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Anesthesia in Cardiac Surgery

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1. Introduction

The cardiac surgical procedures are increasingly performed each year up to a number >700000 (data in 1997 in US) per year, of which >600000 are coronary artery bypass grafting (CABG) procedures. After 1997, there has been a gradual decrease in CABG procedures as percutaneous coronary interventions (PCI) grow. In 2005, a total of 699000 cardiac surgical procedures were reported, including 469000 surgical coronary revascularization procedures. It is still debated whether CABG procedures will continue to decrease as relative benefits of PCI continue to be evaluated. As the number of aging population increases and risk factors (e.g., obesity and diabetes) occur, cardiovascular diseases are also estimated to increase; however, it is not clear that changes in life style or advancing medical management will reduce the prevalence and incidence of these diseases. Although the cardiac surgery is not the primary solution, CABG procedures are still the most commonly performed cardiac procedures and it will remain one of the management options (Thys, 2009; London et al, 2008).

There is an explosive growth in these procedures due to improvements in operative outcomes, inclusion of older and sicker patients for cardiac surgeries and expansion of these surgeries to community hospitals. However, although the physicians develop greater confidence and capacity to perform the procedures, the morbidity, mortality and resource utilization are still higher in the elderly population; especially in octagenarians. Scott et al. (2005) reported longer intensive care unit (ICU) and hospital stay with higher rates of postoperative renal failure and neurologic complications; and Baskett et al. (2005) reported more death and stroke after CABG in octagenarians. As the cardiac surgical procedures grow with an aging population with increased mortality and morbidity, more anesthesiologists become specialized in cardiovascular anesthesiology, practicing cardiac anesthesia exclusively in active cardiac surgical centers; changing their focus from anesthetic management of patients with cardiovascular diseases to cardiovascular medicine; medical and surgical management of cardiovascular patients (Thys, 2009).

2. Anesthetic management

The primary goal of cardiac surgery is not just a minimally acceptable outcome where the patient survives without life-threatening complications or persistent clinically manifest

organ dysfunctions or simply hospital survival; but a healthy, productive long-term survivor (Murphy et al,2009).

Anesthetic protocols in cardiac surgery are investigated and analyzed in terms of their effect on postoperative mortality and incidence of myocardial infarction following cardiac surgery, postoperative cardiac troponin release, need for inotropic support, time on mechanical ventilation, ICU and hospital stay (Landoni et al,2009).

2.1 Preoperative evaluation and premedication

In order to reduce the fear and anxiety of the patient, provide analgesia for painful interventions such as vascular cannulation before anesthetic induction and to provide amnesia to some degree, pharmacological interventions are used. These agents are also supposed to prevent the anginal episodes which are clinically silent preoperatively. Oral, intravenous or intramuscular benzodiazepines are the agents that are most frequently chosen (London et al,2008). Agents and their dosages to be selected depend on the patients' age and physiologic status. High doses are desirable for the patients with coronary artery disease, whereas low doses are more appropriate for patients with valvular diseases whose physiologic status is compensated with enhanced sympathetic tone (Liu et al,2004). However, on arrival to the operating room the patients may receive further medications in case of an inadequate sedation, prior to the interventions that are planned before the induction. The beneficial effects of premedication should also be secured by the proper conditions of the operating room including the temperature and also the verbal interaction with the patient (London et al,2008).

Most popular premedicants

For anxiolysis and amnesia;

- Diazepam oral: 0.1-0.15 mg/kg
- Midazolam intravenous: 1-2 mg

For analgesia;

- Morphine intramuscular: 0.1-0.15 mg/kg
- Fentanyl intravenous: 50-75 µg

The anesthetist has an important role in preoperative administration of cardiovascular medications especially the anti-anginal medications, ensuring that these agents are ordered for morning with sips of water, as the cardiac anesthesiologist is becoming a 'perioperative physician' (London et al,2008).

2.2 Monitoring

On arrival to the operating room, before induction of anesthesia, preoxygenation, monitoring with pulse oximetry, ECG, non-invasive BP and radial artery cannulation for ABP, ECG and also for the high-risk patients central venous catheters and pulmonary artery catheter should be in place (Reich et al,2008).

2.2.1 Electrocardiogram (ECG)

A multi-lead ECG system with a continuous paper writeout and online ST-segment trending system is useful in early diagnosis of myocardial ischemia and detecting arrhythmias. Also a preinduction rhythm strip or frozen on the monitor screen may help to assess the changes intraoperatively (Morgan et al,2002). An angiographically identified areas that are at risk for transmural ischemia can be observed more sensitively by specific placement of the leads

(Reich et al,2008). The electrocautery may interfere with ECG recordings resulting in difficulty in dysrhythmia analysis in the operating room (Morgan et al,2002).

2.2.2 Arterial blood pressure monitoring (ABP)

The radial artery is used for the CABG procedures to monitor the blood pressure. The cannulation is applied before anesthetic induction in order to observe the hemodynamic response closely (Reich et al,2008). Radial artery cannulation requires the testing of the competency of ulnar collateral circulation of the hand in case of radial artery thrombosis. This test is the Allen test; however it is not completely reliable. Some centers prefer the non-dominant side for cannulation and some other prefer to use the side opposite to the proposed internal mammary artery dissection to avoid inaccurate measurements caused by the sternal retractors tenting the subclavian artery. Furthermore, after the period of hypothermia there can be alterations in the measurements from radial artery (lower than aortic pressure with a gradient 10-30 mmHg) which is mainly caused by decreased vascular resistance. Temporarily measuring blood pressure directly from the aorta via a needle or cardioplegia cannula can be an acceptable approach (Morgan et al,2002).

2.2.3 Central venous cannulation

Cardiac surgery is associated with large fluid shifts and need for multiple drug infusions (Morgan et al,2002). In order to measure pressure to regulate volume infusion and for both volume and vasoactive drug administration, central venous catheterization (CVC) has become a routine practice (London et al,2008). CVC is used for measuring the right ventricle (RV) filling pressures giving an estimate for intravascular volume status and RV function. For accurate measurement of the pressures, the catheter tip should be in one of the large thoracic veins or the right atrium. With a short and straight course to the right atrium (RA) assuring RA or superior vena cava (SVC) localization of the catheter tip, internal jugular vein is preferred for the site of this central catheterization (Reich et al,2008).

Following serial measurements to observe the trends is more reliable and safe when compared to individual numbers. Central venous pressure (CVP) is not a direct indicator of left heart filling pressure, but it may provide an estimate for these pressures in patients with good LV function. The catheter can also be used for both indicating the RA pressures and cerebral venous pressure if the tip is in SVC. The increase in CVP may result in a decrease in cerebral perfusion pressure. Occasionally this may be caused by a malposition of the catheter during CPB, which is to be corrected immediately by the surgeon to avoid cerebral edema and poor cerebral perfusion (Reich et al,2008).

CVC may be applied before induction using sedation including small doses of midazolam and fentanyl supplemented by oxygen via a face mask avoiding hypoxia, or after induction of anesthesia. Multi-lumen catheters allow for both fluid administration and drug infusions at the same time (Morgan et al,2002).

2.2.4 Pulmonary artery catheterization (PAC)

The PAC providing various physiologic information has been shown to have little effect on clinical outcome, leading to a lower use currently; decreased 60-80% over the past decade. Although the criteria to use PAC have not been demonstrated clearly, it is recommended to be reserved for high-risk patients, as the patients with multi-system dysfunction are increasingly scheduled for cardiac surgical procedures (Reich et al,2008).

High-risk patients requiring PAC (Reich et al,2008)

1. Significant impairment of ventricular function
 - EF<40%
 - Acute or Chronic congestive heart failure
 - Elevation of left ventricular end-diastolic pressure (LVEDP) on preoperative catheterization
 - Need for preoperative intraaortic balloon pump (IABP)
 - Acute or chronic severe mitral regurgitation due to ischemia
 - Ventricular septal defect after myocardial infarction
 - Other mechanical complications
2. High-risk for intraoperative ischemia or difficult revascularization
 - Recent, large myocardial infarction
 - Severe unstable angina
 - Known poor revascularization targets or severe microcirculatory disease
 - Reoperation
 - Catheterization laboratory PCI 'crash'
3. Severe co-morbidities
 - Renal failure (need for dialysis)
 - Severe chronic obstructive pulmonary disease
4. Combined procedures that prolongs the duration of surgery or add significant blood loss (CABG-carotid, other vascular procedures)

PAC provides detailed information with various parameters such as PCWP, PA diastolic pressure and derived parameters, estimating the left ventricular filling pressures-preload more precisely than CVC (Reich et al,2008;Morgan et al,2002). However, there are some limiting factors altering the accuracy of these measurements such as mitral stenosis, LA myxoma, pulmonary venous obstruction, elevated alveolar pressure, decreased left ventricular compliance and aortic insufficiency; which are to be considered during the anesthetic management (Reich et al,2008).

2.2.5 Transesophageal echocardiography

One of the earliest signs of acute myocardial ischemia is diastolic dysfunction followed by systolic segmental wall motion abnormalities which occurs within seconds after acute coronary occlusion. Coronary artery disease is associated with segmental wall motion abnormalities more than ECG changes. However, these wall motion abnormalities are not specific for myocardial ischemia; that they may occur during CABG procedure due to loading conditions altering pre- and afterload, transient motion abnormalities caused by myocardial stunning during the ischemic periods of weaning from CPB and also inotropic agents or elevated catecholamine levels. TEE is recommended for high-risk patients for myocardial ischemia with a category II indication (*TEE may be helpful in improving clinical outcomes*) by ASA. This indication is strengthened when ECG cannot be used for detection of ischemia in situations such as the existence of LBBB, extensive Q waves or ST-T segment changes on baseline ECG. However, it is weakened when there are wall motion abnormalities due to fibrotic, calcified or aneurysmal myocardium at the baseline (London et al,2008).

Category I indications (*TEE is useful in improving clinical outcomes*) for the usage of TEE includes, suspected thoracic aortic aneurysm-dissection or disruption in unstable patients

in the preoperative period; life-threatening hemodynamic disturbance, valve repair, congenital heart surgery, hypertrophic obstructive cardiomyopathy repair, endocarditis, aortic valve function in aortic dissection repair, evaluation of pericardial window procedures intraoperatively and unexplained hemodynamic disturbances in ICU setting. Category II (*TEE may be helpful in improving clinical outcomes*) indications include hemodynamic disturbances, cardiac aneurysm repair, tumour excision, air emboli, intracardiac embolectomy, aortic dissection repair, pericardial surgery and also increased risk of myocardial ischemia. Category III (*TEE is infrequently useful in improving outcomes*) indications include evaluation of myocardial perfusion, coronary artery anatomy, graft patency, repair of non-HOCMs, endocarditis in non-cardiac surgery, monitoring emboli in orthopedic surgeries, repair of thoracic aortic injuries, uncomplicated pericarditis, pleuropulmonary disease, monitoring cardioplegia administration and also placement of IABP, ICD or PA catheters (Roscoe,2007).

2.3 Anesthetic induction

Anesthetic induction of cardiac surgical patients requires titration of drugs in order to avoid any increase in oxygen consumption and decrease in oxygen supply. Titration of induction agents with monitoring of the hemodynamics is more important than the type of the drug chosen (Barnes,2002a). During induction hypertension and tachycardia in patients with normal ventricular function, hypertension and LV hypertrophy should be avoided as well as hypotension and myocardial depression in patients with depressed ventricular function or stenoses. These agents should also provide smooth intubating conditions for those patients. These major concerns of cardiac anesthetic practice can be managed by using small doses of vasopressors for hypotension and by deepening anesthesia or administering β -blockers for the hyperdynamic responses. In terms of intraoperative ischemia, postoperative myocardial infarction or death, there is no single technique superior to others (London et al,2008).

The choice of the anesthetic method depends mainly on left ventricular (LV) function and whether the patient is suitable for early extubation or not. LV function determines the dosages of the anesthetic agents depending on the hemodynamic response of the patient. Early extubation is a desired method in order to reduce the postoperative need for mechanical ventilation resulting in shorter periods of ICU stay, decreasing the cost. There is no single strategy to be recommended for all cardiac surgical patients; hypnotics, opioids and volatile anesthetics are used in different combinations for both the induction and maintenance of anesthesia (London et al,2008).

2.3.1 Thiopental

Thiopental is the sulphur analogue of the oxybarbiturate pentobarbitone. It is used 3-7 mg/kg intravenously for the induction of anesthesia, rapidly entering the CNS and producing unconsciousness within 30 seconds (Peck,2006; Stoelting&Hillier,2006). The dose that is required for induction depends on patients' age (decreasing with age), weight and cardiac output (Stoelting&Hillier,2006). At sufficient plasma concentrations which is most easily maintained by continuous infusion, thiopental produces an isoelectric EEG, contributing to a maximal reduction of cerebral oxygen requirements. At these concentrations inotropic support may be required to maintain adequate cerebral perfusion (Peck,2006). However, thiopental is seldom used as infusion, because of its long context-sensitive half-time leading to a prolonged recovery period (Stoelting&Hillier,2006).

Thiopental causes a dose-dependent reduction in cardiac output, stroke volume and systemic vascular resistance associated with a compensatory tachycardia. At a dose of 5 mg/kg intravenous thiopental causes a transient 10-20 mmHg decrease in blood pressure with a compensatory 15-20 bpm increase in heart rate. A decrease in myocardial contractility may occur, however it has been shown to be a less reduction when it is compared to volatile anesthetics (Stoelting&Hillier,2006).

Along with the induction of anesthesia with barbiturates mild and transient reduction in systemic blood pressure occurs, which mainly depends on the peripheral vasodilation, depression of the medullary vasomotor center and decreased sympathetic outflow. These minimal alterations in blood pressure and cardiac output with barbiturate induction mainly depend on carotid sinus-mediated baroreceptor reflex responses offsetting the effects of vasodilation. This mechanism explains the vulnerability of the hypovolemic patients to the effects of barbiturate induction (Stoelting&Hillier,2006).

The adverse effects including airway resistance, bronchospasm and postoperative nausea and vomiting, have led to a tendency towards the use of propofol, especially depending on its predictable pharmacokinetics and dynamics (London et al,2008).

2.3.2 Propofol

Propofol is an isopropylphenol (2,6 diisopropylphenol), replacing the barbiturates for induction, particularly for operations where rapid awakening is desirable, because of the complete awareness after propofol without any residual CNS effects (Peck,2006;Stoelting&Hillier,2006). The major advantage of using propofol as a part of the anesthetic protocol is the early extubation leading to reduced costs by shortening the LOS in ICU (D'Attelis et al,1997; Myeles et al,1997).

In healthy adults the induction dose of propofol is 1.5-2.5 mg/kg intravenous, with a 25-50 % reduction to be used in elderly patients, with 2-6 µg/ml blood level producing unconsciousness depending on combined medications and age, and 1-1.5 µg/ml blood level resulting in awakening (Stoelting&Hillier,2006).

Propofol decreases systemic blood pressure with corresponding changes in cardiac output and systemic vascular resistance. The blood pressure effects may be overt in hypovolemic patients, elderly patients and also patients with coronary artery disease compromising the left ventricle. Adequate hydration is often recommended to offset this effect of propofol. Unlike the effect of thiopental on blood pressure compensated by the increase in heart rate, propofol does not change heart rate. Furthermore, bradycardia and asystoli may also occur most probably because of the reduction in sympathetic outflow more than parasympathetic. It has been shown not to have any effect on sinoatrial or atrioventricular node in normal patients and patients with WPW syndrome allowing the usage of this drug for ablation procedures (Stoelting&Hillier,2006).

2.3.3 Etomidate

Etomidate is an imidazole derivative and an ester, which is used as an alternative to propofol and thiopental for induction of anesthesia, at a dose of 0.2-0.4 mg/kg intravenously, especially in patients with unstable hemodynamics, because of its least cardiovascular disturbance when compared to other agents (Peck,2006).

After induction, involuntary myoclonic movements can occur, which can be attenuated by using opioids. Awakening after a single dose is more rapid than barbiturates, however duration of action prolongs with intermittently increased dosage or continuous infusion.

The main limiting factor of usage is the depression of adrenocortical function (Stoelting&Hillier,2006).

The peripheral vascular resistance may fall slightly but there occurs no change in myocardial oxygen supply, contractility, stroke volume, cardiac output and blood pressure. In a dose-dependent manner, especially at the concentrations more than in clinical practice, etomidate may result in cardiac depression (Peck,2006;Stoelting&Hillier,2006).

2.3.4 Ketamine

Ketamine is a phencyclidine derivative, which results in a 'dissociative anesthesia' caused by the dissociation between thalamocortical and limbic systems. The dissociative anesthesia mimics a cataleptic state contributing to open eyes with slow nystagmic gaze; that wakefulness may appear to be present. Amnestic and analgesic properties are profound (Peck,2006;Stoelting&Hillier,2006).

Unlike other induction agents, ketamine produces sympathetic nervous system stimulation with a rise in circulating levels of adrenalin and noradrenalin; increasing the heart rate, cardiac output, blood pressure and myocardial oxygen requirements (Peck,2006). These stimulating effects may be blunted by combination of ketamine with benzodiazepines or opioids or inhaled anesthetic agents (Stoelting&Hillier,2006). It does not seem to precipitate arrhythmias (Peck,2006).

Induction doses of ketamine is 1-2 mg/kg intravenously and 2-4 mg/kg intramuscularly, allowing unconsciousness within 30-60 seconds and 2-4 minutes, respectively. Awakening or return of consciousness occurs 10-20 minutes after induction, but full consciousness takes 60-90 minutes. Intermittent doses or continuous infusions lead to prolonged emergence times (Stoelting&Hillier,2006).

2.3.5 Midazolam

Midazolam can be used for anesthetic induction with a dose of 0.1-0.2 mg/kg intravenously administered over 30-60 seconds. However, thiopental usually produces 50-100% faster induction when it is compared with midazolam, furthermore awakening from general anesthesia including midazolam induction has been shown to be 1-2.5 times longer than that of thiopental (Stoelting&Hillier,2006) (see also the maintenance of anesthesia).

2.3.6 Neuromuscular blocking agents

All of the available neuromuscular blocking agents (NMBA) have been used for cardiac surgical patients. Pancuronium offsetting the bradycardia effect of high-dose opioids has been the preferred NMBA, however it has also been shown to have potential to produce a tachycardia causing myocardial ischemia during induction. Rocuronium has been compared with pancuronium and reported to provide more adequate conditions especially for fast-track anesthesia due to its less residual blockade and shorter time to extubation. Neuromuscular transmission monitoring is advised especially if fast-track anesthesia is planned (London et al,2008).

2.4 The maintenance of anesthesia

2.4.1 Intravenous anesthetic agents

The anesthesia should be adequate in order to prevent ischemia during incision and sternotomy/sternal spreading; which are the periods of hyperstimulation. Anesthetic

dosages and the type of the drugs that are to be used depend on the desire of 'fast-tracking' the patient (Barnes,2002).

High-dose opioid based anesthetic management of the cardiac surgical patients, with more stable hemodynamics providing a long-term mechanical ventilation ensuring the safety of the newly revascularized myocardium, was popular in cardiac anesthetic practice. However the growing interest in fast-track anesthesia and associated intraoperative awareness with high-dose opioid technique limited its usage (London et al,2008;Stoelting&Hillier,2006). As the sickest patients undergoing multi-vessel bypass grafting combined with valve-repair or replacement, repeat operations and other complex procedures such as ventricular septal defect repairs with CABG after acute myocardial infarction require a long duration of surgery, resulting in greater cumulative doses of anesthetic agents leading to a prolonged period of mechanical ventilation; the anesthetic management evolves into a plan including short-acting agents (e.g.sufentanil, propofol, remifentanil), avoiding agents with long half-lives (e.g.midazolam), depending mainly on volatile agents, identifying the adequate candidates and applying a 'wait and see' technique for early extubation (London et al,2008).

Combinations of opioids with benzodiazepines especially low doses of midazolam, because of its ease of use, low cost, hemodynamic stability and postoperative amnesia effects, have been used in order to overcome the adverse effects (Stoelting&Hillier,2006). However, some investigators believe that the combination of midazolam and opioids should be abandoned as general anesthetics; because they believe that this combination only provides general amnesia (Vuylteke et al,1996;Russell et al,1993;Absolam et al,2000). Midazolam has been used in combination with propofol and/or inhaled anesthetics, as well as opioids (Stoelting&Hillier,2006;Barr et al,2000;Lehmann et al,2000;Barvais et al,2000).

Remifentanil is a short-acting, esterase-metabolized without any active metabolites, rapid-onset μ -opioid receptor agonist. It provides stable hemodynamics in high-risk cardiac surgical patients. Remifentanil-propofol combination has been proven to be safe with stable hemodynamics, delivering an adequate depth of anesthesia (Lehmann et al,2000).

Sufentanil is a synthetic opioid, that has been used in combination with midazolam, propofol and inhaled anesthetics. Sufentanil combined with propofol has been shown to provide more stable hemodynamics when it is compared with fentanyl-based anesthetic protocols (Howie et al,1991).

Propofol has already been used for maintenance of anesthesia in cardiac surgical patients with reduced left ventricular function or with low cardiac output states in combination with opioids such as fentanyl, remifentanil, sufentanil or alfentanil; providing stable hemodynamics at the recommended doses of 3-8 mg/kg/hour (Philips et al,1993;Sherry et al,1995;Bailey et al,1996). In combination with ketamine propofol provides more stable hemodynamics than its combination with fentanyl (Stoelting&Hillier,2006).

2.4.2 Volatile anesthetic agents

It was commonly believed that the choice of primary anesthetic agent in cardiac anesthesia does not lead to a different outcome (Tritapepe et al,2007). In 1988, Warltier et al. (1988) reported that both halothane and isoflurane applied before ischemia improved left ventricular systolic function; in 1997 Cason et al. first described the term anesthetic preconditioning, by showing protective effect of isoflurane applied shortly before ischemia. Since then numbers of experimental studies revealed the cardioprotective efficacy of volatile

anesthetics (Landoni,2009). The first clinical trial that investigates the clinical efficacy of the halogenated anesthetics was in 2002 reporting that sevoflurane preserves global hemodynamic and left ventricular function with a lower postoperative troponin I compared with total intravenous anesthesia (Cason,1997). Desflurane has also been shown to have cardioprotective effect in terms of ICU stay and weaning from mechanical ventilation (De Hert et al,2003). Anesthetic agents were also investigated for the timing of their usage, before or after ischemic episode or continuously during the procedure; sevoflurane has been shown to exert its protective effect more when it is used throughout the whole procedure (DeHert et al,2004).

Despite these beneficial effects, it has also been shown that there is no difference in outcome of the patients with already jeopardized myocardium. The patients without previous unstable angina or recent myocardial infarction, had lower postoperative mortality after sevoflurane anesthesia (Jakobsen et al,2007). In non-coronary cardiac surgeries, desflurane and sevoflurane have also been shown to reduce troponin I release and result in better outcome in terms of incidence of atrial fibrillation and ICU stay (Landoni et al,2007a;Cromheecke et al,2006). However, volatile anesthetic agents revealed no difference in interventional cardiac procedures (Landoni et al,2009).

The lack of data demonstrating the adverse effects, primarily the coronary steal, of volatile anesthetics, the preconditioning effects of these agents, resulting in a safe and effective fast-tracking for patients especially when number of off-pump coronary revascularization is rising; has led to an anesthetic management mainly based on volatile anesthetics (London et al,2008). Volatile anesthetic agents, in comparison to TIVA, provide reductions in the rates of all major end points of cardiac surgery; reduce the risk of myocardial infarction and all-cause mortality; increasing in-hospital survival, reducing troponin I release, reducing the need for inotropic support, shortening ICU stay, time to hospital discharge and time on mechanical ventilation. These effects are valid for CABG surgery with or without cardiopulmonary bypass (Landoni et al,2009).

A recent meta-analysis the choice of desflurane and sevoflurane results in better outcome in terms of mortality and cardiac morbidity in cardiac surgical patients (Landoni et al,2007b). Although the results are controversial, the most recent American College of Cardiology/American Heart Association guidelines recommend the usage of volatile anesthetic agents for non-cardiac surgical patients at risk for MI (Fleisher et al,2007).

2.4.2.1 Preconditioning effects of volatile anesthetic agents

Myocardial infarction is one of the most serious perioperative complications, that makes myocardium one of the most important vital organ to be protected from ischemia during cardiac and non-cardiac surgeries (Landoni et al,2009; Lango&Mrozinski et al, 2010). Ischemic insult is an integral part especially of cardiac surgery, that reducing the risk of myocardial infarction has led to researches and revealed anesthetic management as an important factor in protecting myocardium.

A powerful cardioprotective phenomenon was first described in 1986, as an adaptive response to brief sublethal ischemic episodes that are exerted on myocardium, providing protection against subsequent lethal ischemia. This is called ischemic preconditioning, which is not very easy to apply clinically, because of the risk of worsening the vulnerable myocardium (Landoni et al,2009). Oxygen inflow to the heart is discontinued for short terms before the main ischemic episode in ischemic preconditioning, which has been shown to provide higher levels of ATP in myocardium and lower levels of troponin I after surgery. As

reperfusion begins, ischemia will result in rapid changes during the reperfusion period; which is called reperfusion injury contributing to impaired function of endothelium and reduced metabolism of cardiocytes. Reperfusion injury may also be attenuated by ischemic preconditioning by restoring blood flow intermittently through the organ. In order to provide optimum protection, timing becomes important as the intervention should be performed within a few minutes or during the first minute of coronary blood flow restoration (Lango&Mrozinski et al,2010). Since the ischemic preconditioning is difficult to apply in clinical practice, pharmacological preconditioning comes to our way.

In general, the mechanisms of the myocardial protection provided by anesthetic agents may include; an effect like ischemic preconditioning, prevention of excessive calcium influx to the cell, an effect like antioxidants and an effect on the relationship between neutrophil/platelet-endothelium. The signalling throughout the cell during anesthetic preconditioning include protein kinase C (PKC), protein tyrosine kinase (PTK), mitogen-activated protein kinases (MAPK), protein kinase-B, mitochondria and ion channels (sarcolemmal and mitochondrial ATP-dependent potassium channels) (Figure 1) (Lorsomradee et al,2008).

In pharmacological preconditioning, activators of protein kinases, agonists of adenosine receptors, scavengers of free radicals, opioids, ethyl alcohol, acetylcholine, bradykinin, angiotensin II, noradrenalin, platelet-activating factor were all used, but most of them can not be used for their protective effects because of their side effects or insufficient data of their clinical efficacy (Lango&Mrozinski,2010). In experimental studies, although the exact mechanism is not known, volatile anesthetic agents, known to have cardiac depressant effects that reduces myocardial oxygen demand, were demonstrated to have direct cardioprotective effects that are not related to their anesthetic or hemodynamic effects (Landoni et al,2009).

Anesthetic preconditioning depends on the concentration of the drug and also the duration of administration, it does not depend on ischemic preconditioning and does not need pre-emptive ischemic episodes, furthermore it may have only slight protective effects on the heart that is already exposed to ischemic preconditioning (Landoni et al,2009;Lango&Mrozinski,2010). There are also some factors such as β -blocker usage and perioperative hyperglycemia that may limit the effectiveness of volatile anesthetics. Volatile anesthetic agents can provide their protective effects both before and after ischemia and also during the reperfusion period. In order to achieve maximum cardioprotection in surgeries including ECC, volatile anesthetics should be used before aorta clamping at >1 MAC for longer than 15-30 minutes. Also for the postconditioning effect, to provide adequate concentrations in blood after unclamping, the agents should be initiated several minutes before unclamping via the oxygen-air supply line of ECC and continued for the first 2-5 minutes of reperfusion. The effectiveness of usage during aorta clamping and late reperfusion period has not been clearly demonstrated yet (Lango&Mrozinski,2010). As an analogy to ischemic postconditioning, anesthetic postconditioning describes the usage of volatile anesthetic agent after ischemic period contributing to the reperfusion period. This should be done within the first 2 minutes, lengthening the period does not improve the protective effects (Obal et al, 2003). The protection occurs at two stages; early, lasting for one or 2 hours and late preconditioning, reappearing after 24 hours, lasting up to 72 hours; which means that the protective effect markedly exceeds the drugs elimination time (Landoni et al,2009;Lango&Mrozinski,2010).

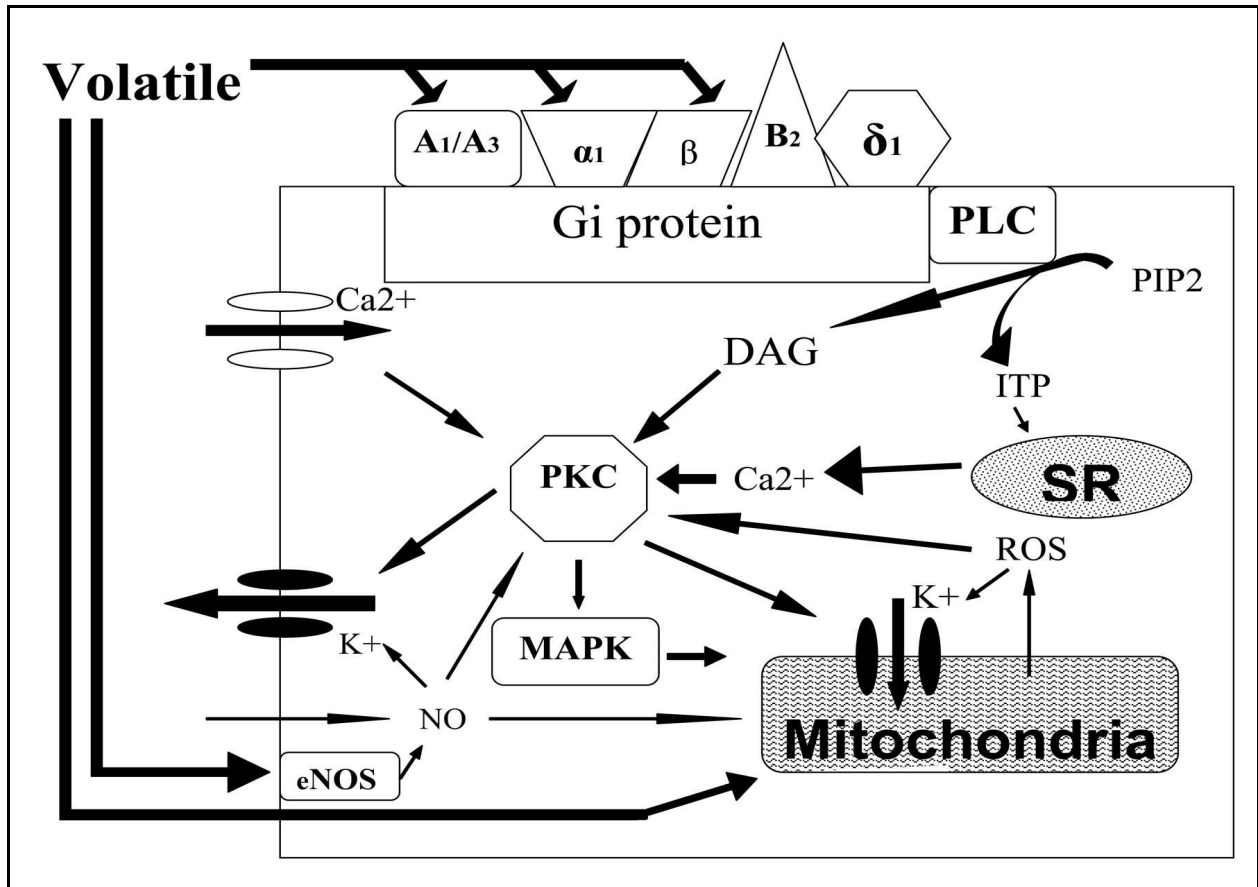


Fig. 1. The cellular mechanism of the preconditioning with volatile anesthetic agents. Volatile anesthetic agents activate phospholipase-C (PLC) and provide opening of the ATP-sensitive potassium channels by stimulating the adrenergic receptors by adenosine A1 and A3 (A1/A3) and activating nitric oxide synthase. (Lorsomradee et al,2008). B2: bradikinin receptors, Gi protein: Inhibitory guanine nucleotide binding proteins, MAPK: mitogen activated protein kinases, PIP2: phosphatidyl inositol bisphosphate, DAG: diacylglycerol, ITP: inositol 1,4,5 triphosphate, NO: nitric oxide, α_1 : α_1 -adrenergic receptor, β : β -adrenergic receptor, δ_1 : opioid receptors, PKC: protein kinase-C, ROS: reactive oxygen species, SR: sarcoplasmic reticulum (Lorsomradee et al,2008).

2.4.3 Fast-track cardiac anesthesia (FTCA)

FTCA contributes to an anesthetic management with a goal of allowing rapid recovery after surgery (Bainbridge&Cheng,2009). Fast-tracking with early extubation (4-8 hours postoperatively) has become the standard of care recently. The patients with normal LV function preoperatively and an uneventful intraoperative course, as long as the hemodynamic stability is ensured, by avoiding high doses of respiratory depressant anesthetics, with adequate rewarming and postoperative analgesia may be candidates for early extubation (London et al,2008).

The two most actively investigated methods in FTCA practice are; intraoperative narcotic that best facilitates FTCA and the pain control during the recovery period. The narcotics examined for their efficacy are fentanyl, remifentanyl and sufentanyl, which have been found to result in similar times to extubation (Cheng et al,2001;Engoren et al,2001;Mollhoff et al,2001). TEA has been reported to be superior to placebo and spinal

narcotics in terms of pain control (VAS), narcotic consumption, pulmonary complications, dysrhythmias and time to tracheal extubation. However, the risk of epidural hematoma formation limits its usage (Liu et al,2004;Ho et al,2000). A meta-analysis demonstrated that PCA in cardiac surgical patients has little benefit whereas NSAIDs provide a reduction in VAS scores and morphine consumption (Bainbridge et al,2006a,2006b). Nurse administered or patient administered narcotics combined with NSAIDs (if there is no contraindication) is the recommended approach for postoperative pain management (Bainbridge &Cheng,2009).

The delay in tracheal extubation may be caused by many factors such as; age, female sex, postoperative bleeding, inotrope use, IABP and atrial arrhythmias (Wong et al,1999). During the operation, the usage of low dosage of narcotics balanced with inhaled agents and/or propofol providing a rapid reversible state facilitates early extubation. The complications associated by inadequate control of temperature, hemodynamics, and/or coagulation may also result in delayed extubation (Bainbridge &Cheng,2009).

The criteria that is suggested for early tracheal extubation includes a stable body temperature of 36-38 C, an arterial pH >7.30, adequate arterial blood gases contributing to $\text{PaO}_2 > 70\text{-}80$ mmHg ($\text{FiO}_2 = 0.4\text{-}0.5$), $\text{PaCO}_2 < 40\text{-}45$ mmHg. The patient should be awake, cooperative, alert and able to move all extremities with adequate motor strength. The hemodynamic parameters should be stable with minimal or no need for inotropes with stable rhythm or good response to pacing. The patient should be spontaneously breathing with minimal respiratory support at a rate of >10-12 and <25-30 breaths/min with a VC>10 ml/kg, a maximal negative inspiratory force>-20 cmH₂O and a chest radiograph without major abnormalities such as atelectasis. Also adequate urine output, stable electrolytes, adequate hemostasis should be achieved (London et al,2008).

2.4.4 Regional anesthesia techniques

Advances in anesthesiology improves outcome after cardiac surgeries by combining the regional anesthesia techniques with general anesthesia. Thoracal epidural anesthesia (TEA) may enhance coronary perfusion, improve myocardial oxygen balance, reduce the incidence of tachyarrhythmias, perioperative myocardial ischemia through sympaticolytic effects; and also by providing superior analgesic effect it facilitates early tracheal extubation and may prevent respiratory complications (Svircevic et al,2011). However, because of the complications especially the epidural hematoma or abcess formation, TEA usage in cardiac surgeries is controversial. Moreover, the chronic use of antiplatelet agents, use of systemic anticoagulation and platelet inhibition for acute therapy of unstable angina and systemic anticoagulation and potential coagulopathy induced by CPB may increase the incidence of these complications (Ho et al,2000;London et al,2008). Also the systemic hypotension caused by intense sympaticolysis may be difficult to correct. The beneficial effects on respiratory system has also been shown to be provided by other strategies; such as spinal anesthesia (Cheng et al,1996; Silbert et al,1998). A meta-analysis by Liu reported that pulmonary complications can also be reduced by spinal anesthesia; as the incidence of hematoma formation is lower after a single spinal injection, this technique can be a choice for cardiac surgical patients at risk for pulmonary complications (Liu et al,2004). Also, modern general anesthetics can also provide other beneficial effects such as earlier extubation. TEA should be used with caution until its benefit-harm profile is clearly demonstrated (Svircevic et al, 2011).

2.4.5 Awareness and recall

The cardiac surgical patients are at increased risk for intraoperative awareness and recall, especially due to intentional avoidance of the cardiodepressant volatile anesthetics in the presence of hemodynamic instability, mostly caused by surgical manipulations of the heart and great vessels, leading to light anesthesia periods. As the volatile anesthetics have been proven to provide preconditioning before CPB, they began to have a major role in cardiac anesthesia protocols reducing the risk of awareness (London et al,2008).

3. Management during cardiopulmonary bypass

Cardiac surgical patients are often dehydrated and hypoglycemic on admission for the operation. Rehydrating the patient and administering sufficient glucose increase the heart's ability to tolerate ischemic arrest. Initiation of bypass results in hypotension, requiring vasoactive drugs (e.g. phenylephrine) to maintain coronary perfusion pressure (CPP). Also ventricular distention should be avoided in order to maintain CPP and avoid the reduction in subendocardial oxygen delivery. After initiation of bypass TEE helps for the intravascular volume monitoring. The heart rate should be maintained <80 bpm in patients with ischemic heart disease during the pre-bypass period. For this purpose β -receptor antagonists can be used to provide a reduction in myocardial metabolism and maximize coronary blood flow (London et al,2008).

The sternotomy is the most distressing period, particularly in reoperations, in which there is a higher risk of right ventricular perforation, damage to existing vein grafts and ventricular fibrillation caused by electrocautery energy transmission through sternal wires; requiring at least 2 units of RBC readily available in the operating room (London et al, 2008)

During dissection of left internal mammary artery, the operating table should be elevated and rotated to left, while tidal volumes are to be reduced to facilitate surgeon's exposure.

Anticoagulation is provided by administering 300-400 IU/kg heparin and its adequacy is measured by using activated clotting time (ACT) which is desired to be 450-500 seconds. Higher doses of heparin may be required in case of resistance, however resistance can be treated with 1 unit of FFP or recombinant AT III (Kanbak M, 1999;London et al,2008). If anesthesiologist is the one to administer heparin, then the central venous line is the site of injection, whilst many surgeons prefer to give heparin themselves directly into the RA. Before or after anticoagulation, antifibrinolytic therapy may be initiated for bleeding prophylaxis. Aprotinin, being once the most popular agent, has been withdrawn from the market because of the safety concerns including mortality rate, anaphylaxis and renal dysfunction. Tranexamic acid and aminocaproic acid are the major agents that can be used instead of aprotinin (Henry et al,2007;Umscheid et al,2007)(see also bleeding and transfusion).

After heparinization, aortic cannulation is established often using the ascending aorta, following the examination of the cannulation site to be free of disease (London et al,2008;Morgan et al,2002) . In order to minimize the risk of dissection during cannulation systolic blood pressure should be lowered to a lowest safe level of 90-100 mmHg (London et al,2008).

Myocardial preservation involving antegrade or retrograde cardioplegia or both, arrest with high-potassium cardioplegia and hypothermia (systemic, topical and by cardioplegia)

is provided by surgeon and perfusionist (London et al,2008). During cardiopulmonary bypass, pump flows, temperature and glucose control, blood gas analysis and management, ventilation strategies will be discussed later in this chapter.

After revascularization, with adequate rewarming (which will be discussed later in this chapter), stable rhythm-preferably sinus-good response to pacing, acceptable levels of pH, calcium, potassium and hematocrit, adequate ventilation with 100% oxygen; CPB is considered to be terminated (Morgan et al,2002). In case of a potential need, inotropes or other vasoactive drugs should be readily available. Heparin is reversed by protamin at 1:1 ratio empirically avoiding rapid injection. The TEE is removed and stomach is aspirated with an orogastric tube. The chest tubes and mediastinal drainages are secured as chest is closed and get ready for transport (London et al,2008).

3.1 Oxygen delivery during CPB

Delivery of oxygen depends on two variables that determine tissue oxygenation; hematocrit values and pump flow rates; that the calculation is: $DO_2 = \text{pump flow} \times ((\text{hemoglobin concentration} \times \text{hemoglobin saturation} \times 1.36) + (0.003 \times \text{arterial oxygen tension}))$. In the clinical setting, increasing pump flows, increasing hematocrit concentrations (transfusion of PRBCs or use of ultrafiltration for hemoconcentration), or increasing hemoglobin saturation and the amount of dissolved oxygen (increasing the inspired oxygen concentration $[F_{IO_2}]$) can improve delivery of oxygen (Lango&Mrozinski,2010).

Delivery of oxygen during CPB is typically less than that measured in the awake and anesthetized subjects. This is primarily caused by the decrease in the arterial oxygen content that occurs from hemodilution at the onset of bypass. The reduction in the DO_2 is compensated by increasing the oxygen extraction ratio which narrows the safety margin between oxygen supply and demand. At first this compensation maintains oxygen consumption (VO_2) stable (flow independent oxygen consumption), when the maximum extraction ratio is reached VO_2 and tissue oxygenation begin to decrease and lactic acidosis develops (flow dependent oxygen consumption). The critical DO_2 has not been defined, although there are many trials investigating this value; however it is shown that the organs undergoing bypass have hierarchy, that with a low pump flow the DO_2 of the brain is maintained at the expense of other organ systems; kidneys, pancreas, muscle beds. In order to preserve organ functions there should be a critical value to be targeted for DO_2 rather than targeting pump flow rates or a specific hematocrit value (Lango&Mrozinski, 2010; Ranucci, 2009).

3.1.1 Hemodilution

Hemodilution is used during the CPB to offset the effect of hypothermia on blood viscosity and reduce the need for blood transfusion. However with the decreasing hematocrit level, the oxygen carrying capacity decreases and brain compensates for it by increasing CBF and tissue oxygen extraction; which leads to increased embolic load. Although an optimum level for hematocrit during CPB has not been clearly defined, there is data supporting the reservation of transfusion of blood products for the hemoglobin levels of <6 g/dl during CPB and <7 g/dl after surgery (Ferraris et al,2007). When there is a risk for end-organ ischemia these critical values can be increased by 1-7 gr/dl during CPB. Also it is important to know that the critical values can be altered by the clinical situation of the patient (Grogan et al,2008).

Extreme hemodilution in the elderly should be avoided; a decrease in hematocrit from baseline of 12 percentage points or greater has been shown to be associated with neurocognitive decline (Lombard et al,2010).

Recent guidelines state that heparin-coated bypass circuits (oxygenator alone or the entire circuit) are not unreasonable for blood-conservation (Class IIb, LOE B) (Lango&Mrozinski,2010;Ferraris et al,2007).

Methods to limit the degree of hemodilutional anemia (Lango&Mrozinski,2010)

- Delaying elective surgery to restore red cell mass to normal levels by using iron, erythropoietin
- Limiting the volume of crystalloid administered pre- and post-CPB
- Reducing blood sampling in the perioperative period
- Using retrograde autolog priming of the CPB circuit
- Minimizing tubing size
- Using miniaturized CPB circuits

3.1.2 Intraoperative hemodynamics

Small and microvascular disease could be a leading cause of dementia in up to two thirds of the patients with dementia. The patients who have dementia at baseline have higher incidence of postoperative cognitive dysfunction, that may be caused by their susceptibility to cerebral hypoperfusion (Lombard et al,2010). Even clinically asymptomatic (no dementia) many patients have infarctions and abnormally perfused areas in brain; these patients are also vulnerable to cerebral hypoperfusion as the surgical population ages with structural changes leading to stiffness in their arteries (Tolwani et al,2008). Cerebrovascular disease may then result in oxygen imbalance during surgery. The use of jugular venous bulb monitoring or near infrared spectroscopy (NIRS) revealed oxygen desaturation 27-43% during rewarming period while cerebral metabolic rate increases (Croughwell et al,1994;HL,2005). DWI detects mostly the watershed stroke, which indicate hypoperfusion brain injury that has been shown to be caused by a decrease from baseline mean arterial pressure (MAP) of ≥ 10 mmHg during CPB (Gottesman et al,2006). Maintaining the pre-CPB cerebral perfusion pressures may be an acceptable approach (Burgers et al,2006). NIRS has been used for the detection of oxygen saturation in order to use interventions such as ensuring adequate CPB flow rate, raising the MAP, ensuring normocarbia, deepening anesthesia, raising FiO_2 and initiating pulsatile CPB flow; and reported to provide lower rates of major organ injury (death, myocardial infarction, stroke) and shorter ICU length of stay (Murkin et al,2007).

Blood pressure during CPB is often kept >50 mmHg, however many trials and retrospective analysis supporting high pressures as a neuroprotection strategy led the institutions to keep the MAP >70 mmHg, especially in elderly; also according to age many centers manipulate this critical value; >70 mmHg for >70 year-old, >80 mmHg for >80 year-old (Grogan et al,2008). Recent investigations report that the lower limit of cerebral autoregulation may be much higher than 50 mmHg, in awake and normotensive adults the lower limit has been demonstrated to be 73-88 mmHg (Murphy et al,2009 as cited in Larsen et al,1994;Waldermar et al,1989;Olsen et al,1995). Noting that most of the cardiac surgical patients are older, hypertensive and have preexisting cerebrovascular diseases, their autoregulatory curve becomes shifted to the right, which requires higher MAPs (>70 mmHg) to reduce the risk of hypoperfusion (Lango&Mrozinski,2010).

Optimum MAP during CPB is affected by many factors, so decision should depend on the individual case. High-risk patients may benefit from higher pressures on bypass (Lango&Mrozinski,2010).

Potential advantages of higher MAPs (Lango&Mrozinski,2010)

- Enhanced tissue perfusion in high risk patients (hypertensive, diabetic, elderly)
- Improved collateral flow to tissues at risk of ischemia
- Allows for higher pump flow rates

Potential advantages of lower MAPs

- Less trauma to blood elements
- Reduction of blood in the surgical field
- Less cardiomy suction
- Allows usage of smaller venous and arterial cannulae
- Enhanced myocardial protection (reduced collateral coronary blood flow)
- Reduced embolic load to the CNS (reduced pump flow)

Minimally safe pump flow has not been established, however the most commonly used flow rate during bypass is 2.2-2.5 L.min⁻¹.m⁻² approximating the cardiac index of a normothermic anesthetized patient with normal hematocrit. During hypothermia pump flow rate as low as 1.2 L.min⁻¹.m⁻² have been reported to have good clinical outcomes. Although there are conflicting results, most studies demonstrated that at pump flow rates of 1.0-2.4 L.min⁻¹.m⁻², CBF remains constant (Lango&Mrozinski,2010). During severe hemodilutional anemia, increasing pump flows can prevent organ injury, that pump flow may be adapted to hematocrit levels (Ranucci et al,2005). As mentioned before, targeting a critical value for DO₂ is more important than targeting pump flows or a specific hematocrit for preserving organ function (Lango&Mrozinski,2010;Ranucci,2005).

3.2 Temperature control

Hypothermia has been used for decades for cerebral protection. The beneficial effects of hypothermia mainly depend on the two physiologic principles, functional and structural cerebral metabolic need for oxygen that are both reduced by temperature; total cerebral metabolic rate of oxygen (CMRO₂) decreases 6-7 % per degree Centigrade reduction; while anesthetic drugs alter only functional CMRO₂ (Grigore et al,2009). Thiopental in particular, reduces cerebral metabolic rate required by brain function and synaptic activity, which are achieved during the isoelectric electroencephalographic state. Additional reduction is provided by concomitantly administered hypothermia while preserving CBF-CMRO₂ coupling, may also further reduce CBF. Moderate hypothermia without major suppression of neuronal function has been reported to provide better neuroprotection compared with isoelectric doses of barbiturates (Klementavicius et al,1996). Similar effect preserving coupling can be achieved by minimal alveolar concentration (MAC) or sub-MAC doses of volatile anesthetics especially isoflurane. Supramaximal doses uncouple CBF and CMRO₂. During profound hypothermia (18-20 C) CBF is disproportionately maintained and is determined more by arterial blood pressure and systemic vascular resistance than by pump flow rates (Grigore et al,2009). Moderate (28 C) and mild hypothermia (32-34 C) was shown to have no difference in terms of cognitive dysfunction, however hyperthermia (especially if the gradient between the temperatures of nasopharyngeal and CPB perfusate is >2C) in the perioperative and postoperative period is clearly associated with neurocognitive decline

(Klementavicius et al,1996). Any potential benefit for cerebral protection of hypothermia can be offset by inappropriate rewarming. More important than the use of hypothermia is avoidance of hyperthermia (Grigore et al,2009). During the rewarming period the returning warmed blood from aortic cannula is in close proximity to cerebral circulation. Also cerebral temperature may be underestimated from the usual monitoring sites (e.g.nasopharynx, esophagus) (Grogan et al,2008). Jugular bulb (JB) is the most reliable site to detect the accurate cerebral temperature, because it receives 99% of the CBF; however it takes time and money with risks associated with placing the device. Nasopharyngeal site and arterial inflow (arterial outlet of membrane oxygenator) temperatures are the closest ones to JB with a gradient of 1-2 C (Grigore et al,2009). Mild hypothermia (32-34 C), slow-rewarming during CPB (maintaining inflow temperature and nasopharyngeal temperature at or below 37 C as the maximum allowable) and avoidance of hyperthermia are the current recommendations (Grigore et al,2009;Grogan et al,2008).

The effects of hypothermia

- Reduction in cerebral metabolism
- Suppression of free radicals
- Inhibition of destructive enzymatic reactions
- Reduction in metabolic requirements in low-flow regions
- Inhibition of the biosynthesis, release and uptake of excitatory neurotransmitters



- Favorable balance between oxygen supply and demand
- Slows the onset of ischemic depolarization
- Decreases the release of ischemic-induced intracellular calcium influx
- Suppresses nitric oxide synthase activity

The effects of hyperthermia

- Increased production of free radicals
- Widening of any cerebral ischemic penumbral zone that developed intraoperatively
- Development or expansion of oxygen supply and demand mismatch
- Increased levels of intracellular acidosis
- Increase in the response of excitatory aminoacid neurotransmitters

3.3 Glucose control

In diabetic patients hyperglycemia may have caused an impaired endothelial function and may attenuate preconditioning. Serum potassium abnormalities should be corrected by glucose and acid-base management. Insulin continuous infusions are recommended for poor glycemic controls, however the possible development of insulin resistance during hypothermic CPB should be considered. Oral hypoglycemic agents; metformin may cause lactic acidosis in patients with low cardiac output state perioperatively, it is to be held several half-lives before the operation and glyburide has been shown to block preconditioning (London et al,2008).

In patients who stays more than 5 days in ICU, aggressive glycemic control was clearly proven to reduce mortality (Van den Berghe et al,2001). Similarly, in a retrospective analysis of cardiac surgical patients a predetermined glucose level (<150 mg/dl) was targeted with a continuous insulin infusion for 3 days postoperatively, had reduced risks of death and deep

sternal wound infections (Furnary et al, 2004). There are conflicting results about the association between hyperglycemia and adverse neurological outcome, and yet whether the glycemic control improves neurological outcome is not clear. In diabetic patients hyperglycemia has no influence on cognitive functions and in nondiabetic patients >200 mg/dl glucose level during CPB has been shown to increase the incidence of cognitive dysfunction (Puskas et al, 2007). Persistent hyperglycemia (>200 mg/dl) for the 24 hours after stroke, is an independent indicator for the expansion of cerebral infarction (Baird et al, 2003). AHA guidelines state that it is reasonable to initiate insulin therapy when glucose level is >140-185 mg/dl (Class IIa, LOE C) after stroke (Adams et al, 2007). The NICE SUGAR trial recommends moderate glycemic control compared to intensive control (Finfer et al, 2009).

3.4 Blood gas management

Arterial blood gas pressures are monitored during the bypass period in order to measure the adequacy of oxygenation and CO₂ exchange. Hypothermia results in a rightward shift in CO₂ dissociation (increased solubility) leading to alkalemia. There are two measurement and management techniques of arterial blood gases depending on the temperature-dependent solubility of CO₂; pH-stat (temperature corrected) and α -stat (not temperature corrected). During CPB mostly the measurement and management are done without correction. In α -stat management blood is taken from the hypothermic patient and measured at 37 C; the results are uncorrected and the patient remains alkalotic during CPB. In pH-stat management, the measured partial pressures are corrected for the patients temperatures from the published nomograms, CO₂ is added to gas mixture to correct the respiratory alkalosis and low PaCO₂. Although there are controversies about the method to be used, pH-stat has been shown to increase the incidence of cerebral injury via obliterating the pressure autoregulation of cerebral blood flow, while α -stat remains to be used in adults preserving pressure autoregulation (Oakes & Mangano, 2009).

4. Most common adverse events after cardiac surgery

4.1 Postoperative atrial fibrillation

Postoperative atrial fibrillation (POAF) is the most common atrial arrhythmia after cardiac surgery; its importance has become considerable because of the adverse effects it is associated with; such as congestive heart failure, increased need for intraaortic balloon pump, ventricular arrhythmias, cardiac tamponade, perioperative myocardial infarction, need for permanent pacemaker implantation, infection, increased postoperative bleeding, pneumonia, prolonged mechanical ventilation, increased need for tracheostomy, renal failure, stroke and neurological complications including cognitive dysfunction persisting 6 weeks after surgery, although the role of POAF as a cause of these adverse effects has not been clearly defined (Nair, 2010). POAF occurs 30% after isolated CABG, 40% after valve surgery and 50% after combined CABG and valve surgery; mostly between days 2 and 4 (Echahidi et al, 2008). The attribution of the mechanisms of atrial fibrillation in general population to POAF is difficult that it is not clear. Multiple factors such as ectopic focal depolarization originating from pulmonary veins and inferior vena cava, redistribution of fluid into vascular compartment causing atrial stretch, inadequate atrial protection during aortic cross-clamping, systemic inflammatory response syndrome thus elevated inflammatory mediators in the cardiac chambers and oxidative stress, excessive sympathetic

and parasympathetic nervous system activity, as well as physical alterations resulting from incisions to atria may cause POAF (Nair,2010; Grogan et al,2008).

Postoperative atrial fibrillation (POAF) as being associated with various adverse events should be assessed preoperatively and measures to prevent this adverse event should be considered before the operation. Most of the anti-arrhythmic agents that is to be used for prevention of POAF have their own side-effects, that prophylactic usage of these agents should be reserved for patients who are at increased risk for developing POAF. Prevention begins with identifying the patients with potential to develop atrial fibrillation after cardiac surgery (Nair,2010).

Risk factors for POAF;

- Valvular heart disease
- Right coronary artery stenosis
- Preoperative digoxin use
- Male gender
- Rheumatic heart disease
- Left ventricular hypertrophy
- Chronic obstructive pulmonary disease
- Diabetes mellitus
- Mild renal dysfunction
- Type of surgery
- Duration of surgery
- Prolonged aortic cross-clamping
- Withdrawal of beta-blockers and/or ACE inhibitors
- Bi-caval venous cannulation (vs single atrial cannula)
- Right superior pulmonary vein cannulation (for left ventricle decompression)
- Cardioplegia
- P wave duration more than 140 ms (Nair, 2010, as cited in Steinberg et al,1993)
- Left atrial appendage area $>4 \text{ cm}^2$ and post-CPB left superior pulmonary vein systolic/diastolic velocity ratio <0.5 (combined with >75 years of age; probability is 0.83)(Nair, 2010, as cited in Karthikeyan et al,2009)
- Elevated preoperative BNP/NT-BNP (N-terminal pro-B type natriuretic peptide) (Nair, 2010, as cited in Karthikeyan et al,2009)
- Perioperative use of milrinone causing elevated cyclic AMP levels (Nair,2010,as cited in Fleming et al, 2004)

4.1.1 Prevention of postoperative atrial fibrillation

Pharmacological methods

B-Blockers: The withdrawal of β -blockers is a well known cause for POAF. American Heart Association (AHA), American College of Cardiology (ACC) and European Society of Cardiology recommends usage of β -blockers for prevention of POAF (Class I, LOE A) and give a Class IIb, LOE B indication for sotalol (Fauster et al,2006). In a meta-analysis investigating the effect of sotalol vs the other β -blockers revealed that it is superior to the others in preventing POAF, but although not statistically significant sotalol has major bradycardia and hypotensive effects with a significant incidence of torsade-de-pointes (Mitchell et al,2007).

Amiodarone: Amiodarone can be used oral or intravenous both before and after the surgery for the prophylaxis of POAF. Amiodarone has been shown to be associated with bradycardia and hypotension (Nair,2010). ACC/AHA/ESC give a Class IIa LOE A indication for amiodarone (Fauster et al,2006). American College of Chest Physicians (ACCP) suggests that amiodarone should be an alternative for patients who have contraindication for β -blockers and Canadian Cardiovascular Society also gives a Class IIa recommendation for amiodarone for the patients who have not been on β -blockers for the prevention of POAF (Bradley et al,2005;Mitchell et al,2005).

Calcium-Channel Blockers: Calcium-channel blockers were shown to reduce the incidence of myocardial infarction, ischemia and also tend to reduce mortality. However, these agents exert negative inotropic and negative chronotropic effects which may cause an increase in the incidence of atrioventricular block and low-output syndrome (Nair,2010).

Magnesium: Magnesium deficiency occurs and may persist for at least 4 days after cardiac surgery. Although ACC/AHA/ESC do not recommend the usage of magnesium as prophylaxis for POAF and ACCP is against its usage, CCS gives Class IIa indication for magnesium usage for patients who are not on beta-blocker therapy (Fauster et al,2006; Nair et al,2010). If magnesium therapy is to be used, it should not be limited to the early postoperative period, that the magnesium deficiency may persist for at least 4 days after cardiac surgery (Nair et al,2010).

Other Pharmacological Methods: Digoxin (limited effect) (Mitchell et al,2005), statins (shown to have beneficial effects) (Liakopoulos et al,2009), procainamid (limited usage because of the well-known side effects of Class I antiarrhythmic agents on structural heart diseases) (Nair,2010) and methylprednisolon (beneficial with anti-inflammatory activity but limited usage because of renal adverse side-effects) (Prasongsukarn et al,2005) has been investigated for the prophylaxis of POAF. In patients who have high-risk for the development of AF it is important to continue beta-blockers including the operation day and restart at the earliest postoperative period and as a prophylactic measure to initiate intravenous amiodarone therapy.

Other methods

Since pericardial effusion has been shown to be an important cause for POAF, posterior pericardiotomy allowing drainage to left pleural space has been investigated and shown to reduce the incidence of supraventricular arrhythmias (Nair,2010). Prophylactic atrial pacing has been shown to reduce the development of POAF. Bi-atrial pacing revealed more significant reduction in POAF vs left or right atrial pacing or no pacing (Fan et al, 2000). It has also been shown to be as effective as the pharmacological measures (Crystal et al,2004;Burgers et al,2006).

4.1.2 Treatment of postoperative atrial fibrillation

POAF is a self-terminating but recurrent tachyarrhythmia that usually subsides in 6-8 weeks after cardiac surgery. It should be kept in mind that the adrenergic response in the postoperative period will reduce the effectiveness of any therapy that does not include beta-blockers (Nair,2010). POAF treatment should prevent thromboembolism, control ventricular rate, improve hemodynamics, convert and maintain the sinus rhythm and in-long-term prevent tachycardia-associated cardiomyopathy. The treatment strategy that targets only the rate control may not prevent the adverse effects that are caused by atrial fibrillation. Rhythm control has been shown to be no superior than rate control, however, if the symptoms are

not over with rate control only, then rhythm control should also be managed. Rhythm control is recommended for patients who are still symptomatic despite adequate rate control and who cannot achieve an adequate rate control despite therapy. Since it is self-limited, there is no need for long-term therapies for the patients who have normal left ventricular function and restored sinus rhythm. Amiodarone at a maintenance dose for 1 month, up to 3 months maximum, can be used for that kind of patients. Patients with impaired left ventricle function may require longer therapy. ACC/AHA/ECS recommend anticoagulation in addition to rate control (Nair,2010; Fauster et al,2006).

Rate Control: The goal in the control of heart rate is 80-90 beats/min after cardiac surgery, however it should be kept in mind that rate should be titrated in order to achieve a stable hemodynamic profile and myocardial oxygen balance. Beta-blockers and amiodarone are the first-line agents to be used for the treatment of POAF (Class I) (Nair,2010;Mitchell et al,2005). Calcium-channel blockers are the other effective agents to be used; diltiazem has been shown to be better tolerated than verapamil. Although digoxin is recommended for the ventricular rate control in patients with AF and congestive heart failure, without pre-excitation syndromes, has limited efficacy in the postcardiac surgery setting most probably because of the increased sympathetic response after surgery (Nair,2010).

Rhythm Control: Although it is self-limited, frequent recurrence is a rule for POAF. After pharmacotherapy in normal setting and also in the settings of recurrence and refractoriness, pharmacological and/or electrical cardioversion to sinus rhythm is also recommended. Amiodarone is the anti-arrhythmic agent to be used for pharmacological cardioversion, propafenone has been shown to be as effective as amiodarone; procainamide, dronedarone are the agents investigated for efficacy and safety, however they have side-effects and limited efficacy compared to that of amiodarone (Nair,2010).

Electrical Cardioversion: Postoperative atrial fibrillation may cause hemodynamic deterioration, myocardial ischemia, worsening left ventricle function, rapid ventricular response, which requires electrical cardioversion. The adequate waveform and energy level should be chosen; 120-200 j biphasic and 360 j monophasic is the Class IIa, LOE A recommendation (Neumar et al,2010). When it comes to increasing the dose stepwise, it is important to differentiate the 'failure to cardiovert' and 'early re-initiation of AF'. If even a single beat of sinus rhythm does not occur after cardioversion, it is failure to cardiovert, then increasing the delivered energy level, greater pressure on paddles, internal cardioversion and repeating cardioversion after anti-arrhythmic therapy can be tried. However, if it is early re-initiation of AF, additional measures may also end up in the same situation and may be harmful; that initiation of antiarrhythmic therapy (intravenous amiodarone (high ventricle rates) or diltiazem) and correction of the possible contributing factors (e.g. pain, electrolyte imbalance) before the next electrical cardioversion attempt (24-36 hours later) is recommended. If the instability continues, DC cardioversion should be given after a bolus dose of amiodarone. For the patients who are stable with a low ventricular rate, observation is recommended until 24-48 hours, if AF still continues DC cardioversion may be attempted (Nair,2010). Combining the pharmacological therapy (amiodarone for at least 7 days, if recurrent AF at least 1 month) with electrical cardioversion prevents the recurrence of atrial fibrillation.

As mentioned earlier, anticoagulation is recommended for patients who receive pharmacological and/or electrical therapies, because in both cardioversion strategies there is 1-7% risk of thromboembolism. Although the applicability of anticoagulation strategy after

cardioversion in non-surgical patients (3-4 weeks of anticoagulant therapy before cardioversion in AF more than 48 hours) for cardiac surgical patients is not clear, it is acceptable to use echocardiography especially for left atrial appendage mural thrombus, immediately placing patient on heparin and continue with oral anticoagulants for 3-4 weeks after cardioversion (Echahidi,2008). POAF is well known to increase the incidence of thromboembolism and stroke, but it is also well known that anticoagulation may result in bleeding and cardiac tamponade. Risk-benefit should be considered before anticoagulant therapy is initiated, especially for patients with advanced age, uncontrolled hypertension and history of bleeding.

4.2 Postoperative bleeding and transfusion

One of the most important adverse events after CABG is excessive blood loss, resulting in blood transfusion which increases mortality risk, ischemic morbidity, infections, hospital stay and overall health care costs following CABG (Augoustides et al,2009).

In order to prevent blood loss, it is important to identify the patients with increased risk of bleeding and also the patients who may develop adverse events related to transfusion. Advanced age, low preoperative red cell volume, preoperative usage of antithrombotic and antiplatelet drugs, reoperations, combined procedures, emergency surgery and co-morbidities are the major contributing factors to the risk of bleeding (Augoustides et al,2009). Limiting bleeding and transfusion after CABG begins with adequate preparation of the operating room and ICU with full institutional support. A guideline to lead a systematic, standardized approach is also an important factor for limiting bleeding and transfusion (Ferraris&Spiess,2007).

In the preoperative period usage of anticoagulants leads to an increased risk of bleeding, thus if clinically feasible, the anticoagulants should be stopped allowing coagulation system to recover (Augoustides et al,2009). Clopidogrel, a high-intensity platelet blocker, is reasonable to be discontinued for at least 5-7 days before surgery (Ferraris&Spiess,2007). The low-intensity antiplatelet aspirin therapy is recommended to be stopped in elective patients without acute coronary syndromes (Ferraris et al,2002).

In combination with appropriate erythropoietin and iron therapy, donation of 2 units of autologous blood before CABG, significantly reduces allogenic blood transfusions. Kahraman et al. reported that acute intraoperative hemodilution reduces the blood requirements without affecting RBC volume loss and high-volume phlebotomy does not provide any additional benefit (Kahraman et al,1997). Antifibrinolytic agents can be used to limit bleeding and transfusion; tranexamic acid and aminocaproic acid are the major agents that can be used instead of aprotinin, providing a reduction in bleeding and blood transfusion; especially recommended for their usage in the high-risk subgroups (Henry et al, 2007; Umscheid et al, 2007). Desmopressin is reserved for patients who have platelet dysfunction in the preoperative period and also factor 7a therapy has been shown to be effective in the management of refractory bleeding after CABG (Warren et al,2007).

As it exerts a mechanical pressure on the heart PEEP can be used to limit bleeding and need for transfusion.

Off-pump CABG is a reasonable alternative for the prevention of blood loss, however emergent conversion to CABG with CPB increases blood loss and risk of transfusion (Jin et al,2005).

Several parts of CPB circuit have been improved for patient safety. Membrane oxygenators, centrifugal pumps, heparin-coated circuits, minimized low-prime CPB circuits are the recommended types for these parts of the circuit (Augoustides et al,2009).

High-dose heparin therapy preserves coagulation during CPB and also may decrease bleeding and transfusion. The reversal of heparin with protamine may affect bleeding and tranfusion as protamine itself is an anticoagulant. Despite the lack of definitive data, titration and empiric low-dose regimen of protamine therapy may both lower the dosage of protamine and reduce bleeding and tranfusion (Jobes et al, 1995; Shore-Lesserson et al, 1998).

Leukofiltration, ultrafiltration or infusion of shed mediastinal blood are other interventions that are addressed in clinical trials (Augoustides et al,2009).

In general, in CPB, it is reasonable to maintain hemoglobin >10 gr/dl in patients who are at risk of non-cardiac end-organ ischemia; and >7 gr/dl in patients who are at risk of critical end-organ injury (Augoustides et al,2009).

4.3 Neurocognitive dysfunction

Adversely affected central nervous system is a well-defined problem following cardiac surgeries especially requiring hypothermic circulatory arrest. However, it is not clear that these neurological problems are related to procedure itself or to the underlying cardiovascular disease. In that point of view Wahrborg et al. found no difference between percutaneous coronary interventions and CABG (Wahrborg et al,2004). The most frequently reported form of brain injury is postoperative neurocognitive decline (POCD), of which recovery is variable, mostly transient, also which may prolong for several years and has no known treatment, leading the search for finding various interventions to reduce this decline (Lombard et al,2010;Grigore et al,2009). The other forms of brain injury such as stroke and encephalopathy have incidences of 1-5.2% and 10% respectively; when compared to POCD the difference is striking; 10-60% at 6 months (Funder et al,2009;Newman et al,2006). Early decline rate is 50-70% within the first week, 30-50% after 6 weeks and 20-40% at 6 months and first year. As mentioned before, multiple factors influence cognitive functions including surgical recovery and analgesic and sedative requirements, that it is difficult to accuse procedures only for the adverse neurocognitive decline. It is well-known that most patients with advanced coronary artery disease already have neurocognitive decline before surgery and have more potential to develop further decline independent of surgery (Lombard et al,2010). Selnes et al (2008) reported that there is a significant late decline in neurocognitive functions after CABG sugeries, however no significant difference compared to non-surgical patients with coronary artery disease. The degree of preexisting vascular disease may influence adverse neurocognitive outcomes after CABG more than expected, as the results of many trials suggest the natural progression of cerebrovascular disease is the main determinant of cognitive decline rather than CABG (Lombard et al,2010;Grogan et al,2008).

The clinical forms of brain injury and their frequencies (Grogan et al, 2008)

- Stroke
 - Low risk patients ≤1%
 - High risk patients 5%-16%
- Encephalopathy 8.4%-32%
- Neurocognitive dysfunction
 - Hospital discharge 40%-75%
 - 1 month after surgery 12%-30%

In the preoperative period, brain imaging can detect the prior brain infarction, white matter lesions and/or lacunar infarcts that are clinically asymptomatic and also abnormal brain perfusion areas can be detected by SPECT prior to the operation; demonstrating the high-risk patients for the development of POCD.

There are several factors that have been associated with neurological problems such as patient risk factors including aortic atherosclerosis and surgical risk factors including type of surgery, temperature control, glucose control and intraoperative hemodynamics.

4.3.1 Risk factors of neurocognitive dysfunction

Patient Risk Factors; Neuroprotective anesthetic, surgical and perfusion techniques should be the key element in the management of these procedures guided by the identification of the high risk patients in the preoperative period.

Patient risk factors (Lombard et al,2010;Grigore et al,2009)

- Advanced age (>70 yr)
- Non-coronary manifestations of atherosclerosis;
History of cerebrovascular disease with symptoms or silent infarctions (presence of one or more lacunar infarcts on preoperative magnetic resonance imaging)
Peripheral vascular disease
- Chronic neurologic illness
- Congestive heart failure
- Fewer years of education
- Limited social support
- Insulin-dependent diabetes mellitus
- Genetic predisposition (minor alleles of C-reactive protein (CRP; 3'UTR 1846C/T), IL-6;-174G/C, platelet glycoprotein IIb/IIIa receptor variants are the candidates requiring further knowledge)(Grogan et al,2008)

Surgical risk factors;

- CPB
- Blood gas management
- Cerebral embolism
- Cell salvage
- Valve surgery
- Temperature control
- Hemodilution
- Oxygen delivery
- Glucose control
- Intraoperative hemodynamics
- Aortic atherosclerosis
- Systemic inflammatory response

4.3.2 Prevention of adverse neurological outcome

CPB; Cerebral hypoperfusion, temperature fluctuations, high incidence of cerebral embolism, inflammatory response, brain swelling and elevated levels of biomarkers of brain injury explains the potential of CABG surgeries for the development of POCD. However, in

recent trials the cardiac surgical patients with or without CPB were investigated and no difference was described between them in terms of neurological outcome (Lombard et al,2010; Grigore et al,2009).

Blood gas management; Although there are controversies about the technique to be used during CPB period, α -stat has been shown to preserve pressure autoregulation and recommended for the technique to be used in adults (see also management during CPB).

Cerebral Embolism; Long-term dysfunctions might be mostly related to macroemboli from aortic lesions due to aortic manipulation, rather than gaseous microemboli which is the predominant type of microemboli during bypass period (Wahrborg et al,2004). However, the macroemboli to be a major cause of cognitive dysfunction is unlikely that it has been defined to be more associated with stroke (Bar-Yosef et al,2004). As being the most common type of cerebral emboli detected by transcranial Doppler during CPB are air emboli; in order to increase the rate of absorption of intravascular emboli, CO₂ has been used for wound insufflation to replace air in the pericardium, as it is more soluble than air. Although it reduced the number of arterial emboli, it has not been investigated for the brain protection, and also this technique is not without risks (Grogan et al,2008). The imaging techniques improves every year and one of them is the magnetic resonance diffusion-weighted imaging (DWI), which identifies regions of cerebral ischemia with a high sensitivity and specificity differentiating the acute from chronic infarction. 25-50% of patients undergoing cardiac surgery develop new lesions on DWI, however, very few of them show clinically significant infarction. On the other hand there are trials reporting significant correlation between the lesions on DWI and cognitive impairment proving that for the development of cognitive dysfunction, necrosis is not necessary, whereas other trials did not reveal any correlation (Knipp et al,2005;Cook et al,2007). More sensitive imaging techniques such as functional MRI may be used for assessing neurocognitive dysfunction after cardiac surgery.

Cell Salvage; Continuous flow cell saver when compared with conventional cardiectomy suction, may reduce the lipid microemboli (resulting in small arteriolar capillary dilatations) by processing the shed blood a major source of lipid microparticulates, thus reduce the cognitive decline after cardiac surgery (Grogan et al 2008, as cited in Djaiani et al,2007). Simply discarding the pericardial aspirate, when the shed blood is low, is an acceptable choice; and on the other hand using the cell-saver may cause thrombocytopenia and decrease the concentration of coagulation factors leading to bleeding and high rates of transfusion. Thrombocytopenia is a major concern because transfusion of platelets increases the risk of stroke in cardiac surgical patients. The increased requirement for transfusion has been shown by both Rubens et al. (Grogan et al,2008 as cited in Rubens et al,2007) and Djaiani et al. (Grogan et al 2008, as cited in Djaiani et al,2007), although their results in terms of the effects of cell-saver and cardiectomy suction on neurocognitive dysfunction are conflicting.

Valve Surgery; The valve surgeries have an increased incidence of cognitive dysfunction, because of the open heart chambers during the procedure. Furthermore the cognitive dysfunction following valve surgery lasts longer than CPBG surgeries most probably because of the ongoing microemboli (Lombard et al,2010).

Temperature Control; Hypothermia has been the major intervention that is used for cerebral protection. Moderate and mild hypothermia were not dissimilar in terms of POCD, however hyperthermia has been proven clearly to be associated with adverse neurologic outcome. The potential benefit of hypothermia is clearly offset by inappropriate rewarming, which leads to cerebral hyperthermia. Mild hypothermia (32-34 C), slow rewarming,

avoiding hyperthermia are the current recommendations (Grigore et al,2009;Grogan et al,2008) (see also management during CPB).

Hypothermic Circulatory Arrest: Moderate or profound hypothermia with periods of circulatory arrest combined with selective antegrade or retrograde brain perfusion periods has become an acceptable technique. Selective antegrade perfusion has been proven to be comparable or better than hypothermic circulatory arrest alone or retrograde perfusion; furthermore it has been reported that shortened period of brain ischemia via selective antegrade perfusion and use of less profound hypothermia is associated with good clinical outcomes (Reich et al,2010).

Hemodilution; In order to avoid the adverse effects of hypothermia on blood viscosity, hemodilution is used, which also reduces blood requirement during cardiac surgery. As hematocrit level decreases, oxygen carrying capacity decreases which in turn increases CBF leading to a high risk of cerebral emboli. Although a definitive recommendation is not available, transfusion of blood products are supported to be reserved for patients with hemoglobin level of <6 gr/dl during CPB and <7 gr/dl after surgery (Ferraris et al,2007) (see also management during CPB).

Oxygen Delivery; Delivery of oxygen during CPB period is less than in awake and anesthetized patients; particularly because of the hemodilution at the onset of bypass reducing the arterial oxygen content. During CPB, delivery of oxygen to the brain is preserved at low pump flow rates at the expense of other organs. A critical DO_2 value should be targeted to preserve organ functions (Murphy et al;2009) (see also management during CPB).

Glucose Control; Moderate glycemic control is recommended instead of tight glycemic control, given a Class IIa, LOE C indication for insulin therapy when the glucose level exceeds 140-185 mg/dl (Adams et al,2007;Finfer et al,2009).

Intraoperative Hemodynamics; The patients with pre-existing cerebrovascular diseases (CVD) are more vulnerable to cerebral hypoperfusion during CPB. Considering the increased age of these patients, most of them already have a symptomatic or asymptomatic CVD, which requires maintenance of pre-CPB cerebral perfusion pressures. $MAP > 70$ mmHg is supported to be the goal especially in the elderly (Grogan et al,2008). Although there is no clear data, pump flow rates of 1-2.4 L/min/m² have been shown to preserve CBF (Murphy et al,2009).

Aortic Atherosclerosis; As being an important risk factor for the development of cognitive dysfunction, detection of atherosclerosis of the ascending aorta provides risk stratification in the preoperative period that may lead to a decision of 'off-pump' CAB or 'no touch' approach to ascending aorta in order to prevent any adverse neurological outcome. Avoiding ascending aorta manipulations or searching for the atherosclerosis free areas may be beneficial, however after CPB it has been shown that CPB itself (due to sandblasting effect) may result in new mobile lesions on the sites where previously was mild-to-moderate atherosclerosis; at the sites of aortic cannulation and clamping (Reich et al,2010) .

Systemic Inflammatory Response; It is well-known that CPB causes a profound systemic inflammatory response. High baseline level of CRP was found to be associated with greater risk of neurocognitive decline. Cerebral ischemia-reperfusion injury also produces a profound inflammatory response; p-selectin expression on platelets resulting in platelet accumulation, rendering the brain vulnerable to microthrombosis, leading to ischemia (Lombard et al,2010). According to recent guidelines it is not unreasonable to use reduced

circuit surface and biocompatible surface-modified circuits which are useful and effective in reducing systemic inflammatory response (Class IIa, LOE B) (Shann et al,2006).

Pharmacological Interventions; One of the methods that is investigated for the prevention of neurological dysfunction after CPB, is pharmacological protection, though remains controversial. It has been reported that the incidence of neurocognitive dysfunction can be lowered by using short-acting anesthetic and analgesic agents, providing a faster recovery from general anesthesia (Chen et al,2001). Shorter emergence times can be achieved by using low blood-gas partition coefficient and rapidly eliminated volatile anesthetics such as sevoflurane and desflurane (Frink et al,1992;Tsai et al,1992). In their preliminary report, Kanbak et al. reported that isoflurane and propofol were similar in terms of neuropsychological test scores and neurological examination after CPB, despite increased levels of S100BP in the propofol group (Kanbak et al,2004). Kanbak et al. also investigated the effects of isoflurane, desflurane and sevoflurane on cognitive function after CABG, comparing them in terms of neurological tests and S100BP levels. Isoflurane has been reported to provide better cognitive outcome (Kanbak et al,2007).

Pexelizumab, lidocaine, magnesium, ketamine, 17 β -estradiol, donepezil, aprotinin are the pharmacological agents that are investigated for their efficacy on neurocognitive functions after cardiac surgery, however, all require further evaluation. There are no ideal pharmacological agent for neuroprotection during cardiac surgery (Lombard et al,2010; Grogan et al,2008).

Recommendations to reduce brain injury during cardiac surgery (Grogan et al,2008)

- A membrane oxygenator and an arterial line filter ($\leq 40\mu\text{M}$) should be used for CPB (Class I, LOE A)
- Epiaortic ultrasound for detection of atherosclerosis of the ascending aorta (Class I, LOE B)
- Hyperthermia should be avoided during and after CPB (Class I, LOE B)
- A single aortic-cross-clamp technique should be used for patients at risk for atheroembolism (Class IIa, LOE B)
- During CPB in adults, α -stat pH management should be considered (Class IIa, LOE A)
- Arterial line temperature during CPB rewarming should be limited to 37 C (Class IIa, LOE B)
- NIRS monitoring should be considered, especially in high-risk patients (Class IIb, LOE B)
- Arterial blood pressure should be maintained At >70 mmHg during CPB in high-risk patients (Class IIb, LOE B)
- Serum glucose should be kept <140 mg/dl with an infusion of insulin (Class IIb, LOE C)
- Transfusion of packed RBC should be considered in high-risk patients when hemoglobin is ≤ 7 gr/dl or higher depending on other patient-specific considerations (Class IIb, LOE C)
- Processing cardiectomy suction aspirate with a cell-saver device as a means for preventing neurocognitive dysfunction (Class indeterminate (LOE A))
- There are no pharmacological neuroprotective agents with proven efficacy in humans (Class indeterminate (LOE B))

4.4 Acute kidney injury (AKI)

Acute kidney injury known to be an independent predictor of mortality in cardiac surgery, has an incidence of 50% by some definitions, doubling the postoperative and intensive care unit costs (Park et al,2010). The pathophysiologic processes of cardiac-surgery associated AKI (CSA-AKI) were concluded to be; exogenous and endogeneous toxins, metabolic factors, ischemia-reperfusion, neurohormonal activation, inflammation and oxidative stress, which are interrelated and probably synergistic (Garwood,2010).

A common terminology and definition is necessary to determine the high-risk patients for the development of CSA-AKI. The term acute renal injury reflects the entire spectrum of the disease process; from minimal changes in serum creatinin to anuric renal failure, from functional deviations to structural changes and from prerenal azotemia to acute tubular necrosis (Dennen et al,2010). The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) group published a classification system for AKI based on the changes in serum creatinin and/or urine output. In this 5-stage classification, first 3 describes the risk, injury and failure for the severity of the AKI based on the changes in serum creatinin, glomerular filtration rate (GFR) and urine output. Last 2 stages describe outcome as loss and end-stage kidney disease, making the acronym RIFLE classification (Bellomo et al,2004). Acute Kidney Injury Network (AKIN) proposed a modification to this classification and used a time frame of 48 hours in which the AKI has to occur and included lesser degrees of serum creatinin elevation. ADQI subdivided this classification into stages as early (within the first 7 days) and late (occurring between 7 and 30 days after cardiac surgery) (Hoste et al,2008).

In order to prevent cardiac surgery associated acute kidney injury (CSA-AKI) the most important approach is providing adequate renal perfusion throughout the surgery. Although there is no guide for any specific fluid or vasoactive agent to improve renal function, it is important to identify patients who are at increased risk such as patients in volume depletion and have congestive heart failure (Tolwani et al,2008). However it should be kept in mind that pathophysiological events other than changes in RBF are also responsible for development of AKI (Garwood,2010,as cited in Bonventre et al,2004 & Friedewald et al,2004). The patients known to have renal disease are more prone to have systemic acidosis and electrolyte disturbances mainly hyperkalemia, requiring more frequent blood gas and electrolyte sampling. Intraoperatively adequate fluid and medication management should be done for the dialysis patients ensuring that they have a recent dialysis with an adequate serum potassium level (London et al,2008). The ongoing investigations have a goal to define a single or a panel of early biomarkers to prospectively identify the potential for developing AKI after cardiac surgeries (Garwood,2010).

Cardiac surgery patients are particularly at risk of volume-responsive AKI; which is the term used more favorably than prerenal azotemia, emphasizing that despite the reversibility of early stages of AKI, even minor increases above baseline may result in adverse outcomes and any degree of renal insufficiency no matter how small may result in significant clinical consequences even in the absence of complete loss of function (Garwood,2010).

The non-volume responsive AKI also may occur in cardiac surgical patients. Ischemic period which has been clearly defined in experimental models, is also clearly defined to be associated with multiple injurious events in humans during the perioperative period. The key sign is a rapid, progressive and profound decline in GFR, which continue and progress even after return of renal perfusion to baseline (Garwood,2010).

Pathophysiological events other than changes in RBF are also responsible for the development of AKI (Garwood,2010,as cited in Molitoris et al,2004Bonventre et al,2004 & Friedewald et al,2004).

As the AKI is a multifactorial adverse consequence, it is crucial to address these interreacting factors for the prevention and treatment of CSA-AKI. The disease process includes ischemia, endothelial and epithelial dysfunction and tubular injury (Garwood,2010). Despite their limitations and variabilities in the AKI definitions and targeting mostly the prevention rather than treatment, there are many trials investigating the effects of vasodilators-primarily increasing the renal blood flow (dopamine, dopexamine, fenoldopam, angiotensin-converting enzyme inhibitors (ACEI) (captopril, enalaprilat), diltiazem, prostacyclin, nifedipine, PGE-1, sodium nitroprusside, theophylline), interventions inducing natriuresis or diuresis or both (atrial natriuretic peptid, brain natriuretic peptid, urodilatin, diuretic agents (loop diuretics and mannitol), anti-inflammatory agents (N-acetyl cyctein, aspirin, glutathion, corticosteroids, leukodepletion), clonidine, albumin infusion, isotonic saline infusion, insulin therapy, early continous venovenous hemofiltration and also off vs on-pump technique. Fenoldopam, ACEI, atrial natriuretic peptide (nesiritide), B-natriuretic peptid, urodilatin were associated with reduction in the incidence of CSA-AKI. Off-pump surgical technique and pulsatile flow techniques also were reported to reduce the incidence (Park et al,2010). The recent trials are investigating reactive oxygen molecule scavengers, anti-inflammatory agents and antiapoptotic agents. AKIN also identifies the antiapoptotic agents (e.g.tetracyclines, human recombinant erythropoietin (HrEPO)) as potentially useful for AKI, though further researchs are needed (Garwood,2010).

4.5 Acute lung injury

Impaired pulmonary function is a well-known complication of cardiac surgeries, however it has multiple factors to be related with such as anesthesia, temporary cardiac dysfunction, infused catecholamines, altered mechanics of thoracic cage, duration of mechanical ventilation, neurological, renal and infectious complications rather than a single factor; CPB being the mostly accused. Although it is not possible to perform all the cardiac procedures without CPB, avoiding bypass alone cannot prevent the lung injury completely (Apostolakis et al,2010).

Although there are limited, insufficient data supporting the broad clinical use heparin-coated circuits and miniaturized circuits, minimizing the extracorporeal surface area and being biocompatible and free of any material that activates blood should lower the incidence of lung injury (de Vroeghe et al,2004). Leucocyte depletion may reduce the entrapment into lung capillaries, that in experimental studies it has been shown to reduce the heart and lung reperfusion injury (Apostolakis et al,2010,as cited in Bando et al,1990). Ultrafiltration and controlled hemodilution reduce interstitial lung edema, improving the lung functions after surgery (Apostolakis et al,2010). Using a controlled cardiac suction device, reducing the time between the contact of shed blood with pericardium and its re-transfusion, becoming activated only when the blood is accumulated in pericardium-minimizing air entrance may also improve lung functions. Furthermore, since the heparin level of pericardial blood is lower than systemic level, topical heparin administration may also diminish the inflammatory reactions contributing to lung injury (Tabuchi et al,1993).

Apnoea during CPB has been shown to be associated with increased incidence of pulmonary dysfunction. The results of clinical trials are conflicting, that some revealed

improvement in lung functions by maintaining ventilation (with or without CPAP) together with pulmonary artery perfusion during CPB, whereas others revealed no difference (Stanley et al,1977;John et al,2008).

The rules of myocardial protection during ischemia and reperfusion, indirectly protect the lungs from several proinflammatory factors produced during the process (Apostolakis et al,2010).

5. Coronary artery bypass grafting without cardiopulmonary bypass

Cardiopulmonary bypass is still the most common technique used for coronary artery bypass grafting procedures. Offpump coronary artery bypass (OPCAB) grafting, being the major improvement in cardiac surgeries, is performed at a rate of 20-30%. Despite the lack of definitive literature, its safety and efficacy in providing improvement in several outcomes have been proven, especially in high-risk patients with co-morbidities associated with higher mortality and morbidity from CPB (e.g. cerebrovascular and renal disease), avoiding the adverse effects of cannulation and CPB including hypothermia, risk of rewarming, coagulation abnormalities, renal impairment, arrhythmias, manipulation and cross-clamping of the ascending aorta (which increases the risk of aortic dissection/ neurologic sequelae) and prolonged postoperative ventilation. These procedures shorten the duration of the procedure, length of stay in ICU and hospital, and possibly decrease the cost (London et al,2008; Barnes, 2002b).

OP-CAB or minimally invasive direct CAB (MIDCAB) are the alternatives to be used in order to avoid CPB. In these settings the anesthetists encounters more surgeon-induced hemodynamic changes when it is compared to routine CABG; having a major role for anticipating and communicating with the surgeon about the adverse events that occur during surgical manipulation. The operation on the beating heart may be more prone to develop arrhythmias because of ischemia, manipulation and reperfusion. Antiarrhythmics, asking the surgeon to temporarily stop manipulation and treating severe bradycardia pharmacologically or with epicardial or transvenous pacing are the main strategies. During the exposure of the arteries, the heart is lifted and rotated, when the heart is repositioned venous return will be compromised leading to a decrease in preload reducing the cardiac output. Fluid resuscitation, inotropic medications and peripheral vasoconstrictors may be required. Maintenance of adequate coronary perfusion is provided by the maintenance of the mean blood pressure close to baseline. In OP-CAB for the proximal anastomoses a side-biting C-clamp is placed on the aorta providing that the blood pressure is lowered. Nitroglycerin and nitroprusside can be used for this purpose (Barnes,2002b). With a skilled surgeon, the changes are modest and can be managed by using simply the Trendelenburg position, inotropes and vasoconstrictors, however severe changes associated with acute ischemia, mitral regurgitation or unrecognized right ventricular compression necessitate emergent conversion to CPB (London et al,2008).

A large bore cannulae should be in place, cross-matched blood should be readily available and CPB circuit should be set up with a perfusionist on standby. In MIDCAB method, since the access to the heart is limited, external defibrillator and pacing pads should be ready during the operation (Barnes,2002b). Although there is no definitive type of monitoring described, most observational studies have used extensive monitoring including PAC and TEE. However, as the practice improves, particularly for the low-risk patients the recommended type of monitoring will probably become less sophisticated (London et al,2008).

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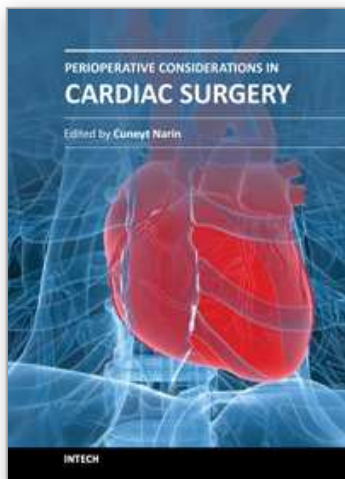
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This book considers mainly the current perioperative care, as well as progresses in new cardiac surgery technologies. Perioperative strategies and new technologies in the field of cardiac surgery will continue to contribute to improvements in postoperative 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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