function, reducing excitatory amino acid release, and inhibiting apoptosis, helping to reduce neuronal damage associated with ischemia-reperfusion. In hypoxic/reoxygenated hippocampal neurons, DEX suppresses excessive mitochondrial division by downregulating the expression of Drp1 and Fis1, maintaining mitochondrial integrity and decreasing apoptotic signaling [109]. In glutamate-exposed PC12 cells, DEX prevents intracellular calcium overload and inhibits mitochondrial-mediated apoptosis pathways, thereby improving cell survival [110]. In a rat model of cerebral ischemia-reperfusion, DEX activates the Sig-1R pathway, stabilizes mitochondrial membrane potential, inhibits cytochrome c release, reduces Bax levels, and increases Bcl-2 expression, thereby inhibiting intrinsic apoptosis and promoting neuronal function recovery [111]. Preclinical studies also suggest that DEX may stimulate the PI3K/Akt signaling pathway, promoting mitochondrial stability and reducing apoptosis after ischemia-reperfusion injury [10].

In summary, DEX counteracts ischemia-reperfusion-induced neuronal damage by maintaining mitochondrial integrity, regulating intracellular calcium levels, and inhibiting apoptotic signaling. These effects may build upon its prior antioxidant and anti-inflammatory effects, further enhancing overall neuroprotective effects in the later stages of CHS.

White-matter integrity and CHS-related cognition

Cognitive impairment is a recognized clinical sequela associated with delayed cerebrovascular disease. Postoperative hyperperfusion, whether clinically apparent or subclinical, is associated with cognitive deterioration after cerebral revascularization, and cognitive deficits can persist for up to 2 years [3, 4, 26]. The underlying mechanisms appear to be multifactorial, including cerebral microbleeds, neurotransmitter activity disturbances, and damage to the ipsilateral hemisphere white matter microstructure [3, 40, 112-114]. Sudden congestion following revascularization can subject fragile microvessels to excessive shear and pulsatile stress, which is associated with endothelial injury, disruption of tight junctions mediated by MMP-9, and BBB impairment [115, 116]. In addition to vasogenic edema, BBB disruption accompanying endothelial injury and microvascular fragility is associated with a higher risk of cerebral microbleeds [40]. Simultaneously, BBB disruption allows circulating inflammatory mediators and proteases to enter the brain parenchyma, further exacerbating white matter injury [116]. In short, microbleeds and white-matter network disruption provide a plausible structural basis for CHS-related cognitive deficits, especially slowed processing speed and impaired executive function [117]. These findings collectively suggest

that therapeutic strategies focused on protecting BBB integrity and reducing white matter damage may help alleviate cognitive impairment associated with CHS.

Within this BBB-centric framework, DEX has attracted significant attention because it can inhibit sympathetic excitation and stabilize perioperative hemodynamics, potentially reducing shear and pulsatile stress on fragile microvessels during reperfusion. Meanwhile, experimental ischemia-reperfusion studies have revealed that DEX inhibits MMP-9 activity and protects tight junction proteins, contributing to the maintenance of BBB integrity.

Importantly, DEX is associated with improved cognitive function and BBB protection. In a sepsis model, DEX improved behavioral performance while decreasing BBB disruption and neuroinflammatory burden, and exerted an immunomodulatory effect on the Th1/Th2/Th17 balance [118]. In a hyperlipidemic model DEX improved postoperative cognitive impairment, associated with decreased BBB permeability and upregulation of endothelial Mfsd2a, consistent with a possible Mfsd2a-mediated BBB stabilizing effect [119]. A recent study on postoperative delirium showed that DEX activates Nrf2, maintaining tight junction proteins and leading to better cognitive outcomes (drug inhibition of Nrf2 weakens the protective effect of the BBB) [120]. Although these studies were not conducted in cerebrovascular disease populations, they provide evidence for the principle that BBB stability and measurable cognitive improvement may coexist, and provide a rationale for testing BBB-centered interventions in CHS where BBB failure is a significant damage amplifier.

In addition to stabilizing the BBB, emerging evidence suggests that DEX may support white matter protection by modulating oligodendrocyte vulnerability and myelination under hypoxic or inflammatory stress. In neonatal models, DEX has been shown to promote oligodendrocyte precursor survival and maturation, promote myelination, and improve long-term neurobehavioral outcomes [121]. Similarly, DEX improves myelination defects and neurobehavioral disorders following early postnatal inflammatory exposure [122]. In a mouse model of traumatic brain injury DEX decreased the immunoreactivity of protein β-APP associated with axonal injury and decreased synaptic loss as observed by synaptophysin staining, which may help maintain network structural integrity at the synaptic level [123]. Perioperative studies have also reported decreased circulating markers of neuronal injury, such as S100β and neuron-specific enolase, while increasing neurotrophic mediators, such as brain-derived neurotrophic factor, which are consistent with reduced neuronal injury and enhanced recovery signals [124-126]. Despite limited clinical validation in CHS, the BBB stabilization and protective effects on white matter and oligodendrocytes suggest that DEX may be a promising adjunctive therapy for alleviating postoperative hyperperfusion and CHS-related cognitive sequelae.

In summary, existing evidence indicates that DEX may contribute to supporting postoperative cognitive function by acting at multiple points in the CHS cascade. DEX may buffer hemodynamic fluctuations during reperfusion, limit damage amplification centered on the BBB within a critical window of 24-72 hours, and promote subsequent cellular and white matter recovery. This temporal consistency and multi-target nature provides a strong mechanistic basis for using DEX as an individualized strategy to enhance neurocognitive outcomes in patients undergoing various cerebral revascularization procedures.

Evidence of DEX's potential to reduce CHS

Over the past two decades, the use of DEX in neurosurgery has generated a wealth of information regarding its potential benefits compared to other sedatives. Recent studies have focused on the impact of perioperative DEX use on the incidence of CHS following revascularization, demonstrating its beneficial effects on hemodynamic stability and neuroprotection. However, although recent randomized trials have provided more direct evidence of efficacy, the clinical role of DEX in CHS prevention still needs to be fully clarified, particularly regarding optimal timing of administration and possible dose-response relationships.

Efficacy signals in carotid revascularization (CEA/CAS)

The best existing evidence of efficacy comes from randomized trials of CAS and mechanical

thrombectomy, both of which employed a continuous low-dose DEX infusion strategy postoperatively. In a double-blind randomized controlled trial of CAS (N=160), continued administration of DEX at a dose of 0.1 μg/kg/h until day 3 post-procedure reduced the incidence of CHS compared to placebo (2/80 vs. 11/80; OR 0.16, 95% CI 0.02-0.63; **Table 1**) [127]. In another double-blind randomized controlled trial of thrombectomy (N=141), a DEX regimen administered for 72 hours post-procedure also reduced CHS events on day 7 (2/70 vs. 10/71; OR 0.20, 95% CI 0.05-0.89; P= 0.033; **Table 1**) [128]. Although differences in endpoint definitions and monitoring protocols between trials, both sets of data indicated a protective effect when DEX administration covered the early post-procedure period. In the CAS trial, DEX was also associated with elevated levels of the neurotrophic factor brain-derived neurotrophic factor and decreased levels of neurofilament light chain protein, consistent with milder neurovascular injury; however, these changes in biomarkers should be considered as supporting evidence rather than effective surrogate markers for CHS prevention.

Evidence in MMD: intraoperative-only DEX exposure and CHS outcomes

In existing comparative studies, differences in outcomes appear to be more closely associated with the timing and duration of DEX administration than simply with the type of sedative. The two randomized trials in **Table 1** used a continuous low-dose postoperative infusion regimen covering the typical vulnerable period of 1-3 days postoperatively and reported fewer CHS events. In contrast, in MMD bypass surgery, intraoperative DEX administration alone was not found to be associated with a reduced CHS incidence, although the duration of symptoms was slightly shortened [129]. This difference is clinically reasonable because CHS can occur within 24-72 hours after revascularization, during which endothelial stress can accumulate and exacerbate downstream injury. Therefore, dosing regimens that do not cover this critical window period, even if they slightly reduce the duration of symptoms, may have a limited influence on incidence. It is noteworthy that existing data provide limited information on dose-response relationships because most studies use a single low-dose strategy rather than a dose-range study design. The implications of optimizing dosing regimens and risk stratification at the patient level will be discussed below.

Safety and individualization: signals from pediatric and high-risk case reports

Observational studies and case reports in the pediatric bypass surgery cohort primarily provide information on the feasibility and safety of DEX (**Table 2**), rather than its comparative efficacy. In the pediatric case series, there have been reports of clinically significant respiratory depression, including the absence of hypocapnia, with postoperatively titrated DEX under mild sedation [130]. Comparative neurological safety data remain scarce; in a retrospective cohort study, there was no significant difference in the incidence of transient neurological events between the DEX exposure and control groups [131]. Given that DEX is known to cause bradycardia and hypotension, careful titration and close hemodynamic monitoring are particularly important in cases of impaired CVR, as maintaining adequate perfusion pressure is crucial.

Reports in high-risk CEA and complex arteriovenous malformation cases suggest that DEX-assisted sedation helps achieve strict postoperative blood pressure control [132] and in certain cases, has been associated with clinical stability without significant edema or hemorrhage complications [133]. These descriptive observations should be considered as supportive clinical signals rather than definitive evidence of prevention of CHS.

Although there is preliminary evidence that DEX may lower the risk of CHS, the overall data quality is limited. Most existing studies are retrospective, small in scale, and vary in outcome definitions and dosing strategies. Therefore, based on a simplified GRADE assessment, the certainty of the evidence is low to moderate, and should be considered as generating hypotheses rather than confirming conclusions. To date, only two randomized controlled trials have been conducted, one directly addressing CH/CHS after CAS and the other addressing reperfusion injury after thrombectomy, providing indirect supporting evidence. Importantly, there is currently no review integrating mecha-

Table 1. Clinical evidence for dexmedetomidine (DEX) in preventing cerebral hyperperfusion (CH) and cerebral hyperperfusion syndrome (CHS)

Author (Year)	Population/ Model	(DEX/Ctrl)	Study Type	DEX Regimen	Outcomes	Effect estimate (95% CI); *P* value	Evidence Level	Risk of Bias
Chang et al., 2025 [127]	Adult CAS	160 (80/80)	Randomized, double-blind RCT	0.1 μg/kg/h until POD 3	CHS: 2/80 (2.5%) vs. 11/80 (13.75%); CH: 9/80 (11.2%) vs. 30/80 (37.5%); BDNF↑, NfL↓	CHS: OR 0.16 (95% CI 0.02-0.63); *P*=0.020; CH: OR 0.21 (95% CI 0.09-0.48); *P* <0.001	B	Moderate
Gao et al., 2025 [128]	AIS after thrombectomy	141 (70/71)	Double-blind RCT	Loading 0.5 μg/kg (10 min) + 0.1 μg/kg/h for 72 h	CHS by day 7: 2/70 (2.86%) vs. 10/71 (14.08%)	CHS by day 7: OR 0.20 (95% CI 0.05-0.89), *P*=0.033	B	Moderate
Seo et al., 2016 [129]	MMD after STA-MCA bypass	117 (48/69)	Retrospective study	Loading 1.0 μg/kg + 0.3-0.5 μg/kg/h, intraoperative	CHS incidence: 22/48 (45.8%) vs. 28/69 (40.6%); CHS duration: median 5 (3-7) vs. 8 (5-10) days	*P*=0.708 (Incidence) *P*=0.021 (Duration)	C	High

Evidence certainty was evaluated using a simplified GRADE-based framework and expressed as letter categories for readability: A = High certainty, B = Moderate certainty, C = Low certainty, and D = Very Low certainty. Risk of bias was categorized as low, moderate, or high based on methodological rigor, including randomization, blinding, sample size adequacy, endpoint assessment, and control of confounding factors. Notes: AIS, acute ischemic stroke; BDNF, brain-derived neurotrophic factor; CAS, carotid artery stenting; CH, cerebral hyperperfusion; CHS, cerebral hyperperfusion syndrome; CI, confidence interval; DEX, dexmedetomidine; MMD, moyamoya disease; NfL, neurofilament light chain; OR, odds ratio; POD, postoperative day; RCT, randomized controlled trial; STA-MCA bypass, superficial temporal artery-middle cerebral artery bypass.

Table 2. Clinical safety and feasibility of DEX in pediatric and high-risk adult cerebrovascular populations

Author (Year)	Population/ Model	*N* (DEX/Ctrl)	Study Type	DEX Regimen	Outcomes	Statistical Results (95% CI); *P* value	Evidence Level	Risk of Bias
Kanamori et al., 2022 [131]	Pediatric MMD bypass	84 (27/57)	Retrospective study	0.2-1.5 μg/kg/h, postoperative	TNEs POD0-1: 7.4% vs. 7.0% (NS); Hospital TNEs: 40.7% vs. 24.6%	TNEs POD0-1: *P*>0.99. Hospital TNEs: no significant	C	Moderate-High
HONJO et al., 2019 [130]	Pediatric MMD	10 (16 hemispheres)	Case report	0.4-0.7 μg/kg/h (Postoperative)	No hypocapnia or ischemic events	N/A (Descriptive)	D	High
Suehiro et al., 2010 [132]	Adult CEA with CHS risk	2	Case report	Loading 1.0 μg/kg (10 min) + 0.2 μg/kg/h until POD 7	Effective BP control: neurological deficits improved	N/A (Descriptive)	D	High
Kitsiripant et al., 2017 [133]	AVM (Pregnant)	1	Case report	Loading 1.0 μg/kg (10 min) → 0.2 μg/kg/h; ICU 0.35 μg/kg/h	No postoperative cerebral edema/ hemorrhage reported	N/A (Descriptive)	D	High

Abbreviations: AVM, arteriovenous malformation; BP, blood pressure; CEA, carotid endarterectomy; NS, not significant; TNEs, transient neurological events.

nistic, clinical, and cognitive findings in this specific context. Given the heterogeneity in study design, patient populations, surgical methods, and dosing regimens, there is an urgent need for multicenter randomized controlled trials with sufficient sample sizes, standardized dosing regimens, and clearly defined clinical endpoints to determine whether DEX provides meaningful and sustained neuroprotective effects in this context.

Discussion

Clinical insights and therapeutic implications

CHS is a major problem after carotid artery and vascular reconstruction surgery. The capillary structure of the brain is fragile due to chronic ischemia, making it prone to rupture or hemorrhage during sudden reperfusion, leading to endothelial damage, microthrombus formation, and disruption of the BBB. These factors work together to cause CHS.

Although preoperative hypertension is an important predictor of postoperative blood pressure elevation, strict perioperative blood pressure control cannot completely prevent CHS, suggesting that multiple mechanisms besides systemic hemodynamics are involved in the development and progression of CHS. Moreover, even mild CHS can cause long-term cognitive decline, underscoring the necessity of specific pharmacological treatments.

Currently, no drugs have been proven effective in preventing or treating CHS. Treatment primarily focuses on maintaining hemodynamic stability, supportive care, and symptom control. DEX is a highly selective α2-receptor agonist with perioperative sympathetic inhibition and various neuroprotective properties. It reduces inflammatory and oxidative responses, maintains mitochondrial function, and preserves the integrity of the BBB and endothelial cells. Clinically, the benefits of DEX include synergistic sedation, analgesia, sleep promotion, reduction of sympathetic activity, and stabilization of CBF. These combined effects may contribute to improved neurological function recovery; however, the quality of evidence for its use in preventing CHS is limited.

Due to the need for continuous monitoring, DEX is currently primarily limited to use in the operating room and ICU. However, the development of intranasal and transdermal DEX formulations offers new opportunities for safer and more convenient administration in general wards and even at home. These routes of administration can achieve long-term low-dose administration during the critical 24-72 hours postoperatively, or even longer, providing stable and continuous neurovascular protection.

In summary, these factors suggest that a single standardized DEX regimen may not be suitable for all patients. Developing individualized dosing regimens based on surgical type, cerebral perfusion status, and postoperative hemodynamic patterns may help balance the potential neuroprotective benefits with safety. Although emerging studies support this strategy, current evidence suggests that DEX is more of an adjunct than a standardized treatment. Therefore, the use of DEX in patients at high risk of postoperative cerebral hyperperfusion should be considered exploratory.

Optimization of DEX regimen

While long-term administration of DEX is becoming increasingly feasible, its optimal dosing strategy remains unclear. Current evidence suggests that the duration of infusion may be more critical than the initial bolus dose. Recent randomized controlled trials have shown clinical success with a 72-hour postoperative regimen, which appears to cover a “amplified phase” of 24-72 hours. For high-risk patients, brief intraoperative exposure may be insufficient, as it fails to cover the period of delayed molecular cascade response.

Not all patients undergoing cerebral revascularization are equally susceptible to CHS. Differences in underlying pathology and perfusion patterns among patients undergoing CEA, CAS, and MMD imply that a one-size-fits-all DEX protocol may not be suitable for all surgical cases. In CAS/CEA, acute blood pressure fluctuations are a primary concern, and a phased regimen initiated during induction may primarily serve to buffer hemodynamic fluctuations during reperfusion. In contrast, in MMD patients, the focus may shift to continuous postoperative administration aimed at stabilizing the BBB within the first 72 hours postoperatively. For high-risk patients, such as those with impaired CVR, preoperative asymmetric

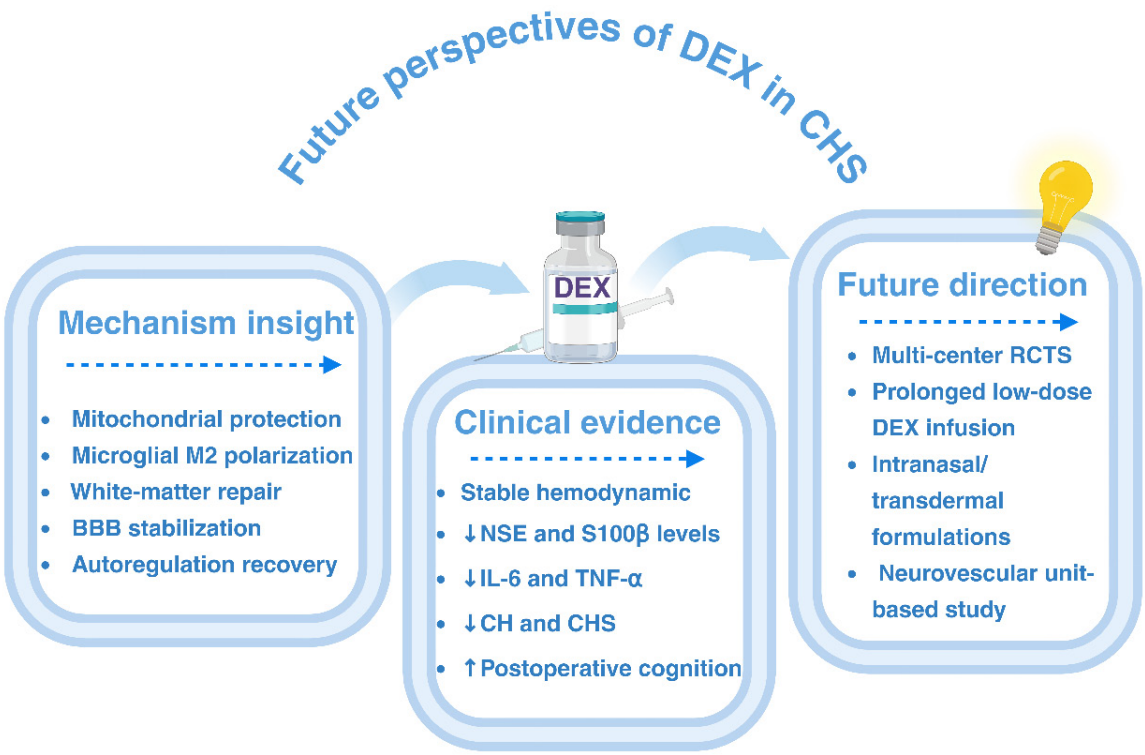

Figure 3. Future perspectives of dexmedetomidine in postoperative cerebral hyperperfusion syndrome: integration of mechanistic insights, current clinical evidence, and future research directions.

perfusion, microvascular fragility, or significant postoperative blood pressure fluctuations, any potential neuroprotective benefits should be weighed against the risks of hypotension and excessive sedation.

Limitations and future directions

Although several recent studies have reported the neuroprotective potential of DEX in CHS, existing evidence remains limited. Only a few observational and randomized studies have directly explored this topic, and a comprehensive review integrating mechanistic, clinical, and cognitive perspectives on the role of DEX in CHS is lacking. Key evidence gaps and future research priorities integrating mechanistic insights, clinical evidence, and future directions are summarized in **Figure 3**. The relatively low incidence of CHS (especially in MMD) and its predominance in Asia limits the development of large-scale studies. Future research should incorporate multicenter data and mechanistic endpoints to more definitively assess the role of DEX in the prevention or improvement of CHS.

Another limitation is the lack of continuous and reliable tools for monitoring CBF, oxygenation, and metabolism during and after surgery. Current technologies, such as near-infrared spectroscopy and transcranial Doppler ultrasound, are susceptible to interference from patient positioning, surgical aseptic requirements, and anesthetic effects. These limitations can lead to incomplete perfusion assessments and reduce the utility of monitoring in guiding clinical management.

Additionally, CHS after CAS/CEA differs in pathophysiological mechanisms from that following revascularization for MMD, although both share important features such as endothelial dysfunction, BBB disruption, and postoperative cognitive decline. Understanding these similarities and differences is crucial for developing personalized prevention and management strategies.

Finally, while DEX has significant benefits in stabilizing hemodynamics and reducing oxidative and inflammatory damage, its optimal dosage and timing remain unclear. Continuous low-dose infusions for up to 72 hours postopera-

tively have shown potential benefits, but have not yet been directly compared to shorter durations or risk stratification protocols. Future multicenter randomized trials should test individualized, risk-adaptive dosing strategies in different surgical populations, including standardized assessments of cerebral perfusion and cognitive function, and systematic monitoring of cardiovascular adverse events, including bradycardia and hypotension.

Conclusion

DEX is a promising adjunct neuroprotective agent for the prevention and management of postoperative CHS. By maintaining endothelial integrity, reducing BBB permeability, and mitigating oxidative and reperfusion-related injury, DEX may help stabilize cerebral hemodynamics and improve neurological outcomes. Its additional benefits in sedation, analgesia, and stress modulation are further reasons for its use in perioperative neurovascular protection. However, current evidence remains limited, and the optimal dosing strategy, timing, and duration have not been determined. Well-designed multicenter clinical trials and mechanistic studies are required to confirm these effects and establish DEX as a targeted treatment option for CHS.

Acknowledgements

This work was supported by the Pudong New Area Science and Technology Development Foundation of Shanghai, China (PKJ2023-Y88); the Young Medical Talents Training Program of Shanghai Pudong New Area Health Commission (PWRq2022-27); and Shanghai Punan Hospital of Pudong New District Research Project (PN2021b11).

Disclosure of conflict of interest

None.

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