Update on anesthetic neuroprotection

Richel Zwerus and Anthony Absalom

Purpose of review
Perioperative cerebral injury can result in a wide range of clinical consequences from subtle cognitive changes to devastating or fatal strokes. Although the overall incidence of perioperative stroke is low, the large and growing number of aging patients undergoing surgery and anesthesia is placing an increasing number of vulnerable patients at risk. The purpose of this review is to evaluate recent evidence concerning the use of pharmacological and nonpharmacological strategies to protect against perioperative cerebral injury.

Recent findings
Although a growing body of preclinical literature suggests that anesthetic agents such as barbiturates, volatile anesthetics, and propofol might have neuroprotective properties, clinical evidence of long-term benefit is lacking. Magnesium shows promise, although timing and dosing require clarification. Despite some early promise, there is no strong evidence that erythropoietin is neuroprotective. Remote ischemic preconditioning is the subject of intense study. It is noninvasive, cheap, and reasonably well tolerated and shows promise as a preconditioning neuroprotective intervention. A recent development has been a focus on the potential role of enhanced cardiorespiratory fitness in neuroprotection.

Summary
The evidence of benefit of current strategies remains sparse. Given the complex pathophysiology of cerebral ischemia and hypoxia, a multimodal approach to neuroprotective strategies seems sensible. The many variables and confounds associated with the clinical setting of patients, their comorbidities and concurrent medications, pose challenges to translate from experimental studies to clinical practice.

Keywords
anesthetics, ischemic preconditioning, neuroprotection, preconditioning

INTRODUCTION

There is a substantial risk of perioperative cerebral injury in patients who undergo surgery and anesthesia. Among patients undergoing noncardiac, non-neurosurgical, and noncarotid artery surgery, the reported incidence varies from 0.05 to 7.4%. The clinical consequences can vary from mild (subtle cognitive deficits, which might still impact strongly on quality of life) to severe (such as stroke resulting in severe disability or death). The mortality associated with perioperative stroke (26%) is double that associated with nonperioperative strokes [1]. Moreover, perioperative strokes increase the length of hospital stay and cause a three-fold increase in 30-day perioperative mortality rates. [2] These problems highlight the need for strategies to attenuate or prevent perioperative cerebral injury.

Definitions

In 2013, the Stroke Council of the American Heart Association/American Stroke Association published an updated definition of stroke. They defined a central nervous system (CNS) infarction as follows: 'CNS infarction is brain, spinal cord, or retinal cell death attributable to ischemia, based on 1. Pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or 2. Clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting $\geq$24 h or until death, and other etiologies excluded'. Ischemic stroke was thereby defined as 'an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction' [3].

Department of Anesthesiology, University Medical Center Groningen, Groningen, The Netherlands

Correspondence to Anthony Absalom, Department of Anesthesiology, University Medical Center Groningen, Post box 30.001, 9700 RB Groningen, The Netherlands. Tel: +31 50 3612892; e-mail: a.r.absalom@umcg.nl

Curr Opin Anesthesiol 2015, 28:424–430
DOI:10.1097/ACO.0000000000000212

KEY POINTS

- There is no strong overall evidence for the assumed neuroprotective properties of barbiturates, volatile anesthetics, and propofol.
- Magnesium appears to be a promising and well tolerated neuroprotective agent, but questions remain about timing and dose.
- RIPC is cheap, noninvasive, and well tolerated, but further studies are required to confirm neuroprotective efficacy.
- Although exercise to improve CRF is a promising potential neuroprotective strategy, the current evidence is weak.

For many years, anesthetic and nonanesthetic drugs have been studied for their possible neuroprotective qualities. Recent literature contains a vigorous discussion about the quality of previous trials. One study used modern standards and guidelines to evaluate previous preclinical and clinical literature, and concluded that the quality of the studies was so poor that it was not possible to draw conclusions on the potential neuroprotective potential of the anesthetic and other drugs studied [4▪]. Bilotta *et al.* [5] reviewed randomized clinical trials and concluded that although pharmacological neuroprotective strategies may reduce the incidence of new postoperative neurological or cognitive deficits, no effects on mortality have been shown, and further that the questionable caliber and small number of trials do not justify any firm conclusions.

The discussion presented here will focus on recent studies on this topic. The term 'neuroprotection' is used in a broad sense, to include administration of a drug not only before or during an (potential) ischemic episode (often called preconditioning and perconditioning, respectively), but also after a hypoxic/ischemic event (so-called postconditioning, but also sometimes referred to as 'neuroresuscitation'). The purpose is to evaluate the recent literature concerning the ability of anesthetic agents and/or other strategies to attenuate perioperative cerebral ischemic injuries.

ANESTHETIC AGENTS

Barbiturates

The aim of early neuroprotective strategies was to reduce cerebral ATP requirements and thereby enhance the brain's ischemic tolerance time. Thiopental and other barbiturates were thus used to achieve electroencephalographic suppression and maximally reduce ATP requirements. Analyses of clinical trials performed in previous decades have produced conflicting opinions and no conclusive evidence of barbiturate neuroprotection [5]. The few recently published studies still provide no clear answers. Schwer *et al.* [6] demonstrated molecular evidence that thiopental prevented hypoxic neuronal death by reducing cerebral metabolism and global protein synthesis, thereby helping maintain energy equilibrium in oxygen and nutrient-deprived cells [6], but the clinical debate continues.

Among patients with type A acute aortic dissection, barbiturates were associated with neither a reduction of permanent neurological dysfunction nor a significant reduction of 30-day mortality [7]. A recent review focused on studies published since the 1950s on barbiturate neuroprotection in the setting of deep hypothermic circulatory arrest for cardiac or aortic surgery [8]. Conflicting evidence was found. Although it seemed clear that thiopental does lower oxygen consumption when used as part of a neuroprotective strategy, and that it may indeed have overall beneficial effects, the timing of administration of thiopental is important. Administration too soon before circulatory arrest can have adverse effects as it may be associated with depletion of energy reserves and may cause hypotension and ischemia prior to the induction of circulatory arrest [8].

In a different setting (major elective abdominal or thoracic surgery), Saporito and Sturini [9▪] found that induction of anesthesia with thiopentone significantly increased the relative risk of postoperative delirium when compared with propofol. In a retrospective study of adults with raised intracranial pressure (ICP) caused by traumatic brain injury, thiopental significantly reduced ICP, but to a lesser extent than hypertonic saline [10]. Similarly, a report of three children with raised ICP caused by focal lesions showed that intraoperative and postoperative administration of pentobarbital was associated with reductions in ICP and brain swelling [11]. However, as in the previously mentioned adult study, no beneficial effects on outcome were demonstrated.

In summary, although barbiturates reduce cerebral metabolism and may have temporary benefits in specific circumstances, there is no clear evidence of a favorable effect on outcome.

Volatile anesthetics

Many studies have investigated the ability of routinely used volatile anesthetic agents to attenuate ischemic cerebral injury, and this has aroused great

interest in the topic. Recently, Deng *et al.* [12▪▪] published a comprehensive review of studies from the past decades on the neuroprotective effects of several classes of gases and vapors. They found that although preclinical studies provide strong evidence of a neuroprotective effect of isoflurane and sevoflurane, clinical studies provide conflicting evidence on their neuroprotective potential during surgical interventions, especially when focusing on (long-term) neurological outcome.

Numerous recent studies involving rodent infarct models have shown promising results, with sevoflurane preconditioning and postconditioning being associated with reducing infarct volume and improved neurological deficit scores [13–15]. Different pathways and sites of action seem to be involved and include beneficial effects on mitochondrial processes [13,14], inhibition of carboxy-terminal modulator protein [15], and activation of antioxidant enzymes [16]. In a traumatic brain injury rodent model, isoflurane administration before and during controlled trauma was better than propofol at limiting secondary neuronal injury associated with cortical spreading depolarizations [17]. Baseline blood flow and plasma glucose levels were also higher in the isoflurane group, suggesting better metabolic conditions.

A systematical review comparing propofol and volatile anesthetics (mostly sevoflurane and isoflurane in combination with nitrous oxide) in patients undergoing elective craniotomy showed that propofol maintenance of anesthesia is associated with a significantly lower ICP and higher cerebral perfusion pressure, but not with better brain relaxation scores [18]. Clinically, relevant outcomes such as neurological morbidity and mortality were not adequately evaluated in the studies reviewed.

Overall, the volatile anesthetics show promise as neuroprotectant agents. Volatile agent administration prior to an ischemic insult appears to induce similar protective responses to that produced by ischemic preconditioning (and also preconditioning associated with hyperoxia). Therefore, as in studies of cardiac protection, further work on the timing of exposure to volatile agent – to separately assess the effects of preconditioning, continuous inhalation, or postconditioning – deserves attention in future research, and should be followed by studies of dose–effect relationships and eventually also of long-term outcome.

Propofol

As for the barbiturates, proving the neuroprotective effects of propofol in clinical studies has been difficult. Extensive recent laboratory investigations (in particular, in-vitro and in-vivo rodent models) has, however, revealed different potential molecular pathways by which propofol may offer protection against hypoxic damage. Results of these studies suggest that the mechanisms of postconditioning effect of propofol administered after cerebral ischemia/reperfusion injury was the result of increased neuronal tolerance to hypoxia or improved recovery [19–21], attenuated inflammatory reactions [22,23], or reduced endoplasmic reticulum stress-induced apoptosis [24]. Administration of a combination of propofol and dexmedetomidine seems to have a stronger neuroprotective effect in rats [25].

Strong clinical evidence of propofol neuroprotection has remained elusive. In a recent randomized clinical trial, the effect of propofol titrated to burst suppression prior to and during temporary clipping for intracranial aneurysm surgery, on postoperative cognitive dysfunction, was assessed. Cognitive dysfunction was defined as a decline of the minimental state examination score to below 24. No difference was found between the propofol and control groups, but it should be borne in mind that the minimental state examination is a blunt and insensitive tool for assessment of subtle cognitive function changes [26].

In spite of the supportive nonclinical data, further high-quality clinical trials are needed, to attempt to determine optimal timing and dosing of propofol administration and evaluate the neuroprotective efficacy.

OTHER PHARMACEUTICALS

Remifentanil

A recent study in gerbils showed that the administration during surgery of the potent short-acting opioid remifentanil may provide neuroprotection by suppressing apoptosis [27]. In a rat ischemia-perfusion model, reductions in infarct volume and improved neurological outcome were shown and appeared to have been mediated by activation of δ-opioid receptors, reduced expression of tumor necrosis factor-α, and suppression of extracellular signal-regulated kinases 1/2 activity [28]. Another group showed that remifentanil postconditioning improved memory function after global cerebral ischemia in rats via inhibition of neuronal apoptosis (in the CA1 region of the hippocampus, in particular) via effects on the PI3K signaling pathway [29]. Nonetheless, recommendations for practical clinical use cannot yet be made.

Magnesium

Several recent animal and human studies have investigated the neuroprotective potential of

magnesium, a N-methyl-D-aspartate glutamate receptor antagonist.

Intracarotid infusion of cold magnesium solution after induction of ischemic injury in rats resulted in reduced infarct volumes, decreased brain water content, and improved neurological outcome [30]. A laboratory study suggests that the neuroprotective effects of magnesium might be related to inhibition of L-type calcium channels and nuclear factor-κB signaling thereby attenuating microglial release of inflammatory mediators [31].

In humans, magnesium has been shown to have neuroprotective efficacy during surgical procedures associated with ischemia [e.g., coronary artery bypass graft (CABG) and endarterectomy] and also when administered after preterm neonatal hypoxia [32▪]. However, the benefits of magnesium in the treatment of ischemic stroke and intracranial hemorrhages are not proven. The lack of evidence of neuroprotective value of magnesium in ischemic stroke might be explained by suboptimal timing of treatment [33].

In a review of the literature on administration of magnesium after aneurysmal subarachnoid hemorrhage, Golan *et al.* [34] concluded that although magnesium reduces the risk of delayed cerebral ischemia, it does not increase the probability of good neurological outcome. A recent randomized controlled trial showed no significant difference in neurological outcome after cardiac surgery between a group receiving a magnesium bolus and 3-h infusion and a placebo group [35]. More promise has been found in the setting of ischemic stroke. A clinical trial performed by Afshari *et al.* [36] suggested that treatment with magnesium within the first 12 h after onset of acute ischemic stroke is well tolerated and associated with improved neurological outcome.

Comparisons among studies of magnesium are confounded by heterogeneity in methodology, and patient groups and outcomes studied.

Erythropoietin

Recently, neuroprotection has become a novel potential indication for erythropoietin. Preclinical data demonstrates neuroprotective properties and has prompted some clinical research.

A pilot dose-finding study of darbepoetin-α (a recombinant form of erythropoietin) administered before descending aortic surgery showed nonsignificant trends toward reductions in neuronal injury biomarkers and improved neurological outcomes [37]. This study was, however, terminated prematurely after publication of the German Erythropoietin Stroke Study that raised safety concerns. The latter study showed excess mortality associated with the administration of erythropoietin in acute stroke patients, particularly those who had been pretreated with thrombolysis [38].

In 2013, Andropoulos *et al.* [39] conducted a randomized pilot study to evaluate safety and neurodevelopmental outcomes associated with erythropoietin administration to neonates undergoing cardiac surgery. There were no safety concerns and no significant differences in neurological outcomes (the study was not powered to show neurological outcome differences). An adult dose-escalation study aimed to investigate the effect of subcutaneous administration of human choriogonadotropin-α followed by intravenous erythropoietin to acute ischemic stroke patients. They claimed safety, but found no difference in neurological outcome, and this study was also underpowered, having been terminated prematurely because of slow recruitment [40]. At present, the use of erythropoietin to attenuate ischemic cerebral injury cannot be recommended.

NONPHARMACOLOGICAL STRATEGIES

Ischemic preconditioning

IPC is a physiological mechanism by which sublethal exposure of an organ or tissue to ischemia protects against a subsequent serious ischemia/reperfusion insult. Just like the heart and kidneys, the brain seems to be an important possible target for therapeutic IPC. Preclinical studies have investigated the molecular pathways and possible intercellular communications that might be involved in the pathophysiology of ischemic stroke as possible therapeutic targets for IPC. A recent review suggests that IPC protects cerebral cells by decreasing mitochondrial permeability, increasing antioxidant expression, enhancing DNA repair capacity, and attenuating inflammatory damage [41]. Recently, a modified form of IPC, remote ischemic preconditioning (RIPC), has been proposed and studied.

Remote ischemic preconditioning

RIPC presents an interesting alternative to cerebral preconditioning because it is less invasive and is more practical in the clinical setting. Most commonly, brief episodes of ischemia are induced in an arm or leg by inflation of a blood pressure or tourniquet cuff to more than 200 or 30 mmHg above systolic blood pressure for 5–10 min in two to five cycles prior to the potentially injurious cerebral ischemia. The majority of clinical studies on RIPC

focus on cardiac protection, but there are promising results for protection against ischemic brain injury. Although there seems to be a sound scientific background for RIPC, demonstration of true clinical beneficial effects remains elusive. At present, published studies of RIPC for neuroprotection in vascular surgery have generally demonstrated reductions in biomarkers for organ injury but were insufficiently powered to detect differences in clinical outcomes [42].

The randomized controlled trial of Hougaard *et al.* [43▪] is interesting and particularly novel as it evaluated prehospital remote ischemic perconditioning as an adjunct therapy in patients with acute ischemic stroke. Unfortunately, no beneficial effects on penumbral salvage, infarct growth, final infarct size, and clinical outcome were found. However, after adjustment for baseline perfusion and diffusion lesion severity, a further voxelwise imaging analysis showed a significant overall reduction of infarction. Remote ischemic preconditioning and perconditioning appear to be feasible and well tolerated interventions [43▪,44], also in the setting of unilateral middle cerebral arterial stenosis [44].

Overall, RIPC is a noninvasive cheap and well tolerated technique, which shows promise as a neuroprotective strategy. The results of two prospective trials are eagerly awaited – the RIPCAGE study (RCT on RIPC as neuroprotectant preceding coronary artery bypass grafting) [45] and the ERICCA study (effect of RIPC on clinical outcomes in patients undergoing CABG and or valve surgery) [46].

Exercise

Cardiorespiratory fitness (CRF) is associated with positive postoperative outcomes in several different settings, and recent studies show that reduced preoperative CRF identifies patients at risk of mortality and morbidity after elective major intra-abdominal surgery [47,48▪]. Another study has shown that CRF is an independent predictor of both hospital stay and mortality in patients undergoing major hepatobiliary surgery [49]. These findings have led to the hypothesis that physical exercise may constitute a neuroprotective preconditioning stimulus.

A review of recent studies (mostly in animals), suggests that exercise (e.g., running on a treadmill), on one hand, induces brain tolerance to ischemia [50] and neuroprotection by attenuation of inflammatory responses, glutamate release, blood-brain barrier dysfunction, and eventual neuronal apoptosis, and, on the other hand, promotes neurogenesis and modulates vascular angiogenesis [50].

A systematic review by Austin *et al.* [51] included animal and human studies and showed that aerobic exercise as early poststroke therapy has beneficial effects on short-term outcome including lesion volume, oxidative damage, apoptosis, and inflammation. The pilot study performed by El-Tamawy *et al.* [52] in humans showed that aerobic exercise following acute ischemic stroke improves cognitive performance and increases serum levels of brain-derived neurotrophic factor.

Although a body of literature demonstrates beneficial effects of exercise preconditioning in animals, so far the volume of human evidence is limited. Challenges to translational studies include uncertainty about optimal timing, intensity, and duration of exercise. It thus remains to be seen whether clinical trials will confirm the beneficial effects of preconditioning/postconditioning exercise on outcome after ischemic stroke.

CONCLUSION

During the past few years, several well conducted reviews have summarized decades of research on possible neuroprotective effects of anesthetics and other drugs. Available data indicates that a variety of pharmacological and nonpharmacological strategies might reduce preoperative ischemic brain injury. Despite extensive promising data from experimental studies, the implementation of neuroprotective strategies in clinical practice shows disappointing results. Probably translation of positive animal findings to patients has been hampered by the associated clinical comorbidity and concurrent medication of patients. Given the complex pathophysiology of cerebral ischemia, it is also unlikely that a single intervention strategy will result in clinical relevant neuroprotection. Also timing and dosing of different therapeutic strategies developed in animals probably do not extrapolate well to humans in clinical settings. The results of ongoing preconditioning studies on outcome are eagerly awaited. We remain hopeful that further research on pharmaceutical and nonpharmaceutical preconditioning and perconditioning strategies will eventually provide practical and efficacious neuroprotective tools.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Ng JL, Chan MT, Gelb AW. Perioperative stroke in noncardiac, nonneurosurgical surgery. Anesthesiology 2011; 115:879–890.
2. Sharifpour M, Moore LE, Shanks AM, *et al.* Incidence, predictors, and outcomes of perioperative stroke in noncarotid major vascular surgery. Anesth Analg 2013; 116:424–434.
3. Sacco RL, Kasner SE, Broderick JP, *et al.* An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013; 44:2064–2089.
4. ■ Ishida K, Berger M, Nadler J, Warner DS. Anesthetic neuroprotection: antecedents and an appraisal of preclinical and clinical data quality. Curr Pharm Des 2014; 20:5751–5765.

Critical review on anesthetic neuroprotection research.

5. Bilotta F, Gelb AW, Stazi E, *et al.* Pharmacological perioperative brain neuroprotection: a qualitative review of randomized clinical trials. Br J Anaesth 2013; 110 (Suppl 1):i113–i120.
6. Schwer CI, Lehane C, Guelzow T, *et al.* Thiopental inhibits global protein synthesis by repression of eukaryotic elongation factor 2 and protects from hypoxic neuronal cell death. PLoS One 2013; 8:e77258.
7. Krüger T, Hoffmann I, Blettner M, *et al.* Intraoperative neuroprotective drugs without beneficial effects? Results of the German Registry for Acute Aortic Dissection Type A (GERAADA). Eur J Cardiothorac Surg 2013; 44:939–946.
8. Al-Hashimi S, Zaman M, Waterworth P, Bilal H. Does the use of thiopental provide added cerebral protection during deep hypothermic circulatory arrest? Interact Cardiovasc Thorac Surg 2013; 17:392–397.
9. ■ Saporito A, Sturini E. Incidence of postoperative delirium is high even in a population without known risk factors. J Anesth 2014; 28:198–201.

An observational prospective study that shows a 28% incidence of postoperative delirium in patients on the ICU after major surgery. Compared with propofol, thiopentone was associated with a higher risk for delirium.

10. Colton K, Yang S, Hu PF, *et al.* Intracranial pressure response after pharmacologic treatment of intracranial hypertension. J Trauma Acute Care Surg 2014; 77:47–53.
11. Mansour N, deSouza RM, Sikorski C, *et al.* Role of barbiturate coma in the management of focally induced, severe cerebral edema in children. J Neurosurg Pediatr 2013; 12:37–43.
12. ■■ Deng J, Lei C, Chen Y, *et al.* Neuroprotective gases – fantasy or reality for clinical use? Prog Neurobiol 2014; 115:210–245.

Comprehensive and excellent review of volatiles and their possible neuroprotective effects and underlying mechanisms.

13. Ye Z, Xia P, Cheng ZG, Guo Q. Neuroprotection induced by sevoflurane-delayed postconditioning is attributable to increased phosphorylation of mitochondrial GSK-3β through the PI3K/Akt survival pathway. J Neurol Sci 2015; 348:216–225.
14. Wang JK, Wu HF, Zhou H, *et al.* Postconditioning with sevoflurane protects against focal cerebral ischemia and reperfusion injury involving mitochondrial ATP-dependent potassium channel and mitochondrial permeability transition pore. Neurol Res 2015; 37:77–83.
15. Chen Y, Nie H, Tian L, *et al.* Sevoflurane preconditioning-induced neuroprotection is associated with Akt activation via carboxy-terminal modulator protein inhibition. Br J Anaesth 2015; 114:327–335.
16. Lee H, Park YH, Jeon YT, *et al.* Sevoflurane postconditioning increases nuclear factor erythroid 2-related factor and haemoxygenase-1 expression via protein kinase C pathway in a rat model of transient global cerebral ischaemia. Br J Anaesth 2015; 114:307–318.
17. Takagaki M, Feuerstein D, Kumagai T, *et al.* Isoflurane suppresses cortical spreading depolarizations compared to propofol: implications for sedation of neurocritical care patients. Exp Neurol 2014; 252:12–17.
18. Chui J, Mariappan R, Mehta J, *et al.* Comparison of propofol and volatile agents for maintenance of anesthesia during elective craniotomy procedures: systematic review and meta-analysis. Can J Anaesth 2014; 61:347–356.
19. Zhang DX, Ding HZ, Jiang S, *et al.* An in vitro study of the neuroprotective effect of propofol on hypoxic hippocampal slice. Brain Inj 2014; 28:1758–1765.
20. Wang H, Liu S, Wang H, *et al.* The effect of propofol postconditioning on the expression of K(+)-Cl(-)-co-transporter 2 in GABAergic inhibitory interneurons of acute ischemia/reperfusion injury rats. Brain Res 2015; 1597:210–219.
21. Yue ZY, Dong H, Wang YF, *et al.* Propofol prevents neuronal mtDNA deletion and cerebral damage due to ischemia/reperfusion injury in rats. Brain Res 2015; 1594:108–114.
22. Shi SS, Yang WZ, Chen Y, *et al.* Propofol reduces inflammatory reaction and ischemic brain damage in cerebral ischemia in rats. Neurochem Res 2014; 39:793–799.
23. Zhou R, Yang Z, Tang X, *et al.* Propofol protects against focal cerebral ischemia via inhibition of microglia-mediated proinflammatory cytokines in a rat model of experimental stroke. PLoS One 2013; 8:e82729.
24. Nakajima A, Tsuji M, Inagaki M, *et al.* Neuroprotective effects of propofol on ER stress-mediated apoptosis in neuroblastoma SH-SY5Y cells. Eur J Pharmacol 2014; 725:47–54.
25. Wang Z, Kou D, Li Z, *et al.* Effects of propofol-dexmedetomidine combination on ischemia reperfusion-induced cerebral injury. NeuroRehabilitation 2014; 35:825–834.
26. Mahajan C, Chouhan RS, Rath GP, *et al.* Effect of intraoperative brain protection with propofol on postoperative cognition in patients undergoing temporary clipping during intracranial aneurysm surgery. Neurol India 2014; 62:262–268.
27. Park SW, Yi JW, Kim YM, *et al.* Remifentanil alleviates transient cerebral ischemia-induced memory impairment through suppression of apoptotic neuronal cell death in gerbils. Korean J Anesthesiol 2011; 61:63–68.
28. Jeong S, Kim SJ, Jeong C, *et al.* Neuroprotective effects of remifentanil against transient focal cerebral ischemia in rats. J Neurosurg Anesthesiol 2012; 24:51–57.
29. Hu X, Xie C, He S, *et al.* Remifentanil postconditioning improves global cerebral ischemia-induced spatial learning and memory deficit in rats via inhibition of neuronal apoptosis through the PI3K signaling pathway. Neurol Sci 2013; 34:1955–1962.
30. Song W, Wu YM, Ji Z, *et al.* Intra-carotid cold magnesium sulfate infusion induces selective cerebral hypothermia and neuroprotection in rats with transient middle cerebral artery occlusion. Neurol Sci 2013; 34:479–486.
31. Gao F, Ding B, Zhou L, *et al.* Magnesium sulfate provides neuroprotection in lipopolysaccharide-activated primary microglia by inhibiting NF-κB pathway. J Surg Res 2013; 184:944–950.
32. ■ Chang JJ, Mack WJ, Saver JL, Sanossian N. Magnesium: potential roles in neurovascular disease. Front Neurol 2014; 5:52.

Clear review about magnesium as neuroprotectant and therapeutic agent.

33. Westermaier T, Stetter C, Kunze E, *et al.* Magnesium treatment for neuroprotection in ischemic diseases of the brain. Exp Transl Stroke Med 2013; 5:6.
34. Golan E, Vasquez DN, Ferguson ND, *et al.* Prophylactic magnesium for improving neurologic outcome after aneurysmal subarachnoid hemorrhage: systematic review and meta-analysis. J Crit Care 2013; 28:173–181.
35. Mathew JP, White WD, Schinderle DB, *et al.* Intraoperative magnesium administration does not improve neurocognitive function after cardiac surgery. Stroke 2013; 44:3407–3413.
36. Afshari D, Moradian N, Rezaei M. Evaluation of the intravenous magnesium sulfate effect in clinical improvement of patients with acute ischemic stroke. Clin Neurol Neurosurg 2013; 115:400–404.
37. Messé SR, McGarvey ML, Bavaria JE, *et al.* A pilot study of darbepoetin alfa for prophylactic neuroprotection in aortic surgery. Neurocrit Care 2013; 18:75–80.
38. Ehrenreich H, Weissenborn K, Prange H, *et al.* Recombinant human erythropoietin in the treatment of acute ischemic stroke. Stroke 2009; 40:e647–e656.
39. Andropoulos DB, Brady K, Easley RB, *et al.* Erythropoietin neuroprotection in neonatal cardiac surgery: a phase I/II safety and efficacy trial. J Thorac Cardiovasc Surg 2013; 146:124–131.
40. Cramer SC, Hill MD. Human choriogonadotropin and epoetin alfa in acute ischemic stroke patients (REGENESIS-LED trial). Int J Stroke 2014; 9:321–327.
41. Narayanan SV, Dave KR, Perez-Pinzon MA. Ischemic preconditioning and clinical scenarios. Curr Opin Neurol 2013; 26:1–7.
42. Twine CP, Ferguson S, Boyle JR. Benefits of remote ischaemic preconditioning in vascular surgery. Eur J Vasc Endovasc Surg 2014; 48:215–219.
43. ■ Hougaard KD, Hjort N, Zeidler D, *et al.* Remote ischemic perconditioning as an adjunct therapy to thrombolysis in patients with acute ischemic stroke: a randomized trial. Stroke 2014; 45:159–167.

The authors show promising results concerning reduction of infarction and safety using remote ischemic perconditioning.

44. Li S, Ma C, Shao G, *et al.* Safety and feasibility of remote limb ischemic preconditioning in patients with unilateral middle cerebral artery stenosis and healthy volunteers. Cell Transplant 2014. [Epub ahead of print]
45. Gasparovic H, Kopjar T, Rados M, *et al.* Impact of remote ischemic preconditioning preceding coronary artery bypass grafting on inducing neuroprotection (RIPCAGE): study protocol for a randomized controlled trial. Trials 2014; 15:414.
46. Hausenloy DJ, Candilio L, Laing C, *et al.* Effect of remote ischemic preconditioning on clinical outcomes in patients undergoing coronary artery bypass graft surgery (ERICCA): rationale and study design of a multicentre randomized double-blinded controlled clinical trial. Clin Res Cardiol 2012; 101:339–348.
47. Wilson RJT, Davies S, Yates D, *et al.* Impaired functional capacity is associated with all-cause mortality after major elective intra-abdominal surgery. Br J Anaesth 2010; 105:297–303.

48. West MA, Lythgoe D, Barben CP, *et al.* Cardiopulmonary exercise variables ■ are associated with postoperative morbidity after major colonic surgery: a prospective blinded observational study. Br J Anaesth 2014; 112:665–671.
CRF is an interesting subject of research and will probably be the target of new therapeutic intervention strategies and studies.
49. Snowden CP, Prentis J, Jacques B, *et al.* Cardiorespiratory fitness predicts mortality and hospital length of stay after major elective surgery in older people. Ann Surg 2013; 257:999–1004.
50. Zhang F, Wu Y, Jia J. Exercise preconditioning and brain ischemic tolerance. Neuroscience 2011; 177:170–176.
51. Austin MW, Ploughman M, Glynn L, Corbett D. Aerobic exercise effects on neuroprotection and brain repair following stroke: a systematic review and perspective. Neurosci Res 2014; 87:8–15.
52. El-Tamawy MS, Abd-Allah F, Ahmed SM, *et al.* Aerobic exercises enhance cognitive functions and brain derived neurotrophic factor in ischemic stroke patients. NeuroRehabilitation 2014; 34:209–213.