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PhD THESIS - ABSTRACT

**CARDIOPROTECTION IN GENERAL ANESTHESIA
WITH SEVOFLURANE VERSUS PROPOFOL,
IN HIGH CARDIAC RISK PATIENTS,
UNDERGOING NON-CARDIAC SURGERY**

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Perioperative myocardial ischemia is a common complication that increases mortality and morbidity after cardiac and non-cardiac surgery. To prevent myocardial ischemia and perioperative cardiac complications, some cardiac protective approaches have been proposed: optimization of hemodynamic and cardiac function in order to maintain the delivery-consumption oxygen balance at myocardial level, and pharmacologic preconditioning and postconditioning phenomenon.

Cardioprotection, as a total of pharmacological and non-pharmacological interventions for prevention or limitation of cellular death in reperfusion, remains a priority for fundamental and clinical research.

During time, some studies showed that some anesthetic drugs have cardioprotection effect. First studies considered that volatile anesthetics have cardioprotection effect thru delivery-consumption oxygen balance optimization, due cronotrope and negative inotrope effects. Recent experimentaly studies showed that induced myocardial protection by anesthetics was the result of preconditioning effect, mainly in cardiac surgery where the myocardial ischemia was in a predictable and reproducible way. In non-cardiac surgery, the studies were few, with contradictory conclusions.

The aim of the study is to evaluate the cardioprotective effect of sevoflurane versus propofol, in high cardiac risk patients, undergoing non-cardiac surgery.

The thesis was divided in two parts:

- General part (Chapters 1-2) contains literature data regarding perioperative myocardial ischemia and cardioprotection process by anesthetic preconditioning and postconditioning phenomenon,

- Special part (Chapters 3-6) contains 3 clinical studies; the first and the second study regards cardioprotection effect assesment of sevoflurane versus propofol, in non-cardiac surgery thru 12 months analysis of perioperative acute cardiac events, cardiac and inflammatory biomarkers, hemodynamic and cardiac parameters, optimization of delivery-consumption oxygen balance; the third study regards the anesthetic preconditioning effect of sevoflurane in cardiac risk diabetic patients versus non-diabetic, in non-cardiac surgery.

The objective of **Study 1** was the assesment of cardioprotective effect of sevoflurane versus propofol, thru cardiac and inflammatory markers' analysis.

The concept of the research was made after phase IV clinical model, randomized and prospective, during 32 months (January 2010 – August 2012) and enrolling 68 cardiac risk patients (Lee's score > 3 points, MET < 4), over 18 years old, undergoing elective major abdominal surgery, considered with intermediary cardiac risk, related with the amplitude of the non-cardiac surgery.

Patients with a mean age of 73 ± 9 years, mainly male, were divided into three groups depending on the type of general anesthesia, as follows:

- Group A (n = 24) – general inhale anesthesia by *Volatile Induction and Maintenance Anaesthesia* (VIMA) technique, with sevoflurane,
- Group B (n = 20) – general intravenous anesthesia by *Target Controlled Infusion* (TIVA-TCI) technique, with propofol,
- Group C (n = 24) – general balanced anesthesia (GA), with sevoflurane.

In order to assess myocardial protection we used the following evaluation methods: transthoracic echocardiography to assess left ventricular diastolic function, global and segmental ejection fraction (EF), electrocardiogram (ECG) modification (ST segment, Q necrosis wave presence), serum levels of cardiac biomarkers and enzymes: troponine I (TnI), precursor of brain natriuretic peptide (proBNP),

creatine kinase MB (CKMB) and inflammatory tests: high sensitive C-reactive protein (CRP) and interleukin 6 (IL6).

Patients from all three groups were monitored with standard and invasive methods for 48 h. Serial hemodynamic measurements were performed, cardiac biomarkers, inflammatory tests, acid-base balance and lactate levels were carried out in preoperator period (T0), immediately after induction (T1), and in the postoperative period at 1 h (T2), 12 h (T3), 24 h (T4) and 48 h (T5). Transthoracic echocardiography was performed at 24 h (T4) and 48 h (T5). Subsequently, the patients' evaluations were followed for one year, with repeated examinations at 30 days (T6), 6 months (T7) and 1 year (T8).

As result, the sevoflurane anesthesia in high cardiac risk patients, undergoing non-cardiac surgery, was accompanied with decreasing cardiac biomarkers' concentrations (TnI and CKMB/CK), in the first 24-48 h, versus TIVA-TCI anesthesia with propofol. The incidence of the ischemic cardiac events was low in all groups. We also observed increased preoperative values for proBNP, which correlated with increased cardiac risk. The postoperative and long term high levels of proBNP, CRP and IL6 did not correlated with presence of acute cardiac events because the cardioprotection effect of sevoflurane and propofol. The mortality rate, through acute cardiac events, was low, in comparison with data from medical literature.

The objective of **Study 2**, using the same materials and method as **Study 1**, was the assessment of general anesthesia effects of sevoflurane versus propofol, in the same three groups, over the perioperative oxygen balance, thru hemodynamic parameters analysis (MAP – mean arterial pressure, CF – cardiac flow, SVRI – systemic vascular resistance index), global oxygenation (DO₂ – oxygen delivery, ScvO₂ – central venous oxygen saturation), myocardial contractility (CI – cardiac index, EF – ejection fraction) and tissue perfusion (lactate, pH and base excess).

Due optimization of the hemodinamics and of the oxigen balance, in high cardiac risk patients undergoing abdominal surgery, in GA with sevoflorane and propofol, the incidence of the ischemic cardiac events was low in all three groups. But sevoflurane balanced GA ensured a better intraoperative stability hemodynamic versus propofol, so, this technique is proper in non-cardiac surgery.

The objective of **Study 3** was to evaluate of cardioprotective effect of sevoflurane in patients with type 2 diabetes and increased cardiac risk compared with non-diabetic patients with cardiac risk, undergoing elective abdominal surgery, by tracking the incidence of ischemic cardiac complications, based on the analysis of cardiac biomarkers: troponine I (TnI), myocardial creatine kinase (CKMB), the precursor of brain natriuretic peptide (proBNP) and electrocardiographic (ECG) changes.

The study enrolled 48 patients with increased cardiac risk, mean age 71 ± 6 years, undergoing elective major abdominal surgery with sevoflurane balanced general anesthesia.

The patients 31 M / 17 F were divided in two groups according to the presence of diabetes mellitus, as follows:

- Group A (n = 15) – patients with diabetes,
- Group B (n = 33) – patients without diabetes.

Both groups were standard and invasive methods monitored for 48 h. Glycemia level was maintained below 180 mg/dl by administering insulin in continuous infusion under the hourly control of capillary blood.

The incidence of the acute postoperative cardiac events was lightly higher in diabetic patients, but without any significant differences. Troponine I was the only cardiac biomarker which showed significantly higher values in diabetic patients compared to non-diabetic. Cardiac event deaths number was higher at diabetes group. Survival at 1 year showed no significant differences between the two groups.

Due optimization of the hemodynamics and of the oxygen balance, in high cardiac risk patients undergoing abdominal surgery, in GA with sevoflurane and propofol, the incidence of the ischemic cardiac events was low in all three groups.

Because diabetes did not interfere with cardioprotection sevoflurane and because glycemia has been maintained under 180 mg/dl by insulin administration, may explain the low incidence of postoperative acute cardiac events and also in long term.

The final conclusion of this research, regarding cardioprotection induced by anesthetic preconditioning, is the fact that anesthesia with sevoflurane, in high cardiac risk patients undergoing non-cardiac surgery, was accompanied by the perioperative hemodynamic stability and the decrease of cardiac biomarkers' concentrations (TnI and CKMB/CK), in 24-48 h period, versus TIVA-TCI anesthesia with propofol. Also, the incidence of ischemic cardiac events was low for all three groups.

Additionally, the duration of ICU stay, the positive inotrope substances need and the cardiac decompensation presence, highlighted by ECG parameters, showed no significant differences between sevoflurane group and propofol group.

Cardioprotection in high cardiac risk patient, undergoing non-cardiac surgery, was underlined by the low number of ischemic cardiac perioperative complications and long term, with higher 1 year survival rate.

Keywords: cardioprotection, preconditioning, sevoflurane, propofol, cardiac risk, non-cardiac surgery, diabetes mellitus, cardiac biomarkers.