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Perioperative Organ Protection in Cardiac Surgery

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1. Introduction

Perioperative organ protection refers to the set of strategies to lessen the intensity of the surgical and anesthetic stress. A better understanding of mechanisms involved in tissue hypoperfusion, ischemia-reperfusion phenomena, and the protection triggered by certain anesthetic techniques, drugs and adjuvants have been very useful in perioperative organ protection, especially in patients with comorbidities and / or undergoing high risk surgical procedures.

2. Myocardial protection

Among the methods used during cardiac anesthesia, the use of anesthetic drugs and techniques that increase tolerance to ischemia and contribute to protect myocardial function have been gaining importance in clinical practice and may influence the postoperative course. Myocardial ischemia triggers a cascade of cellular events that start mildly and become increasingly deleterious as the ischemic time passes. Although reperfusion is the end of the ischemic process and is essential for the restoration of normal cell function and survival, it may paradoxically amplify the damage secondary to ischemia and compromise postoperative outcome.

Effects of Anesthetics drugs: For more than three decades, there is growing evidence that inhaled volatile anesthetics can protect the myocardium from ischemic reversible and irreversible injuries (1). The mechanisms by which these drugs promote cardioprotection are not fully known and it is suggested that the mechanism induced by inhaled anesthetics seems to mimic the ischemic preconditioning. Halogenated anesthetics reduce blood pressure, cause depression in myocardial contractility, coronary vasodilation, slow the conduction of electrical stimuli and attenuate the activity of the sympathetic nervous system, which contributes to decrease the myocardial oxygen consumption. However, mechanisms other than the adequacy of oxygen supply and consumption appear to be related to the cardioprotection conferred by inhaled anesthetics, such as the preservation of high energy phosphates(2). The modulation of calcium influx to the cardiomyocyte(3)

and the inhibition of the sodium - calcium pump, with increased expression of calcium channels induced by ischemia-reperfusion injury, are also related with the inhaled anesthetics (4).

Some authors have suggested that concentrations around one minimum alveolar concentration (MAC) of various halogenated anesthetics produce similar effects on the intensity of myocardial protection(5). The inhaled anesthetics have shown consistent effects on myocardial protection in animal models of ischemia-reperfusion, and clinical studies have been conducted to verify these benefits in clinical practice.

Myocardial protection during anesthesia aims to decrease the myocardial oxygen consumption, adapting it to the momentary tissue supply and / or cardiac cells become more resistant to ischemia, attenuating the magnitude of the injury induced by ischemia-reperfusion and its deleterious immediate and late consequences, such as myocardial infarction (MI), arrhythmias, ventricular dysfunction, cardiogenic shock and increased perioperative mortality.

The extent and severity of tissue injury after coronary occlusion is not determined at the onset of ischemia and may be modified by methods of myocardial protection. A great number of experimental studies have investigated the mechanisms of ischemia and modalities of myocardial protection, although only a few therapeutic interventions have been shown to be clinically effective. Despite advances in understanding the determinants of coronary blood flow, the relationship between supply and consumption of oxygen, and the cellular mechanisms triggered by ischemia, the incidence of perioperative MI is still high(6, 7).

During ischemia, oxygen supply is below regional metabolic needs, resulting in depletion of cellular reserves of ATP. In this situation, there is a reduction in the efficiency of the ATP-dependent sodium (Na+) potassium (K+) pump, increasing the levels of intracellular Na+. Hydrogen ion (H+) accumulates intracellularly as a result of decreased excretion of metabolic wastes, inhibition of $NADH_2$ mitochondrial oxidation and ATP break down. The accumulation of intracellular H+ promotes an increase in exchange of H+ by Na+ in an attempt to keep cell pH in its normal range, increasing the intracellular levels of Na+ even higher, causing increased levels of intracellular calcium (Ca2+) due to the exchange of Na+ by Ca2+(8, 9). High levels of intracellular Ca2+ promote activation of protein kinases with degradation of proteins and phospholipids culminating in a decrease of the maximum force generated by calcium-dependent myofilaments. After the onset of ischemia, the production of free radicals derived from neutrophils and mitochondria also contributes to the degradation of proteins and phospholipids, which are the main constituents of the cells structure and enzymes(10-12).

The injury installed after the onset of ischemia appears to be amplified when coronary vessels are damaged and the endothelial cells are swollen, reducing the efficiency of gas exchange. The vascular smooth muscle cells and endothelial cells with abnormal function loose the ability to promote vasodilation and to pair the regional blood flow to the momentary needs. Neutrophils play a central role in the spread of cell injury. These cells are attracted by dysfunctional endothelial cells and migrate into the extravascular space, releasing free radicals, cytokines and pro-inflammatory substances, worsening the endothelial, smooth muscle and cardiomyocyte injuries (13). The aggregation of neutrophils and platelets causing microvascular obstruction contributes to the decoupling of the supply / demand relationship (11, 14). The time required for synthesis of damaged

proteins would explain the period required for recovery of myocardial function after ischemia-reperfusion injury (15, 16). In combination with high levels of intracellular calcium, there is a major increase in the production of oxygen free radicals due to reperfusion with oxygenated blood. Free radicals such as superoxide (O2-), hydroxyl (OH-) and hydrogen peroxide (H2O2) are extremely reactive and are able to damage all cellular components indistinctly, increasing the damage induced by ischemia. The clinical consequences can range from reversible myocardial dysfunction that persists after reperfusion, known as myocardial stunning, up to MI (10, 12). The development of micro-perioperative ischemic areas is recognized as a problem that can lead to low cardiac output syndrome and death in surgical patients. The perioperative myocardial infarction can occur due to increased consumption of oxygen from the induction of anesthesia until postoperative recovery.

The ischemic preconditioning is an endogenous adaptive and protective response against prolonged myocardial ischemia(17). Despite being initially promising to reduce the incidence and extent of MI, this method of myocardial protection may also decrease the incidence of reversible myocardial dysfunction and post-ischemic dysfunction of the coronary circulation(18). Several membrane receptors seems to be involved in the phenomenon of ischemic preconditioning including α-1, β, opioid and adenosine receptors(19).

In cardiac surgery, the observed systemic inflammatory response is the result of direct surgical trauma, ischemia-reperfusion injury and extracorporeal circulation(20) and cardiac injury can be triggered by ischemia, reperfusion, and also by local effects of mediators of the inflammatory response. Additionally, the heart itself may release locally inflammatory mediators and oxygen free radicals that can contribute to the worsening of the cardiac function. Myocardial protection strategies during cardiac surgery aimed at limitation of the reperfusion injury and systemic inflammatory response are essential to reduce mortality, although many anesthetics may have cardioprotective actions, the diversity of proposed mechanisms for protection (e.g. attenuation of calcium influx, anti-inflammatory and anti-oxidants effects, pre and post conditioning). A randomized study comparing the effects of total intravenous anesthesia (TIVA) and balanced anesthesia with desflurane or sevoflurane on the release of troponin T in the post operative period with 414 patients undergoing coronary artery bypass grafting with cardiopulmonary bypass observed that although the maximum postoperative troponin T did not differ between groups, the mortality rate after one year was 12.3% in the TIVA group, 3.3% in the sevoflurane group and 6.7% in the desflurane group(21).

Clinical studies have suggested the cardioprotective effects of volatile anesthetics and the effects of these agents on the early and late morbidity and mortality requires further investigation. The administration of inhaled anesthetics in post-ischemic period can also be cardioprotective by attenuating the reperfusion damage. This mechanism may be useful in situations where the patients has already suffered or is suffering an ischemic event(22, 23).

The contribution of endogenous opioids for organic adaptation to hypoxia and protection against ischemia-reperfusion injuries by opioid receptor agonists has been demonstrated experimentally in several animal models (24) (25). Morphine administered before occlusion of left anterior descending artery caused a decrease in the infarction zone from 54% to 12% of the area at risk in rats(26). This reduction in the infarct area induced by

morphine was also observed in isolated heart models, in *in situ* hearts and in cardiomyocytes(27). It was also observed an improvement in ventricular contractility after ischemic episodes with morphine and fentanyl (28). Besides participating in the triggering of the cascade of ischemic preconditioning, opioids also seem to mediate the memory phase in some animal species and the opioid-induced cardioprotection appears to be modulated by the activation of cardiac receptors, independent of the action of these drugs on the central nervous system [40-41] .

It has been proposed that opioid-induced cardioprotection is processed by the activation of ATP-dependent potassium channels, possibly in the mitochondrial membrane(29). However, the intracellular pathway that makes the transduction triggered by the sigma receptor stimulation to the end effectors is still unclear. Other intracellular pathways of cardioprotection induced by opioids appear to be related to the activation of inhibitory G protein and protein kinase C1 (30).

On the other hand, some studies suggest that propofol can attenuate the mechanical dysfunction after myocardial ischemia, improving functional and metabolic recovery(31). Propofol can decrease the concentration of free radicals and its deleterious effects(32) and it is also able to reduce the intracellular influx of calcium and attenuate neutrophil activity, interfering with critical phases of myocardial reperfusion(33). Although some degree of myocardial protection appears to be conferred by propofol when administered during the reperfusion phase in experimental models of isolated rat heart, the protective effect of propofol appears to be momentary and it is not considered an agent capable of inducing preconditioning or myocardial protection. Sevoflurane, but not propofol, seems to be able to preserve post-operative myocardial function with evidence of reduced myocardial cell injury after coronary artery bypass graft (CABG) (34). On the other hand, the continuous infusion of propofol at the dose of 120 mcg/kg/min, initiated 10 minutes before cardiopulmonary bypass (CPB), resulted in lower levels of troponin I and elevated the cardiac index when compared to isoflurane and lower doses of propofol(35).

Despite the well-established role of ketamine as an anesthetic agent in congenital heart surgery and in patients with circulatory shock, this drug seems to block ischemic preconditioning and enhance myocardial injury. Ketamine reduces the production of 1, 4, 5-triphosphate inositol and inhibits ATP-dependent potassium channels in the sarcoplasmic membrane(36). Barbiturates have also been classified as medications that can inhibit myocardial protection induced by ischemic preconditioning (37).

Adjuvant drugs for myocardial protection: Several medications have been investigated preoperatively, intraoperatively or directly administered in the cardioplegic solution before the start of CPB. Beta-adrenergic antagonists can reduce myocardial oxygen consumption, reduce the sympathetic tone, and stabilize cell membranes. If there is no contraindications for its use, the administration of beta-adrenergic antagonists in the early hours after acute MI, modulating the intense adrenergic stimulation(38), can be beneficial in reducing mortality and complications(39).

Regarding the α2 receptor agonists, clonidine seems to be less effective than high thoracic epidural anesthesia in reducing perioperative stress and troponin release in patients undergoing CABG (40). Additionally, experimental and small clinical trials showed encouraging results for the improvement of myocardial performance in patients undergoing cardiac surgery with the infusion of a solution containing glucose, insulin and potassium (GIK) (41). The mechanism by which GIK solution promotes cardioprotection seems to be

related to the restoration of the activity of the ATP-dependent potassium channels by insulin, since glucose decreases the activity of this channel and insulin infusion can decrease apoptosis induced by ischemia and reperfusion(42). However, despite the beneficial effects observed experimentally and in small studies, the benefit of GIK in high-risk patients undergoing CABG has not been demonstrated.(43).

Thoracic Epidural Anesthesia: Thoracic epidural anesthesia with local anesthetics has been used as a technique capable of promoting perioperative analgesia and reduction of myocardial oxygen consumption by blocking the roots of the thoracic sympathetic fibers from T1 to T5, which provide sympathetic innervation to the heart. The cardioprotection conferred by thoracic epidural anesthesia is related to an improvement in the myocardial oxygen supply induced by the sympathetic blockade, which causes reduction of myocardial oxygen consumption secondary to bradycardia, reduction of the cardiac output, a decrease in systemic vascular resistance and an improvement in the regional perfusion by a post stenotic vasodilation of the segments of arteries partially obstructed. Some studies have shown that thoracic epidural anesthesia can attenuate the endocrine-metabolic response secondary to surgery, with reduction of release and in serum levels of catecholamines, which contributes to a decrease in oxygen consumption(44).This improvement in myocardial oxygen balance is demonstrated clinically by improvement in angina in patients with coronary artery disease (45).

The efficiency of thoracic epidural analgesia allows lower doses of systemic opioids, thereby reducing the time of tracheal intubation and pulmonary morbidity in postoperative cardiac surgery(46). However, despite the beneficial effects of thoracic epidural anesthesia on myocardial oxygen balance, no direct mechanism to increase myocardial tolerance to ischemia and reperfusion has been described, and the additional risk of the procedure in patients under effects of heparin should be considered. In a meta-analysis of 15 studies and 1178 patients the use of thoracic epidural anesthesia in CABG was not effective in reducing mortality (0.7% versus 0.3% general anesthesia) nor the incidence of myocardial infarction (2.3% versus 3.4% general anesthesia). On the other hand, a significant decrease in the incidence of arrhythmia (OR 0.52), pulmonary complications (OR 0.41) and duration of tracheal intubation was evidenced. Analgesia with spinal opioids showed no effect on mortality, incidence of myocardial infarction, arrhythmias, mortality and duration of intubation when compared with general anesthesia(47). In patients undergoing off-pump coronary artery bypass surgery, the addition of thoracic epidural to general anesthesia can reduce the incidence of postoperative arrhythmias and improves pain control and overall quality of recovery, allowing earlier extubation and hospital discharge(48).

Myocardial protection during cardiopulmonary bypass: The technique of myocardial protection used for most CABG is the infusion of hypothermic cardioplegic solution, with blood or crystalloids. Early reports cardioplegia date from the 50's, describing electrochemical cardiac arrest in diastole induced by potassium citrate solutions, allowing the cardiac surgery to be performed on a stopped and flaccid heart(49). However, this solution was associated with high incidence of myocardial necrosis. Cardioplegic solutions rich in potassium have been abandoned in the mid 70's when it was found that myocardial necrosis was related to its high concentration and hypertonicity. Until the 80's, the use of hypothermic crystalloid cardioplegic solution was the main technique for myocardial protection during cardiac surgery. From the 80's, studies have shown that cardioplegic

solutions with potassium and blood promoted more efficient myocardial protection than the crystalloid solution. This was observed by a decrease in the release of CK-MB and in the incidence of perioperative infarction(50). Since then, cardioplegic solutions with blood and potassium have been the cornerstone of myocardial protection with a defined role in intraoperative heart protection. The technique for the infusion of cardioplegic solutions most commonly used is antegrade and intermittent infusion in the aorta, proximal to the heart, after aortic clamping, or directly into the coronary artery ostia, especially when there is associated aortic valve disease. Recently, it has been proposed the infusion of retrograde cardioplegic solutions in the coronary sinus. This technique assumes the possibility of maintaining uninterrupted infusion and distribution of the solution to regions irrigated by stenotic coronary vessels, improving the sub-endocardial protection(51). The optimal temperature for cardioplegia is controversial. Solutions at temperatures below 15°C seem to be more effective in reducing myocardial oxygen consumption, lactate production and markers of cellular hypoxia than solutions at room temperature. However, solutions with temperature around 27 º C seem to have better recovery of left ventricular function in the immediate postoperative period and lower incidence of arrhythmias, need for defibrillation and bleeding volumes (52). Another controversial issue is the time interval between infusions of cardioplegia, being 20 to 25 minutes the mean used by surgeons. Also, there are no consensuses neither on the optimal dose of cardioplegic solution to be infused nor about the addition of substrates such as l-arginine, anti-arrhythmics or beta-adrenergic antagonists.

Therapeutic hypothermia has been another strategy to reduce myocardial injury secondary to ischemia during CPB. The mechanism by which hypothermia exerts its protective role in the myocardium is not completely understood. The classic explanation is a decrease in oxygen consumption induced by a reduction in the cellular metabolic activity and enzymatic reactions, which could limit the areas of myocardial ischemia in regions at risk. In humans cooled to 32 °C, the total body oxygen consumption is decreased by 45%, unrelated to changes in arterial oxygen saturation(53). The increase in the oxygen affinity to hemoglobin is compensated by increasing its blood solubility. As the temperature decreases, myocardial oxygen consumption decreases, being less than 1% at 12 º C(54). This cardioprotective effect is independent of hypothermia-induced bradycardia because it persists after heart rate normalization using a pacemaker(55). The decreased metabolic activity, however, does not seem to be the sole mechanism related to cardioprotection induced by hypothermia. There are evidences of reduction in lipid peroxidation, in free radical production, and lower values of extracellular 2, 3-dihydrobenzoic acid, an indicator of free radical production. Hypothermia helps in the preservation of cell's ATP reserves during ischemia. Animal models of acute MI shows that the cardioprotective effects of hypothermia include: smaller infarct size, preservation of microvascular flow and maintenance of cardiac output. The intensity and duration of hypothermia are determined according to the surgical procedure to be performed. Despite the beneficial effects of hypothermia on organ protection, increasing the duration of hypothermia seems to have paradoxical effects, worsening ischemia-reperfusion myocardial injury. Deep hypothermia for prolonged periods may exacerbate intracellular calcium overload and induce the formation of peroxides and reactive oxygen species(56). Other undesirable side effects of hypothermia are electrolyte disturbances, which is related to coagulopathy and immunosuppression(57), increase in systemic vascular resistance, changes in metabolism and clearance of drugs.

3. Neurologic protection

Neurological injuries after cardiac surgery involve a number of disorders that includes stroke, encephalopathy, and cognitive dysfunction(58). In a large multicenter prospective investigation, it was found that around 6.1% of patients had some type of postoperative neurological complication (59), half of them with type I neurological outcomes, involving death as a result of cerebral injury, nonfatal strokes, transient ischemic attack and stupor. The other half had type II neurological outcome with intellectual function deterioration or seizures(59). In another large study, when no stroke or encephalopathy was present, the hospital mortality was 1.4%, but patients with sustained cerebrovascular accident presented a mortality of 22%, whereas those with encephalopathy had a hospital mortality of 7.5%(60).

The risk factors that are associated with neurological disorders after CPB include history of cardiac failure, diabetes, the presence of extracoronary vascular disease, difficult weaning from bypass; intraoperative mean arterial pressure levels of less than 40 mmHg, and a large drop in hemoglobin levels during surgery (61).

Along with other mechanisms, embolism has been related to neurological disorders in postoperative period and, according to size, embolus can be divided into macro (greater than 200 micrometers) or microemboli (less than 200 micrometers)(62). The clinical manifestations depends on the size of emboli and, consequently, on vessel diameter that it occludes(62). Macroembolus might result in hemiplegia, while a solitary microembolus is unlikely to have an important clinical effect, excluding very susceptible tissues (i.e. retina)(62). The microembolus may have greater clinical manifestations when they are numerous, showing a diffuse lesion in the central nervous system(62). The types of emboli are constituted of gas bubbles (air or anesthetics, in particular nitrous oxide), biologic aggregates (thrombus, platelet aggregates, and fat), inorganic debris (fragments of polyvinyl chloride tubing, and atheroembolism) (62, 63). Another mechanism implied in postoperative neurological disorder is the excitotoxicity, which involves the damage of neurons induced by excessive stimulation with neurotransmitters, in special glutamate, causing acute neuron necrosis during and immediately after the exposure and delayed-onset apoptosis(64).

Neuroprotective strategies include the prevention of: hyperthermia (>37°C) during the rewarming phase; of rapid rewarming after hypothermic CPB; of hyperglycemia; and of introduction of emboli and fat globules by cardiotomy suction(60). Regarding the aorta, the minimization of its manipulation and epiaortic scanning to detect unrecognized aortic atheroma helps to reduce atheroembolism(60). Also, arterial line filters should be used(60). No class I recommendations to minimize neuronal excitotoxicity have been proposed yet. These strategies focus on micro and macroemboli reduction and prevention of hypoperfusion and ischemia(60).

The potential neuroprotective action of volatile anesthetics is related to an increase in cerebral blood flow in ischemic regions, the suppression of seizures, reduced brain metabolism, inhibition of lactic acidosis and the release of excitatory neurotransmitters, preventing the pathological influx of Ca2+ and Na+, inhibition of lipid peroxidation, reducing the formation of free radicals and stimulation of anti-apoptotic processes. This diversity of cited neuroprotective mechanisms resulted from studies that used different anesthetic conditions and different models of cerebral ischemia and incorporated different controls of physiological variables including brain temperature and plasma glucose. Experimental studies of hemispheric ischemia, global or incomplete demonstrated that

volatile anesthetics can reduce the size of cerebral infarction and improves neurological recovery when administered before the ischemic test(65-69). This neuroprotective effect appears to be partly related to the maximal suppression of cerebral metabolism of volatile anesthetics at concentrations above 2 CAM, concentration which corrects the imbalance between supply and oxygen consumption(67). The volatile agents also decrease the frequency and increase the time onset of ischemic depolarization(70) and partially inhibit the release of lactate dehydrogenase resulting from the activity of NMDA (N-methyl-D-aspartate) and AMPA (alpha-amino-D-hydroxy-5-methyl-4-isoxazol-propionate) receptors(71).

These experimental data are consistent with clinical observations, where patients anesthetized with sevoflurane were more tolerant to reductions in cerebral blood flow during carotid endarterectomy (72). Similarly, the incidence, extent, and duration of the episodes of cerebral oxygen deprivation seem to be lower in neurosurgical patients anesthetized with volatile anesthetics.

Some intravenous anesthetics have been implicated to have neuroprotective properties. The effects of barbiturates on neuroprotection were at first attributed to the reduction in the cerebral metabolism, but recent studies have shown that this does not appear to be the sole mechanism involved(73). Although barbiturates are well-known to have neuroprotective properties, a review done with randomized or quasi randomized trials by Cochrane from December 1996 to April 1999 showed no evidences that barbiturates in severe head injury could improve outcomes(74). This review also concluded that barbiturates would cause a decrease in blood pressure that would offset the reduction in the intracranial pressure effect, and this could deteriorate the cerebral perfusion pressure(74).

Propofol has been shown to have in vitro(75) and in vivo(76) neuroprotection properties, but this profile is still controversial(77, 78). For ketamine, the widely known concept that it causes an increase in the intracranial pressure is currently under review. In mechanically ventilated head-trauma patients sedated with propofol, doses up to 5mg/kg of ketamine did not alter cerebral hemodynamics nor increased the intracranial pressure(79). As with propofol, ketamine's neuroprotective properties are still controversial.

Controlled hypothermia has also neuroprotective properties, especially after CPR. Patients under controlled hypothermia presented with better neurologic outcomes and lower mortality rates after cardiac arrest than under mild to moderate hypothermia(80-82). Close monitoring should be made in patients during controlled hypothermia due to risks of coagulopathy and bleeding, mainly after percutaneous coronary interventions, arrhythmias and electrolytes disturbances(82, 83). The association of neuroprotective intravenous anesthetics and hypothermia can have an even higher neurologic protection.

Considering the spinal cord, it is known that paraplegia is one of the most devastating complications of aortic surgery and an understanding of spinal cord perfusion has become important in the attempt to minimize the frequency of spinal cord injury(84). Monitorization of somatosensory-evoked potential, motor-evoked potential, strategies of spinal fluid drainage, distal perfusion, and specific surgical techniques in addition to the protection of hypothermia and anesthetic drugs can contribute to optimize the outcome.

4. Pulmonary protection

The changes in lung function have been reported since the first heart surgery with extracorporeal circulation(85), with a low incidence of respiratory distress syndrome and a

high incidence of atelectasis . During cardiac surgery with cardiopulmonary bypass, lungs are exposed to insults of mechanical ventilation(86), ischemia-reperfusion injury, hypothermia(87), blood transfusions(88, 89) and contact of blood with non endothelized circuit and membrane oxygenator. All of these situations triggers inflammatory reaction and cause lung injury. The resultant alterations in respiratory function observed on postoperative period can prolong mechanical ventilation. Despite major advances in surgical, anesthetic techniques, and equipment for cardiopulmonary bypass, pulmonary complications, which are expressed mainly in the postoperative period, remains a great challenge and are important causes of morbidity and mortality (90, 91).

Although off-pump surgeries can reduce pulmonary changes, it doesn't avoid completely postoperative respiratory changes. Many strategies can be used to minimize or prevent lung injury related to cardiopulmonary bypass, such as (87) reduction the length of cardiopulmonary bypass, the use of miniaturized CPB circuits, heparin-coated circuits and filters can be helpful. The adequate myocardial protection, as well abbreviation of pulmonary ischemia-reperfusion, is important in the prevention of postoperative lung dysfunction**.** Routine use of antifibrinolytic and corticosteroids have controversial effects in the postoperative respiratory outcome.

5. Renal protection

The sensibility of kidneys to ischemic insults can culminate in acute kidney injury (AKI), more common in large surgeries and where extensive bleeding is present, especially if associated with hemodynamic instability, and is an independent risk factor for hospital mortality(92). Although acute renal failure requiring renal replacement therapy after cardiac surgery is rare, it has a devastating impact on outcome(93).

The incidence of postoperative AKI involves multifactorial mechanism, including hemodynamic, inflammatory and nephrotoxic factors(94). The risk factors for post-operative renal injury include increased intra-abdominal pressure, hyperglycemia, inadequate maintenance of the intravascular volume, the use of nephrotoxic drugs (i.e. radiologic contrast), duration of the CPB, and postoperative drugs(95). Also, the inflammatory response associated with the surgery, the formation oxygen-reactive species, and immune response can promote renal injury(96).

Some strategies have been suggested to prevent AKI in perioperative setting. Hypovolemia is attributed as an important risk factor for AKI and fluid therapy is implicated in diminishing the incidence of renal dysfunction, although no controlled randomized trial has directly addressed this issue(96). Currently, restrictive fluid replacement, based on goals rather than pre-defined values appear to reduce morbidity following colorectal surgery. One strategy based therapy is associated with the use of esophageal Doppler, using corrected flow time in the descending aorta and stroke volume response to a fluid challenge(97, 98). Intraoperative intravascular volume loading to optimize stroke volume is associated with a more rapid postoperative recovery and a reduced hospital stay(98). The recommendation for fluid resuscitation is to avoid 10% hydroxyl-ethyl starch 250/0.5, strategies for patients with risk of contrast nephropathy (listed below), prophylactic volume expansion with crystalloids to prevent AKI, especially with known nephrotoxic drugs(99). Also, based on the same Joannidis et al. recommendations, loop diuretics should not be used to prevent AKI(99).

Iodinated contrast has also been associated with AKI. Currently, N-Acetylcysteine and isotonic intravenous bicarbonate have been investigated, but the data supporting these interventions are controversial mainly due to methodological limitations(100). Atrial natriuretic peptide, statins and prostaglandin analogs are under study and there are some evidence of their benefit, but no large, adequately power study is present(100). Currently no grade IA recommendation exists regarding renal protection to iodinated contrasts. Prophylactic volume expansion without hydroxy-ethyl starch and sodium bicarbonate for emergency procedures appears to be beneficial in patients at risk of contrast nephropathy(99).

Pharmacological interventions, such as the use of fenoldopam, are currently under study, but large trials with adequate power are still needed in order to recommend the routine for prevention of renal failure. Atrial natriuretic peptide (ANP) is another drug implicated in renal protection, and low doses of ANP can provide better outcomes when used in low doses in the prevention of AKI and in the postsurgery management(96, 101). Inhalational and intravenous anesthetics can also have effects on renal protection(102). When comparing propofol and sevoflurane, propofol was associated with renal protection during an episode of ischemia and reperfusion in a swine model with lower levels of plasma creatinine(103). Also, lower neutrophil infiltrates, plasmatic cytokines, free radical production, lipid peroxidation and inducible nitric oxide synthase activity were found when propofol was used, suggesting a possible renal protection(103).

In conclusion, only a few recommendations exist regarding renal protection. Most of them are common sense based, maintaining adequate blood pressure, fluid therapy and avoiding the use of nephrotoxic drugs(99, 102).

6. Liver protection

Hepatic injury in cardiac surgery is not frequent but is associated with significant morbidity and mortality. High index of suspicion postoperatively will lead to earlier treatment directed at eliminating or minimizing ongoing hepatic injury while preventing additional metabolic stress from ischemia, hemorrhage, or sepsis(93). Protection may be conferred by modulating the perfusion protocol during bypass and pharmacological interventions which modify the inflammatory response to surgery(104).

The principle underlying the protective ischemic preconditioning is a limitation to the exposure of the liver to ischemia, thus allowing the activation of natural defense mechanisms against subsequent injury(105). Several mechanisms of injury determined by a period of ischemia followed by reperfusion are known. These mechanisms, involving cytokines and oxygen free radicals, determine both local and systemic injury(106) and the nitric oxide plays a crucial role in protection. This effect can last for a few days(107). The possibility of remote (inter organ) preconditioning is a recent observation in which brief ischemia of one organ has been shown to confer protection on distant organs, such as liver, without direct stress to the organ(108), but effective clinical use of this resource needs additional studies.

Despite many advances in preoperative evaluation, technological, pharmacological, surgical, and anesthetic techniques, cardiac surgery continues to cause major organ derangement. There are many unanswered questions regarding perioperative organ protection and many promising therapies may continue to improve postoperative outcome. Considering the evolution of anesthetic and surgical techniques, patients are currently

submitted to surgery with severe diseases and extreme ages. Anesthesiologists are often faced with patients who have heart disease or hemodynamic instability. The combination of anesthetic and postoperative sedation with appropriate cardioprotective anesthetics agents may contribute to the prevention of organ dysfunction and contribute to the reduction of perioperative morbidity and mortality.

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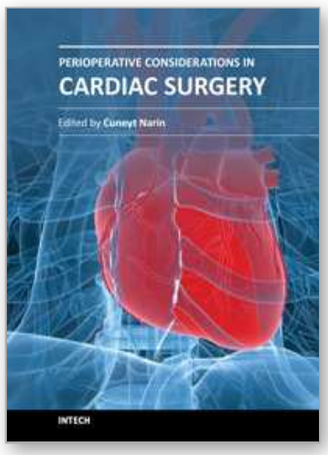

Perioperative Considerations in Cardiac Surgery

Edited by Prof. Cuneyt Narin

ISBN 978-953-51-0147-5
Hard cover, 378 pages
Publisher InTech
Published online 29, February, 2012
Published in print edition February, 2012

This book considers mainly the current perioperative care, as well as progresses in new cardiac surgery technologies. Perioperative strategies and new technologies in the field of cardiac surgery will continue to contribute to improvements in postoperative outcomes and enable the cardiac surgical society to optimize surgical procedures. This book should prove to be a useful reference for trainees, senior surgeons and nurses in cardiac surgery, as well as anesthesiologists, perfusionists, and all the related health care workers who are involved in taking care of patients with heart disease which require surgical therapy. I hope these internationally cumulative and diligent efforts will provide patients undergoing cardiac surgery with meticulous perioperative care methods.

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