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Review Article

Pharmacological Cerebral Protection in Cardiac Surgery: An Update

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ABSTRACT

Aim of review: Postoperative cognitive dysfunction (POCD) remains a major issue in cardiovascular surgery, although advances have been made in anesthesia, surgery and neuroprotective measures. Pharmacological prevention and management of POCD has achieved some progress over the last one to two decades, yet no consensus or guideline being established.

Method: The following key words in PubMed were searched: cerebral protection, brain protection, cardiac surgery, and postoperative cognitive decline, etc. Recent articles and literatures were searched and reviewed on the risk factors for POCD and the cerebral protective effects of pharmacological agents, in order to make a comprehensive review and offer an update.

Recent findings: Risk factors for POCD reported in literatures include older age, male gender, cardiopulmonary bypass (CPB) use, cerebral embolization, pre-existing cognitive disturbance and genetic predisposition. The pharmacological agents with potential neuroprotective effects include volatile anesthetics, intravenous anesthetic agents, steroids, N-methyl-D-aspartate (NMDA) antagonists, nitric oxide carriers and some traditional Chinese herbal medicine such as gastrodin. Cerebral protection in current practice is achieved by a combination of different strategies including surgical (cerebral perfusion during CPB, aortic filter, carotid stents, avoidance of aortic atheroma) and nonsurgical measures (hypothermia, lumbar drain, management of mean arterial pressure, central venous pressure, cerebral perfusion pressure, pre- and post-conditioning, and cerebral regional oxygenation monitoring, etc).

Summary: Multiple factors are associated with the incidence of POCD. Numerous pharmacological agents have been found to have certain degree of neuroprotective effects. Large-scale, randomized, multicenter clinical trials will be needed for the integration of these agents into our clinical practice.

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Despite tremendous advances in anesthetic agents and techniques, surgical procedures and neuroprotective measures, cerebral complications after cardiac surgery remain important source of postoperative morbidity and mortality (1-3). Perioperative cerebral injury is probably among the most serious adverse complications from surgical operations and anesthetic exposure, leading to new onset neurological deficits ranging from transient ischemic attack (TIA), postoperative cognitive decline (POCD), stroke, even to stupor and coma (3, 4). There are tremendous variations in reported incidence of these neurological complications after coronary artery bypass grafting (CABG) from 0.4% to nearly 80%, depending upon how the neurologic deficit is defined (3). These neurological abnormalities after CABG are believed to

be associated with perioperative hypoxia, embolization, hemorrhage, and metabolic abnormalities. Postoperative stroke remains a major problem despite various improvements in surgery, anesthesia and diagnostic tools over last several decades (3). The risk is significantly increased in cardiovascular and (or) neurovascular procedures and in those patients with some predisposing risk factors such as history of stroke, older age (older than 62 years old) and male gender (5, 6). There are two types of neurological deficits after cardiac surgery. Type 1 includes severe neurological dysfunction, stupor and coma, and type 2 includes intellectual deterioration and memory deficits (interchangeably called POCD). Both type 1 and type 2 can have focal, multi-focal or global cerebral lesions (3). There are multiple different approaches in aiming at protecting the brain during and after cardiac surgery. These measures can be categorized as surgical and nonsurgical. Surgical measures include application of antegrade or retrograde cerebral perfusion during cardiopulmonary bypass (CPB), epiaortic scan to avoid aortic cannulation if severe atheroma found in anticipated cannulation site, aortic filter to prevent emboli flowing into cerebral circulation, and carotid stents, etc. Nonsurgical measures include hypothermia, lumbar drain, regional cerebral oxygenation monitoring, cerebral preconditioning and postconditioning, maintaining appropriate central venous pressure (CVP) and $ETCO_2$ and pharmacological neuroprotection. This article aims at reviewing the latest information of pharmacological cerebral protection published in recent literatures.

Cerebral Physiology

Human brain weighs about 1400 grams on average, which is about 4-5% of the total adult bodyweight. The cerebral blood flow (CBF) is about 750 ml/min, roughly 20% of the cardiac output (CO), approximately 50 ml/min/100 g brain tissue (gray matter 75 ml/min/100 g and white matter 45 ml/min/100 g). The human brain is inside the cranium suspended by cerebral spinal fluid (CSF). CSF is a clear, colorless body fluid in the brain and spine, produced in the choroid plexuses of the ventricles of the brain. CSF occupies the subarachnoid space and the ventricular system around and inside the brain and spinal cord. CSF functions as a great cushion or buffer for the brain and provides basic mechanical and immunological protection. Additionally CSF plays pivotal role in CBF autoregulation (7). Neurons are highly differentiated cells and believed to be unable to regenerate, and this concept is likely untrue. The cerebral blood circulation is auto- regulated as shown in figure. CBF autoregulation is a very important feature in maintaining steady and consistent blood flow to the brain over a wide range of cerebral arterial blood pressure (CABP) (50- 150 mmHg). If CABP is over the upper limit, cerebral vascular integrity can be compromised and cerebral edema can develop; if CABP is below the low limit, neurons will not get adequate blood supply and cerebral ischemia will ensue (7).

Assessment of POCD

Neuropsychological Testing

There has not been a standard method applied in the multiple studies in POCD investigations reported in previous literatures. The selection of neuropsychological test instruments, the magnitude of change considered to be significant, the timing of testing, and the inclusion and exclusion criteria have all been varied. That may be part of the reasons for the great variations in reported POCD incidences. Here we list some of the test batteries commonly used in the POCD studies.

The following is the list of all potentially useful tests for POCD (8):

Intelligence: The Wechsler adult intelligence scale (WAIS), The Weschler intelligence scale for children (WISC), Stanford binet (SB), test of nonverbal intelligence (TONI).

Attention: Conner's continuous performance test (CCPT), Wisconsin card sorting test (WCST), Vanderbilt attention deficit disorder test (Vanderbilt), Nepsy attention test (NEPSY).

Language: Gray oral reading test (GORT), Boston naming test (BNT).

Memory and learning: The Wechsler memory scale (WMS), wide range assessment of memory and learning (WRAML), California verbal learning test (CVLT), Rey auditory verbal learning test (RAVLT), Rey- Osterrieth complex figure

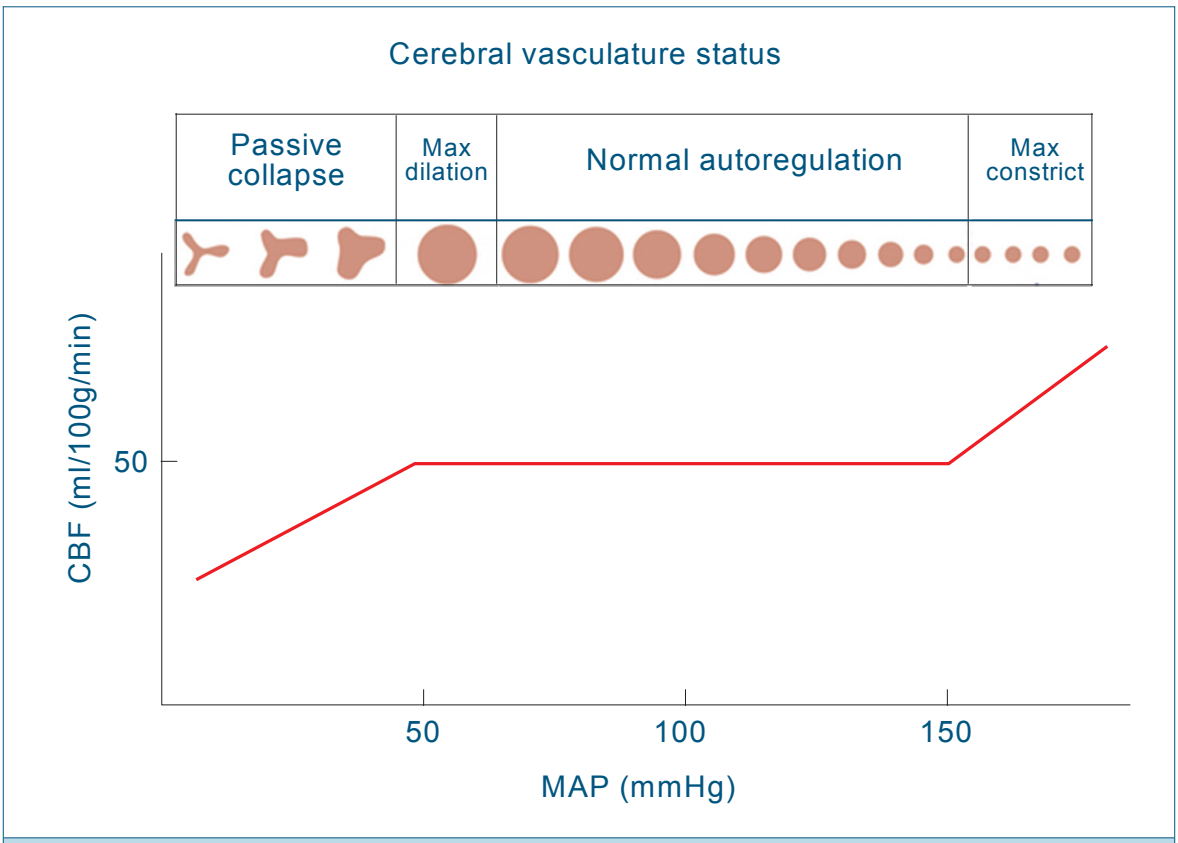

Figure. Autoregulation of Cerebral Blood Flow and Mean Arterial Pressure.
CBF: cerebral blood flow, MAP: mean arterial pressure, Max: maximum.

test (ROCF), NEPSY.

Motor control: Grooved Pegoard, Finger Tapping, Grip Strength, Lateral Dominance.

Visual-spatial: ROCF, Bender visual motor gestalt test (Bender-Gestalt), Hooper visual organizational test (HVOT);

Executive functioning: WCST, behavior rating inventory of executive function (BRIEF), executive functioning skills development (EFSD), Delis- Kaplan executive function system (D-KEFS).

Behavioral: behavior assessment system for children (BASC), The Achenbach child behavior checklist (Achenbach), Vanderbilt.

Commonly used tests in the assessment of POCD

The Wechsler Adult Intelligence Scale (WAIS): WAIS is a test designed to assess the intelligence of adults and older adolescents. It was developed in 1955 and now it is the 4th edition (9). The Mental Control and Digit Span (forward and backward) subtests measure patient's attention and concentration, and high scores indicate better cognitive function; The Visual Retention and Paired Associate Verbal Learning subtests measure figural memory and verbal learning/ memory functions, and high scores indicate better cognitive function. This test requires subjects to reproduce from remembering a series of geometric shapes after a 10-second exposure (resulting in variable scores ranging from 0 to 10, with a higher score indicating better function); The Digit Symbol subtest measures psychomotor speed, where a high score indicates better function. This test requires subjects, first, to repeat in numerical order a series of digits that has been presented to them orally and then, in an independent test, to repeat the digits in reverse order (resulting in two variable scores ranging from 0 to 14, with higher scores indicating better function).

The Halstead-Reitan trail making test: It measures hand-eye coordination, attention, and concentration. A lower score indicates better cogni-

tive function (9).

The Grooved Pegboard test (favorite and non-favorite hand): It measures manual dexterity. A lower score shows better cognitive function (9).

The Short-story module of the Randt memory test: This test requires patients to recall the details of a short story immediately after it is read to them and after a 30-minute delay. Scoring is based on both patients' ability to recall the story verbatim and capture its gist on immediate and delayed testing (resulting in four variable scores ranging from 0 to 10 or 0 to 20, with higher scores indicating better function) (10).

Neurocognitive tests are usually administered preoperatively (base line), on the day before discharge (approximately 7 days after surgery), and 6 weeks, 6 months, and 5 years after surgery. Assessments are performed individually by experienced psychometricians (10).

Biochemical Markers of Brain Injury

Glia

It becomes increasingly convincing that glial cells can influence the synapse development, plasticity and function. The fine cellular processes of astrocytes and microglia are closely associated with pre- and postsynaptic elements and can potentially affect synaptic functions. Synaptic functions will have significant impact on cognitive functions.

S100B: The S100B belongs to the calcium-mediated proteins in the S100 proteins family with a molecular weight of 21 kDa. Some of the S100 protein family are specific for certain localizations. Higher S100B protein concentrations are usually present in astroglial and Schwann cells, adipocytes, chondrocytes, and melanocytes. The S100B protein has intra- and extracellular targets, and it may affect neuronal and glial growth, proliferation, and activation. Increase of S100B concentrations in plasma and CSF was discovered after brain infarction, trauma, and toxic injury. Reportedly the highest S100B protein plasma level was found just after injury and then normalized in 24 hours.

The results from animal studies suggested S100B protein concentrations were correlated with the severity of shock, and they were higher in moderate shock than in severe shock (11). Pearlman et al. (12) also found that changes in S-100 calcium-binding protein B levels are correlated positively with acute changes in depressive symptom severity in patients underwent CABG with CPB, and this finding supported the concept that glial activation and injury and blood-brain barrier disruption can be mechanistically linked to acute exacerbation of depressive symptoms in some individuals.

Glial fibrillary acidic protein (GFAP): GFAP has been proposed as a diagnostic and prognostic biomarker in traumatic brain injury (TBI). Bogoslovsky et al. (13) explored GFAP plasma level changes after TBI. Injury severity was assessed by Glasgow coma scale (GCS) and admission computed tomography (CT). At every time point, GFAP level was increased after TBI compared to controls. Thus GFAP is believed to be a biomarker for TBI. Magruder et al. (14) reported an association of nadir oxygen delivery on CPB with serum GFAP levels in pediatric patients undergoing heart surgery.

Neurons

Calbindin-D: Calbindin D (28KD) is a high affinity calcium-binding protein. Emmanuele et al. studied the potential association between cognitive dysfunction and hippocampal expression of Calbindin D (28KD) in four patients with Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), by using postmortem hippocampal tissues. And they discovered significantly reduced Calbindin D (28KD) levels in all patients by Western blot, immunohistochemistry, and quantitative real-time polymerase chain reaction (rtPCR). Decreased expression of Calbindin D (28KD) has been linked to aging and neurodegenerative disorders, including Alzheimer's disease (AD). The authors suggested that reduced expression of Calbindin D (28KD) may lead to cognitive abnormalities associated with MELAS (15). Ahmadian et al. (16) found that loss of Calbindin-D (28KD) pathology within basal forebrain cholinergic neurons in patients with AD.

Neuron specific enolase (NSE): NSE is an enzyme with a molecular weight of 78 KDa that catalyzes the conversion of 2-phospho-D-glycerate to phosphoenolpyruvate in a glycolytic pathway. NSE is generally found in the cytoplasm of neurons and neuroendocrine cells.

The half-life NSE is about 24 hours and its normal plasma concentration runs between 2 mg/l and 20 mg/l. A level of NSE value >30 mg/l is considered abnormal and ⩾115 mg/l is associated with poor prognosis. Elevated plasma level of NSE was found after cortical brain injury, severe head trauma, in patients with temporal lobe epilepsy and internal cardiac defibrillators. NSE is believed to be effective in predicting neurological outcomes after cardiac arrest and in patients with ischemic stroke. However, studies on cardiac surgery patient were inconclusive, and some studies showed correlation of NSE with POCD was observed, but some investigations did not echo this finding (11, 17). The CSF concentration of NSE in patients after aortic aneurysm repair was found elevated regardless of the presence or absence of neurological symptoms. Gempp et al. (18) investigated the NSE levels in recreational divers, and interestingly they found NSE levels >15.9 μg/l would predict the development of neurological decompression sickness with a specificity of 100%. The results from analyzing the correlation between APO E4 (Apolipoprotein E4) genotype and cognition with NSE serum levels in the postoperative period were unfortunately inconclusive (11).

Inflammatory Mediators and Metabolic Parameters Changes in Cerebral Injury

Alterations in some inflammatory mediators and metabolic parameters have been linked to cerebral injury in some clinical scenarios, such as C-reactive protein (CRP), interleukin-6 (IL-6) (12), IL16, transforming growth factor-β (TGF-β) (19), ICAM-1 (20), E- Selectin (20), neural cell adhesion molecule (NCAM) (21), glutamate (22), and amyloid B (23).

Radiological Imaging Techniques

As technology advances on a daily basis, radiological imaging techniques will increasingly be used to detect anatomical cerebral lesions and functional brain abnormalities. Brown et al. (1) studied 79 cardiac surgery patients with brain MRI, and they found that increased brain ventricular size in cardiac surgery patients was independently associated with postoperative delirium. These results suggest that cerebral atrophy may contribute to increased vulnerability for postoperative delirium. Baseline brain MRIs may be useful in identifying cardiac surgery patients at high risk for postoperative delirium, who might benefit from targeted perioperative approaches to prevent delirium. Patel et al. (24) detected the presence of new MRI lesions in the brains of cardiac surgery patients and cognitive decline postoperatively. Patients are commonly reported to experience POCD and new ischemic lesions following surgery. Modern MRI techniques have enabled clear and accurate identification of ischemic lesions. However, difficulty in assessing subtle/minor changes in cognitive impairment clinically still remains (24). Functional MRI has been proved a very effective imaging tool for the assessment of POCD. Attention and concentration problems are very common in patients with POCD. Complex attention and focus during challenging task performance definitely require the proper coordination and activity of spatially distributed functional brain networks, especially the involvement of working memory and disengagement of brain-at-rest default-mode networks. This kind of brain connectivity is best assessed with functional MRI (25).

Risk Factors

Age: Age seems to be a very important factor. Older patients have significantly increased risk to develop POCD. Habib et al. (26) found that patients older than 50 years old suffer significantly higher POCD incidence of 76.7% versus 23.3% in patients younger than 50 years old. Bartels et al. (27) conducted a literature review and also found that elderly people are more likely to develop POCD.

Gender: Male patients suffer higher incidence of POCD, for those POCD patients after cardiac surgery, male patients account for 75.3% versus female patients 24.7% (26).

Preoperative creatinine level: Preoperative creatinine level higher than 1.4 seemed to predict higher risk to develop POCD after cardiac surgery (26).

CPB: More studies found CPB is an independent risk factor. Among patients who received CPB, 18 patients (62%) cases had early cognitive decline, compared with 16 patients (53%) in the group without CPB. Three months post-

operatively, 11 patients (39%) in the CPB group displayed cognitive dysfunction, compared with 4 (14%) in the non-CPB group (P=0.03). The use of CPB was identified as an independent risk factor for the development of late cognitive dysfunction (P<0.027) (28).

Cerebral embolization: Aortic atherosclerosis, especially severe form with floating atheroma which leads to increased embolic burden, is associated with early postoperative stroke following heart surgery. Intraoperative cerebral embolic burden can be detected via transcranial doppler (29). New cerebral ischemic lesions were associated with embolization entered cerebral vasculature likely intraoperatively. Transcranial doppler has become a very useful tool in detecting cerebral emboli during surgical procedure. Whether intraoperative factors such as CPB machine and surgical interventions generating cerebral embolism were associated with POCD is still debating. Current literatures are divided in this regard (24). And the degree of atherosclerosis burden in the aorta was not necessarily predictive of POCD at 6 weeks postoperatively in a series of 162 patients undergoing CABG (30).

Genetic predisposition: Patients with following polymorphisms will have significantly increased risk of postoperative stroke after cardiac surgery: -174G>C of IL6, 1846C>T of CRP, while these polymorphisms carriers will have increased risk for POCD: E298D of SELP (P-selectin gene), 1059G>C of CRP, L33P of ITGB3 (Integrin beta-3), ε4 or ε2 of APO E. Especially when patients carry both CRP (3'UTR 1846C/T) and IL-6 (-174G/C) (31).

Many other conditions were not found to be associated with higher risk for POCD, such as coexisting hypertension, diabetes, hypotension episodes, previous myocardial infarction (MI), obesity, duration of cardiac surgery, and duration of CPB (26).

Pharmacologic Agents for Cerebral Protection

Volatile Anesthetic Agents

Although the choice of volatile anesthetic agents seems less relevant to outcomes in some surgeries, protection of the CNS is surely a priority in some surgical procedures such as CPB, carotid surgery and cerebral aneurysm surgery, and some clinical scenarios such as subarachnoid hemorrhage, stroke, brain trauma and post-cardiac arrest resuscitation. Treatment of these patients with potentially neuroprotective agents may be an important consideration in improving overall neurological outcomes. Schifilliti et al. (32) reviewed more than 600 articles (including studies in animals, humans and in vitro) published from January 1980 to April 2010 regarding anesthetic agents and neuroprotective effects. What they found seems to indicate that anesthetic agents such as barbiturates, propofol, xenon and most volatile anesthetic agents such as halothane, isoflurane, desflurane, sevoflurane, have some neuroprotective effects that offer protection to cerebral tissue from adverse events as apoptosis, degeneration, inflammation and energy failure induced by ischemia, chronic neurodegenerative diseases, stroke or trauma to nervous system. However, there are also some conflicting reports. Some studies showed that administrations of volatile and intravenous anesthetics (especially isoflurane and ketamine) were linked to dose-dependent and exposure time-dependent neurodegenerative effects in the developing brain in experimental animal models. Currently available data from experimental and clinical investigations do not support the selection of any specific anesthetic agent over the others (32). Any anesthetic agent has its undesirable adverse effects, in combination with the patient's medical conditions and surgical history, which seem to be more decisive in selecting the most suitable anesthetic agent for a specific patient and clinical scenario. And it is very important to point out that some of the studies in the literature were conducted in animals or in vitro, and the results and conclusions may not be applicable to human beings. The likely mechanisms involved in the potential neuroprotective effects include slight increase of intracellular calcium, slight increase in CBF, upregulation of bioenergy metabolism, synthesis of nitric oxide and antiapoptotic factors, reduction of oxidative stress, and increased mitochondrial ATP-sensitive K channel activity.

Traditional Chinese Medicine

Gastrodin

Zhang et al. conducted a double-blind, random-

ized controlled study to investigate its preventive effects of gastrodin on cognitive decline after cardiac surgery with CPB. The authors randomly assigned 200 patients scheduled for mitral valve replacement surgery to receive either gastrodin (40 mg/kg, gastrodin group) or saline (control group) after the induction of anesthesia. The patients' cognitive function was evaluated preoperatively, at discharge, and at three months postoperatively by using a battery of five neurocognitive tests. The adverse effects of gastrodin were also assessed postoperatively. Postoperative neurocognitive decline was defined as one standard deviation or more decline in the test scores of any one of the four domains of cognitive function. The study showed that cognitive decline occurred in 9% of the patients in gastrodin group in comparison to 42% in control group ($P<0.01$) at discharge. Cognitive function was assessed at three months postoperatively in 87 patients in the gastrodin group and 89 patients in the control group. Cognitive decline was detected in 6% of the patients in gastrodin group and 31% in control group ($P<0.01$). Gastrodin did not seem to cause significant adverse effects. These results suggested that gastrodin is effective and safe for the prevention of neurocognitive decline in patients undergoing mitral valve replacement surgery with CPB (33, 34).

Curcumin

Curcumin (present in Chinese medicinal plant) was reported to inhibit microglial inflammation and offer neuroprotection in patients with intracerebral hemorrhage (ICH). Yang et al. (35) investigated whether curcumin could prevent ICH-induced microglial activation and provide some neuroprotection. The investigators measured cytokines of microglia by enzyme-linked immunosorbent assay (ELISA), p38MAPK/PKC, NF-κB by Western blot and electrophoretic mobility shift assay (EMSA), and assessed microglial toxicity by using cell proliferation kit I (MTT) and fluorescence-activated cell sorting (FACS) assays. The authors found that curcumin could prevent ICH-induced inflammatory reactions through NF-κB activation via the p38MAPK/PKC pathway, and curcumin could also protect hippocampal HT22 cells from indirect toxicity mediated by ICH-treated microglia cells. Additionally, curcumin could attenuate ICH-associated neurological deficit in vivo. Thus the authors believed that curcumin could effectively suppress ICH-induced inflammatory injury and represent a novel herbal therapy for ICH.

Leonurine

Qi et al. (36) reported that leonurine has neuroprotective effects on ischemia/reperfusion-induced mitochondrial dysfunctions in cerebral cortex in of experimental animal models. Ischemic brain is particularly susceptible to free radicals mediated secondary neuronal damage, especially mitochondrial dysfunctions. Chinese herbal medicine with antioxidant properties is believed to have potential therapeutic effects. Leonurine, an alkaloid present in Herba Leonuri, has shown biological effects such as antioxidant, anticoagulant, anti-apoptosis and protection against ischemic heart diseases. In this study, neuroprotective effects of leonurine against cerebral ischemia/reperfusion-induced mitochondrial dysfunctions in cortex were experimentally evaluated. The authors used transient rat middle cerebral artery occlusion (MCAO) models of brain ischemia. They found that attenuation of mitochondrial membrane swelling, restoration of mitochondrial membrane potential and content of cytochrome c (Cyt-C) in mitochondria isolated from ischemic cortex could also be detected in leonurine group. Thus these findings suggested leonurine has promising therapeutic effects for ischemic stroke treatment through antioxidant and anti-apoptotic mechanisms.

Lycium Barbarum

Wolfberry (Lycium barbarum) is a fruit that is known for its eye-protective and anti-aging properties in Asian countries. Previous clinical and epidemiological studies have suggested that elevated plasma homocysteine levels increased the risk of AD. Although the underlying mechanisms of its toxicity are elusive, homocysteine can cause neuron damages by inducing apoptosis, DNA fragmentation, and tau hyperphosphorylation. Previous studies have demonstrated that polysaccharides derived from wolfberry (LBA) have the ability to protect neurons from amyloid-beta

(Aβ) peptide neurotoxicity. Ho et al. (37) reported that the neuroprotective effects of wolfberry is not limited to Aβ and can also provide protection against other AD risk factors. This study showed that LBA treatment significantly attenuated homocysteine-induced neuronal cell death and apoptosis in primary cortical neurons as demonstrated by lactate dehydrogenase (LDH) and caspase-3 like activity assay. LBA also significantly reduced homocysteine-induced tau phosphorylation at tau-1 epitopes as well as cleavage of tau. LBA treatment suppressed elevation of both p-ERK and p-JNK. This study demonstrated that LBA exerted neuroprotective effects on cortical neurons exposed to homocysteine. He et al. (38) reported lycium barbarum polysaccharides (LBP) extracted from the wolfberries, are protective to retina after ischemia-reperfusion.

MLC901 (NeuroAid)

MLC901 is a traditional Chinese medicine which protects the brain against global ischemia. Global ischemia usually leads to damage in the hippocampal CA1 region and is associated with behavioral deficits. NeuroAid (MLC601 and MLC901), a traditional Chinese medicine, has been used in China for patients after stroke for many years. The study showed that MLC901 at the dose of 0.074 mg/ml prevented both necrosis and apoptosis of neurons after ischemia up to 3 hours. These effects were associated with a decreased Bax expression and lipid peroxidation product malondialdehyde level. By using the PI3-kinase inhibitor LY294002, the authors demonstrated MLC901-mediated neuroprotection, MLC901 enhanced neurogenesis, and MLC901 improved functional recovery. MLC901 also improved post-ischemic grip strength. If these results can be extended to human beings, MLC901 would represent a novel therapeutic strategy after cardiac arrest (39).

Steroids

Administration of steroid agents in attempt to provide cerebral protection has been controversial for decades. There have been accumulations of publications with both favorable and unfavorable results. It seems making sense to give some steroid medications to patients undergoing cardiac surgery with CPB, since CPB induces a systemic inflammatory syndrome-like presentation. Inflammatory response plays a crucial role in the pathogenesis of cerebral injury after CPB in cardiac surgery, and immunological reactions lead to compromise in vascular permeability and cellular structures in the brain. Shum-Tim et al. (40) reported that systemic steroid pretreatment has been shown to decrease brain injury after cardiac arrest, significantly reduced total body edema and cerebral vascular leak, and was associated with better immunohistochemical indices of neuroprotection after deep hypothermic circulatory arrest (DHCA). They also found that the timing of giving steroid is also very important to confer the protective effects, and different timing of steroid administration results in different inflammatory mediator responses. Steroid treatment effects in CPB prime are not significantly better than that without steroid treatment, while systemic steroid pre-treatment significantly decreases systemic manifestation of inflammatory response and brain damage (41). Krüger et al. (42) reported the results from the German Registry for Acute Aortic Dissection Type A (GERAADA) to see whether cerebral protection during acute aortic dissection Type A (AADA) surgery may be affected by perfusion strategies and ischemic protective drugs. They analyzed the impact of intraoperative steroid, mannitol, barbiturate, and adjunctive cerebral perfusion on 30-day mortality and new postoperative mortality-corrected permanent neurological dysfunction in GERAADA. There were 2137 AADA patients registered over a 4-year span. The overall 30-day mortality was 16.9%. The overall permanent neurological dysfunction incidence was 10.0%. About 48% of the patients received no neuroprotective drugs and served as control group. Monotherapy with steroid was used in 11.2% of the patients, barbiturates in 8.4%, mannitol in 7.3%, and the remainder (25.1%) received a combination of above-mentioned drugs. They found that permanent neurological dysfunction rate was 10.6% in the control group and 7.1% in the steroid group ($P<0.05$), while no significant reduction of permanent neurological dysfunction in mannitol or barbiturates group. Thirty-day mortality was 18.7% in control group and 8.9% in mannitol group ($P<0.005$). Hypothermic circulatory arrest that lasted longer than 30 minutes was asso-

ciated with an increased 30-day mortality rate of 31.4%, while only 21.4% when compared with patients received adjunctive cerebral perfusion > 30 minutes during aortic arch intervention (P= 0.04). Thus the authors concluded that steroid administration may be associated with improved neurological outcomes, but more investigation is required.

Induction Agents

Propofol

Kanbak et al. (43) reported that propofol does not offer any advantage over isoflurane anesthesia for cerebral protection during CPB. The authors compared the effects of two different anesthetic techniques, volatile isoflurane and intravenous agent propofol on neurological outcomes by measuring serum S-100β protein and neuropsychological tests after CABG. This was a controlled, preliminary study with 20 patients underwent CABG, and the patients were randomly allocated into two groups. Isoflurane was used in group I and propofol in group P. Neurological examinations and a neuropsychological test battery consisting of the mini mental state examination and the visual aural digit span test were assessed preoperatively and on the 3rd and 6th postoperative days. Postoperative neurological examinations of the patients were normal. The visual aural digit span test performance declined significantly on the 3rd day ($P<0.05$) in both groups, and there were no significant differences on the visual aural digit span test and the mini mental state examination scores between the two groups. Although there was no deterioration in neuropsychological outcomes, propofol appeared to offer no advantage over isoflurane for cerebral protection during CPB in this preliminary study of 20 patients.

Thiopental

Al-Hashimi et al. (44) conducted a meta-analysis to see whether the use of thiopental could provide cerebral protection during DHCA. They reviewed 62 papers with 7 represented the best evidence to answer the clinical question being analyzed. Four studies used thiopental with other neuroprotective methods and agents, including the use of ice packs to the head, core systemic hypothermia, nicardipine or mannitol. Thiopental lowered cerebral oxygen consumption, which could be advantageous. The neuroprotective effect of thiopental was assessed by the electrical activity of the brain during DHCA. However, there were trials showed adding thiopental during DHCA did not offer extra cerebral protection. The timing of administering thiopental is critical for the claimed benefits, and thiopental may lead to unfavorable outcomes if given before DHCA. The meta-analysis indicated thiopental administration during DHCA is beneficial, but if administered too early, thiopental may replete the cerebral energy state before arrest and lead to detrimental outcomes. Nussmeier et al. (45) in a randomized clinical study of 182 patients undergoing open-chamber cardiac surgery, reported a significant reduction in persistent neuropsychiatric dysfunction after administration of high-dose thiopental titrated intraoperatively to induce electroencephalography (EEG) burst suppression.

Calcium Channel Blocker: Nimodipine

The interest in using calcium channel blocker during cardiac surgery seems to have declined dramatically. Studies looking into the neuroprotective effects of calcium channel blockers were mostly from 15 years ago. Legault et al. (46) reported an early terminated trial in a double-blind, randomized clinical trial on a calcium channel blocker nimodipine. The trial was designed to investigate the potential neuroprotective effects of nimodipine in patients scheduled for cardiac valve replacement surgery. Nimodipine is a dihydropyridine calcium antagonist. There were 400 patients enrolled in this study which was started in May 1992 and stopped in September 1994, with 150 patients randomized to the study. Nimodipine was administered to these patients during the perioperative period. The patients underwent scheduled neuropsychological examinations before surgery and approximately at 1 week, 1 month, and 6 months postoperatively. Parameters for major adverse events including deaths and strokes were monitored on monthly basis. The trial was terminated early because of unexpected disparity in death rates between groups and no evidence of any beneficial effect from nimodipine administration. New neurological deficits were diagnosed in the placebo

group (72%) versus the nimodipine group (77%), and the results from 6-month follow-up showed 8 deaths (10.7%) in the nimodipine group (n=75) compared with 1 death (1.3%) in the placebo group (n=74) (p=0.02). The researchers also found major bleeding in 10 patients (13.3%) in the nimodipine group versus 3 (4.1%) in the placebo group (P=0.04). Six (46.2%) of the 13 patients with major bleeding died, versus 3 deaths (2.2%) in 136 patients without major bleeding. Thus authors concluded that calcium antagonist nimodipine has a prohemorrhagic effect in some patients and suggested nimodipine use should be restricted in patients scheduled for cardiac valve replacement perioperatively. However, another clinical study from Germany showed that nimodipine had neuroprotective effects, and it potentially has synergistic effect with intravenous magnesium (47). In experimental animal models, amlodipine was showed to have some neuroprotective effects. Lemons et al. (48) investigated the effects of nimodipine on high-energy phosphates and intracellular pH during cerebral ischemia in experimental animal models. By using rapid acquisition phosphorus-31 nuclear magnetic resonance (31P NMR) spectroscopy technique, they evaluated the effects of nimodipine on brain energy metabolism in severe ischemia in gerbils, and high-energy phosphates and intracellular pH were measured at baseline and at 2-min intervals following bilateral common carotid artery (CCA) ligation. And serial forebrain spectroscopy was also continued until phosphocreatine (PCr) and adenosine triphosphate (ATP) resonances disappeared. The Control group was compared to the nimodipine group in which animals were administered intraperitoneally nimodipine at 30 minutes prior to carotid ligation, at the following doses: 0.5 mg/kg, 1.0 mg/kg, 2.0 mg/kg, or 4.0 mg/kg. In the control group, PCr and ATP peaks were undetectable after a mean of (5.4±0.47) minutes following CCA ligation. In the nimodipine group, the mean time for depletion of high-energy phosphates following carotid ligation was prolonged at doses of 0.5 mg/kg and 1.0 mg, and much longer than that of control group (P=0.005). Relatively high doses of nimodipine slowed the depletion of high-energy phosphates without altering intracellular acidosis, suggesting that nimodipine may provide cerebral protection by directly altering ischemic cellular metabolism.

β-Blockers

β-blockers may improve postoperative neurological outcomes in cardiac surgery patients. Umehara et al. (49) reported that selective β1-adrenoreceptor antagonists esmolol and landiolol can provide neuroprotection in spinal cord ischemia and reperfusion animal models. Paraplegia is a devastating and unpredictable complication occasionally resulting from surgery of the thoracic and thoracoabdominal aorta. Umehara et al. (49) studied whether β1 receptor antagonists can ameliorate spinal cord injury after transient ischemia and reperfusion in rats. They found that the motor deficit index scores were significantly lower in the esmolol and landiolol groups when compared with saline group (P<0.05). Histopathologic evaluation of the spinal cord also showed less damage in esmolol and landiolol groups than in saline group (P<0.05). These indicated that selective β1-adrenoreceptor antagonists can reduce neurological injury in a rat model of spinal cord ischemia-reperfusion.

Aprotinin

In an analysis of 816 CABG patients from a multicenter international study assessing aprotinin and graft patency, and another study of patients being analyzed for perioperative stroke, the authors demonstrated that aprotinin administration was associated with a significantly (p=0.04) lower overall incidence of stroke, in addition to aprotonin's main advantage to reduce blood loss and transfusion. The incidence of stroke was 1.1% in the aprotinin group versus 2.6% in placebo-treated patients (50). Murkin et al. (50, 51) conducted a meta-analysis of seven placebo-controlled, randomized, double-blind studies of CABG patients receiving full-dose aprotinin or placebo with a total of 1867 patients. This meta-analysis discovered that aprotinin significantly lowered the incidence of stroke in aprotonin-treated patients, and the combined incidence of stroke in the placebo group is 2.6% versus 1.0% in full dose aprotinin group.

Statins

Statins as neuroprotectants were investigated by

both experimental and clinical studies. Sierra et al. (52) reported that monacolin J derivatives (natural and semi-synthetic statins) are the best candidates for the prevention of neurodegenerative conditions due to their higher potential blood-brain barrier penetration capacity, cholesterol-lowering effect on neurons and in vitro protection against cell death caused by okadaic acid in culture, yet with a satisfactory safety profile. They tested nine kinds of statins and found simvastatin presented the best characteristics for preventing neurodegenerative conditions. Durazzo et al. (53) investigated the role of atorvastatin in neuroprotection in patients who underwent vascular surgery. They administered atorvastatin to 100 patients at a dose of 20 mg/d for 45 days preoperatively. Atorvastatin treatment was associated with a significantly lower incidence of new postoperative neurological deficits clinically assessed on daily basis until discharge, monthly until the 6th month, and confirmed by neuroimaging.

NMDA Receptor Antagonists

Remacemide

Arrowsmith et al. (54) tested the hypothesis that remacemide, an N-methyl-D-aspartate (NMDA) receptor antagonist, would provide neuroprotection against cerebral ischemic injury in a randomized clinical trial. They treated 171 patients undergoing CABG by a single cardiac surgery team with remacemide (up to 150 mg every 6 hours) or placebo (the control group) from 4 days preoperatively to 5 days postoperatively. Perioperative monitoring included an incidence estimate of microembolic events detected by transcranial doppler ultrasonography of the middle cerebral artery. And they used a battery of 9 neuropsychological tests to evaluate psychoneurological function before surgery and at 8 weeks postoperatively. And they found that the incidence of cognitive decline was 9% versus 12% in the control group (not statistically significant, may need larger sample size studies to yield statistical significance). However the overall postoperative alterations such as learning ability in addition to reduced deficits, were more favorable in the remacemide group with significantly greater improvement ($P<0.05$) and changes in 3 individual tests ($P<0.05$).

Ketamine

Nagels et al. (55) compared the effects of S(+)-ketamine to remifentanil, both in combination with propofol, on neurocognitive outcomes in 106 patients after open-heart surgery. A battery of neurocognitive tests were administered preoperatively and at the 1st and 10th week postoperatively. They found that 14 patients (25%) in the control group and 10 patients (20%) in the ketamine group had 2 or more tests with a cognitive deficit (decline by at least one preoperative SD of the test in all patients) 10 week postoperatively ($P=0.54$). Z-scores were calculated for all tests. Thus they concluded that S(+)-ketamine offered no greater neuroprotection compared with remifentanil during open-heart surgery.

Lidocaine

Experimental findings showed that intravenous infusion of antidysrhythmic lidocaine before cerebral ischemia could increase surviving neurons in CA1 region of the hippocampus, thus preserve cognitive function in rats (56). Double-blind clinical randomized trials also found that neuroprotective effects of intraoperative infusion of lidocaine in cardiac surgery (9). However there are studies showing different results, Mitchell et al. (57) reported that lidocaine was not neuroprotective. The result of the previous trial may represent a type 1 error. Alternatively, benefits may be more likely for open-chamber surgery patients exposed to larger numbers of emboli or with a longer lidocaine infusion. Peng et al. (58) did not find lidocaine to have any neuroprotective effect in neurosurgical patients either.

Free-Radical Scavenger: Edaravone

Sun et al. (59) explored the potential neuroprotective effects of edaravone, a free radical scavenger, in reducing the incidence of postoperative stroke and cognitive decline induced by hypoperfusion. Edaravone or saline (the control group) was prophylactically administered to compare their different effects on cortical oxygen saturation, cerebral blood flow, blood coagulation, oxidative stress, metabolic products, and learning-memory using some methods that include photoacoustic imaging, laser speckle contrast imaging, solid-state nuclear magnetic resonance (NMR), and Morris water maze. The effects on infarct

size by edaravone application at different time points after transient hypoxic-ischemia were also compared. The authors suggested that edaravone may be a useful strategy to prevent postoperative stroke and cognitive decline in patients with compromised cerebral perfusion.

Adenosine-Regulating Substances: Acadesine

Acadesine is a purine nucleoside analog in a new category of agents commonly termed adenosine regulating agents (ARAs). ARAs can increase the availability of adenosine locally in ischemic tissues. Thus acadesine can potentially have favorable impact on the incidences of fatal and nonfatal myocardial infarction (MI), all adverse cardiovascular (cardiac death, MI, congestive heart failure, life-threatening dysrhythmia, or cerebrovascular accident) and neurological events. The Multicenter Study of Perioperative Ischemia (McSPI) group investigated the effects of acadesine in 633 patients undergoing CABG surgery in 20 medical centers in a randomized and double-blind clinical trial. They found that there was no significant difference in the incidences of adverse events in the acadesine and placebo groups. This outcome was further supported by another large-scale, multicenter, randomized clinical trial which was discontinued early because early results of a pre-specified futility analysis indicated a very low probability reaching a statistically significant efficacious outcomes. The trial was stopped after 3080 of the originally projected 7500 study participants were randomized. They believed that for intermediate- to high-risk patients undergoing CABG surgery, acadesine did not reduce the composite of all-cause mortality, nonfatal stroke, or severe left ventricular dysfunction (SLVD) (10, 60).

Nitric Oxide Carrier: S-nitrosoglutathione

Won et al. (61) found that S-nitrosoglutathione palys a protective role against cognitive impairment in rat model of chronic cerebral hypoperfusion. S-nitrosoglutathione is an endogenous nitric oxide carrier modulating endothelial function, inflammation, and neurotransmission. The effect of S-nitrosoglutathione treatment on chronic cerebral hypoperfusion-associated neurocognitive pathologies was evaluated in vivo by using a rat model of chronic cerebral hypoperfusion induced by CCA occlusion. They found chronic cerebral hypoperfusion leads to significant decrease in learning/memory performance and increases in brain levels of Aβ and vascular inflammatory markers in rats. S-nitrosoglutathione treatment (50 μg/kg/d for 2 months) could significantly improve learning and memory performance of these rats and decrease the Aβ levels and ICAM-1/VCAM-1 expression in the brain. Furthermore, in vitro cell culture studies revealed that S-nitrosoglutathione treatment could also decrease the cytokine-induced proinflammatory responses (as activations of NFκB and STAT3, expression of ICAM-1 and VCAM-1 in endothelial cells). These data indicated that systemically administered S-nitrosoglutathione is beneficial for improvement of cognitive decline under the condition of chronic cerebral hypoperfusion, and suggested a potential therapeutic use of S-nitrosoglutathione for clinical scenarios with cerebral hypoperfusion.

Magnesium

Decreased magnesium level correlates with neuronal cell dysfunction, and moderate brain injury can cause Mg decrease up to 60%. Continuous infusion of magnesium can lead to reduced plasma S100β level, and infusion of Mg may reduce atrial fibrillation and other cardiac dysrhythmia, which all seem to support that magnesium treatment may reduce the incidence of stroke. However, Mathew et al. (62) studied the effects of intraoperative magnesium administration on postoperative cognitive impairment. There were 389 patients undergoing cardiac surgery enrolled in randomized, double-blind, placebo-controlled and prospective clinical trial. The patients were randomized to receive magnesium as a 50 mg/kg bolus followed by another 50 mg/kg infusion for 3 hours or placebo bolus and infusion. Cognitive function was assessed preoperatively and at 6 weeks after surgery using a standardized test battery. The results showed the incidence of cognitive deficit in the magnesium group was 44.4% compared with 44.9% in the placebo group (P=0.93). The cognitive scores and platelet and leukocyte activation were not significantly different either. This study indicated that intraoperative magnesium administered intravenously does not reduce postoperative cognitive dysfunction.

Table. Pharmacological Agents with Potential Neuroprotective Effects in Cardiac Surgery.

Category of agents	Drugs	Notes
Inhalational agents (32)	Isoflurane Sevoflurane Desflurane Xenon	Current data do not support choosing one over the others; There are aslo some conflicting reports
Chinese herbal medicine	Gastrodin (33,34) Curcumin (35) Leonurine (36) Lycium barbarum (37) NeuroAid (39)	Based on individual study report; We need multi-center studies to validate these results.
Steroid	Methylprednisolone (40) Various steroids (42)	Animal study: 30 mg/kg in pump prime or IV at 4 hours before CPB; Clinical studies: beneficial (42)
Anesthetic induction agents	Propofol (43) Thiopental (44)	There are conflicting reports
Calcium channel blocker	Nimodipine (47)	Maybe synergistic with magnesium (47)
β-blocker	Esmolol (49) Landiolol (49)	
Trypsin inhibitor	Aprotinin (50,51)	Meta-analysis shows beneficial; Less stroke in CABG patients
Statins	Simvastatin (52)	Simvastatin is better than other statins
NMDA receptor antagonist	Remacemide (54) Ketamine (55)	Small clinical study: favorable Ketamine: no effect
Sodium channel blocker	Lidocaine (9)	Conflicting reports
Free radical scavenger	Edaravone (59)	Animal studies: beneficial
Nitric oxide carrier	S-nitrosoglutathione (61)	Animal studies: favorable
Electrolyte	Magnesium	Small clinical study: favorable

The pharmacological agents with potential neuroprotective effects are summarized in table.

Conclusions

Pharmacological prevention and management of POCD has seen some progress but not much over the last one to two decades. There is no consensus in terms of what drugs we should use, what dose we should use, when the drugs should be given and what kind of indications and contraindications. Though there is no convincing evidence and widely-accepted management, many anesthesiologists (83% in Europe) and surgeons still use pharmacological prevention of POCD, hoping to better serve the patients (63). The risk factors for POCD include older age, male gender, CPB use, cerebral embolization, pre-existing cognitive disturbance and genetic predisposition. There are some potentially beneficial pharmacological agents which may help to minimize the incidence of POCD. These agents include volatile anesthetics which will be used during surgery anyway, intravenous anesthetic agents (thiopental, propofol, and opioids), steroids, NMDA antagonists (remacemide, ketamine), nitric oxide carriers and some traditional Chinese herbal medicine such as gastrodin. It is very difficult to establish an evidence-based practice guideline for the time-being. Better designed large- scale, randomized, multicenter clinical trials will be needed to build up outcome-based evidences. In clinical practice, prophylaxis of POCD is likely a combination of different strategies including surgical (antegrade or retrograde cerebral perfusion, aortic filter, carotid stents, avoidance of cannulating aorta with severe atheroma, and treatment of atrial fibrillation, etc) and nonsurgical measures (hypothermia, lumbar drain, appropriate management of mean arterial pressure [MAP], CVP, cerebral perfusion pressure [CPP], pre- and post- conditioning, and cerebral regional oxygenation monitoring, etc).

The authors have no conflicts of interest for this work to declare.

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