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# Kyslíková spotřeba u pacientů podstupující kardiochirurgický výkon při vědomí

# Oxygen consumption in awake cardiac surgical patients

Typ závěrečné práce

(Disertační)

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# CONTENTS:

# ABBREVIATIONS

| | |
|---|---|
| AWCS | awake cardiac surgery technique |
| BE | base excess |
| BFR | blood flow rate |
| CABG | coronary artery bypass grafting |
| $CMRO_2$ | cerebral metabolic rate |
| COPD | chronic obstructive pulmonary disease |
| CPB | cardiopulmonary bypass |
| CVP | central venous pressure |
| $DO_2$ | oxygen delivery |
| GA | general anesthesia |
| HR | heart rate |
| ICU | intensive care unit |
| MAP | mean arterial pressure |
| On-pump | cardiac surgery with the use of cardiopulmonary bypass |
| Off-pump | cardiac surgery without the use of cardiopulmonary bypass |
| $PaCO_2$ | arterial partial carbon dioxide pressure |
| $PaO_2$ | arterial partial oxygen pressure |
| RASS | Richmond agitation and sedation score |
| $SaO_2$ | arterial oxygen saturation |
| $ScvO_2$ | central venous oxygen saturation |
| $SjbO_2$ | jugular bulb oxygen saturation |
| TEA | thoracic epidural anesthesia |
| TEA-GA | combined thoracic epidural and general anesthesia |
| VAS | visual analogue scale |
| $VO_2$ | oxygen consumption |

## 1. ABSTRACT

OBJECTIVES:
Standard blood flow rates for cardiopulmonary bypass have been assumed to be the same for awake cardiac surgery with thoracic epidural anesthesia as for general anesthesia. However, compared to general anesthesia, awake cardiac surgery with epidural anesthesia may be associated with higher oxygen consumption due to missing effect of general anesthetics. This may result in insufficient oxygen delivery and lactic acidosis when standard blood flow rates were used. The primary aim of our study was to investigate if standard blood flow rates are adequate in awake cardiac surgery. The secondary aim was to evaluate postoperative clinical outcomes of patients undergoing awake cardiac surgery.
METHODS:
Forty-seven patients undergoing elective on-pump cardiac surgery were assigned to receive either epidural (Group TEA, n=17), combined (Group TEA-GA, n=15) or general (Group GA, n=15) anesthesia. To monitor adequacy of standard blood flow rates, arterial lactate, acid base parameters, central venous and jugular bulb saturation were measured at six time points during in all groups. Blood flow rates were adjusted when needed. Subsequently, early and late postoperative outcome data including hospital and 3-year mortality was recorded and compared among the study groups
RESULTS:
No lactic acidosis has developed in any group. TEA as compared to TEA-GA and GA groups had mildly lower central venous and jugular bulb oxygen saturations during cardiopulmonary bypass and during post cardiopulmonary bypass period. TEA group as compared to TEA-GA and GA groups had also mild hypercapnic respiratory acidosis and mild decrease of arterial oxygen saturation at the end of surgery without any clinical consequences. Thus, no additional blood flow rates adjustments in any study group and no ventilatory support in TEA group was required. There was also no major difference in postoperative outcome data across all study groups, except for lower incidence of atrial fibrillation in the TEA group compared to GA group. TEA and TEA-GA group as compared to GA group had lower pain visual analogue scale scores at 24 hours postoperatively and morphine requirements during the first 24 hours after surgery.
CONCLUSIONS:
Under careful monitoring, the use of standard blood flow rates is adequate for patients undergoing awake on-pump normothermic cardiac surgery. Additionaly, awake TEA showed no improvement in postoperative outcome, except for lower incidence of atrial fibrillation and superior pain relief.

**ABSTRAKT**

CÍLE STUDIE:

V minulosti se v kardiochirurgii předpokládalo, že standardní průtoky krevní pumpou mimotělního oběhu jsou stejné, jak pro pacienty podstupující výkon v epidurální anestezii při vědomí, tak pro pacienty v anestezii celkové. Nicméně, v porovnání s anestezií celkovou, mohou mít pacienti při vědomí z důvodu chybějícího vlivu celkových anestetik vyšší kyslíkovou spotřebu. To v případě použití standardních krevních průtoků může vést k rozvoji metabolické laktátové acidózy. Primárním cílem naší studie bylo zjistit, zda-li jsou standardní krevní průtoky mimotělního oběhu adekvátní pro pacienty podstupující výkon při vědomí. Sekundárním cílem práce bylo klinické zhodnocení pooperačních komplikací u těchto pacientů.

METODY:

Čtyřicet sedm pacientů indikovaných k elektivnímu kardiochirurgickému výkonu s použitím mimotělního oběhu bylo rozděleno do tří skupin, a to podstupující výkon při vědomí v epidurální anestezií (Skupina TEA, n=17), v kombinované (skupina TEA-GA, n=15) a celkové (Skupina GA, n=15) anestezii. K monitoraci dostatečnosti krevních průtoků mimotělního oběhu bylo použito měření koncentrace laktátu v tepenné krvi, kyslíkové saturace centrální žilní krve a krve z bulbu vnitřní jugulární žíly a parametry acidobazické rovnováhy, a to šestkrát během výkonu u všech skupin pacientů. Následně byla analyzována data z časného a pozdního pooperačního průběhu, včetně nemocniční tříleté mortality, a srovnána mezi jednotlivými skupinami.

VÝSLEDKY:

K rozvoji laktátové acidózy nedošlo v žádné ze skupin. V porovnání se skupinami TEA-GA a GA byly ve skupině TEA mírně vyšší kyslíkové desaturace z centrální žilní krve a z krve jugulárního bulbu během mimotělního oběhu a v období po jeho ukončení. U skupiny TEA dále došlo na konci výkonu k rozvoji mírné respirační acidózy a mírnému poklesu arteriální kyslíkové saturace bez patrných klinických důsledků. Na základě těchto měření nebylo nutno ve skupině TEA přistoupit k navýšení krevních průtoků mimotělního oběhu. Taktéž jsme nezaznamenali významné rozdíly v pooperačních výsledcích mezi skupinami, vyjma nižší incidence fibrilace síní u pacientů skupiny TEA v porovnání se skupinou GA. Skupiny TEA a TEA-GA měly ve srovnání se skupinou GA nižší skóre bolesti hodnoceno VAS stupnicí a nižší celkovou dávku morfinu během prvních 24 hodin pooperačně.

ZÁVĚR:

Standardní průtoky mimotělniho oběhu byly adekvátní a poskytly dostatečnou dodávku kyslíku do tkání u pacientů podstupujících kardiochirurgický výkon při vědomí. Metoda výkonu provedeného v epidurální anestezii při vědomí neprokázala zlepšení pooperačních výsledků vyjma nižší incidence fibrilace síní a kvalitnějšího tlumení bolesti.

# 2. INTRODUCTION

Awake cardiac surgery technique (AWCS) with the use of sole thoracic epidural anesthesia (TEA) has recently emerged as an alternative to classic general anesthesia (GA) and combined anesthesia (TEA-GA), following the introduction of minimally invasive cardiac surgical procedures. TEA alone has been used in low risk AWCS off-pump [1,2], and on-pump [3] procedures as well as in high risk on-pump procedures [4].

TEA offers several advantages in comparison to sole GA including thoracic sympathicolysis, attenuated stress response and myocardial blood flow redistribution [5] and has been utilized as combined TEA-GA anesthesia. Moreover, TEA likely decreases incidence of postoperative myocardial infarction [6] and arrhythmias [5,7] , improves postoperative pain control [5] and pulmonary outcome [7,8]. Additionally, TEA awake patients may benefit from spontaneous ventilation, which is likely to be a significant advantage in comparison with tracheal intubation and mechanical ventilation in GA and TEA-GA patients [9].

Contrary to awake TEA, anesthetics and muscle relaxants used for GA and TEA-GA decrease whole body oxygen consumption ($VO_2$) [10]. However, usually only mild sedation or no anesthetics at all have been used in AWCS with TEA, therefore $VO_2$ may be increased and standard blood flow rates (BFRs) during cardiopulmonary bypass (CPB) may not be sufficient enough for these patients. This could lead to inadequate oxygen delivery ($DO_2$), increased tissue oxygen extraction with venous desaturation and eventually result in lactic metabolic acidosis which has been previously related to poor patient's outcome [11]. Moreover, lower doses of anesthetics are used in TEA-GA as compared to GA which may affect $VO_2$, tissue oxygen extraction and venous saturations.

It has been assumed that the standard BFRs of CPB, which were validated only for GA [12], have been sufficient and have been used in all studies with patients undergoing AWCS with TEA [3,4] as well as TEA-GA. Nevertheless, it remains unknown, whether or not the use of standard BFRs in AWCS with TEA is associated with detrimental lactic acidosis and other possible consequences of inadequate BFRs mentioned above.

Thus, in the first phase of our study, we evaluated the adequacy of standard blood flow rates during cardiopulmonary bypass in awake TEA patients undergoing cardiac sugery and made a comparison of this data to patients under GA and TEA-GA.

Subsequently, in the second phase of the study, we focused on clinical outcomes of awake cardiac surgical patients and evaluated the impact of awake TEA technique on major parameters of postoperative complications with comparison to patients with GA and TEA-GA.

# 3. REVIEW OF LITERATURE

## 3.1 Epidural anesthesia in cardiac surgery

The first description of thoracic epidural anesthesia and analgesia applied to cardiac surgical patients occurred in 1954 [13]. However, application of thoracic epidural anesthetic techniques to patients undergoing cardiac surgery during the modern surgical era was initially reported by Hoar et al. [14] in 1976. They described the use of thoracic epidural catheters during the early postoperative period to provide analgesia and effectively control hypertension. The report by El-Baz and Goldin in 1987 [15] was the first to describe the insertion of thoracic epidural catheters in patients before performance of cardiac surgery. Since this time, clinical investigators have subsequently applied thoracic epidural techniques to patients undergoing cardiac surgery [5,7,9]. Most investigators have used thoracic epidural local anesthetics in hopes of providing analgesia, stress response attenuation, or thoracic cardiac sympathectomy. Some investigators have used thoracic epidural opioids to provide intraoperative and postoperative analgesia.

### 3.1.1 The principles of epidural anesthesia

The epidural anesthesia provides somatosensoric and vegetative neural blockade from distinct part of human body. This is achieved by administering a solution of local anesthetic with possible admixture of opioids into the epidural space, where it inhibits the transmission of action potentials in the present neural structures.

Anatomically, the epidural space is the area between the dura mater and the ligaments and periosteum lining the vertebral canal and extending from the foramen magnum to the sacrococcygeal membrane. This has been described as a potential space, because it is normally completely filled with a loose type of adipose tissue, lymphatics, and blood vessels. It is particularly rich in venous plexi. No free fluid exists in the epidural space, in contradistinction to the cerebrospinal fluid, which is found in the subarachnoid space. However, solutions injected into the epidural space spread in all directions owing to the loose tissue structure that occupies this area. Epidural anesthesia is usually subdivided into the three categories, depending on the site of injection: thoracic epidural, lumbar epidural, and caudal anesthesia. Cervical epidural anesthesia is possible but rarely performed.

Thoracic epidural anesthesia is employed mainly for production of a segmented band of analgesia involving thoracic dermatomes. This technique has proved beneficial for relief of pain after thoracic, cardiac or upper abdominal surgery. Lumbar epidural anesthesia is useful as an adjunct to surgical procedures involving the lower abdomen, pelvis, perineum, and lower extremities, and for obstetric procedures. Caudal anesthesia is usually reserved for pelvic and perineal surgery and for vaginal deliveries.

A special, 18 Gauge, Touhy needle with the round tip is used for epidural puncture. There are two techniques used for the detection of epidural space. It is either a "hanging drop" or "loss of resistance" technique. The principle of both of these methods is the creation of the negative pressure in epidural space, caused by a motion of dura mater from ligamentum flavum. The administration of local anesthetic solution into the epidural space follows its puncture.

The quality and extension of neural blockade is determined by the concentration and total volume of administered local anesthetic solution. The higher concentration of local anethetic blocks the neural transmission of faster-conducting myelinated fibers, such as the motor nerve fibers (type Ia**)** or sensory nerve fibers (type II). In the opposite, low concentration of local anesthetics only blocks neural transimission in thin myelinezed fibers, such as preganglionary sympathetic fibers or fibers for pain and heat sensation (type III) or slow-conducting unmyelinated C fibers (type IV). The blockade extension is influenced by the total volume of local anesthetic solution. One spinal segment is usually blocked by 1.0-1.5 ml of local anesthetic solution.

### 3.1.2 Physiological effects of thoracic epidural anesthesia

The surgical procedures can be accomplished with satisfactory anesthesia and analgesia by epidural administration of local anesthetics. In addition, the sympathetic blockade can produce beneficial effects on several organ systems [16] including an increased gastrointestinal motility and perfusion or decreased myocardial ischemia and systemic stress response to surgery [16-19].

The cardiovascular effects of epidural anesthesia comprise of decreased determinants of myocardial oxygen demand [20], improvement of myocardial blood flow [21,22] and left ventricular function [23], and reduced thrombotic-related complications [24]. Furthermore, it has been shown that epidural anesthesia can reduce heart rate and occurrence of arrhythmias during manipulation of the heart [25,26].

The impact of epidural anesthesia on lung function can be ambiguous. Satisfactory analgesia and the avoidance of mechanical irritation must be balanced against the possible alteration of lung function by epidural motor blockade of respiratory muscles and the potentially detrimental effects of sympathicolysis, leaving an unopposed vagal tone with potentially increased bronchial tone and reactivity [27]. The physiological effects of TEA on lung function are determined by the extension of the motor blockade depending on the height of the insertion of the catheter, the choice of local anesthetic, and its concentration [27].
Early postoperative lung function is affected by residual muscular relaxation, the time of extubation, pain therapy, and vigilance. Early after an operation, the ability to cough represents one of the most important factors influencing lung function and is dependent, to a great extent, on the efficacy of diaphragmatic contraction and pain relief. On the other hand, with general anesthesia, reduced vigilance, muscular rest relaxation, and impaired diaphragmatic function may prolong mechanical ventilation, which is a risk factor for pulmonary complications and morbidity [9].

### 3.1.3 Evidence-based clinical outcomes of thoracic epidural anesthesia

A meta-analysis published by Liu et al. [28] assessed effects of perioperative central neuraxial techniques on outcome after coronary artery bypass surgery. Fifteen trials enrolling 1178 patients were included for thoracic epidural analysis, and 17 trials enrolling 668 patients were included for intrathecal analysis. Thoracic epidural techniques did not affect incidences of mortality or myocardial infarction yet seemed to reduce the risk of dysrhythmias (atrial fibrillation and tachycardia), pulmonary complications (pneumonia and atelectasis), the time to tracheal extubation, and analogue pain scores. These authors conclude that central neuraxial techniques do not affect rates of mortality or myocardial infarction after CABG yet may be associated with improvements in faster time to tracheal extubation, decreased pulmonary complications and cardiac dysrhythmias, and reduced pain scores.

The most recent meta-analysis showed that the use of TEA in patients undergoing cardiac surgery reduces the risk of postoperative supraventricular arrhythmias and respiratory complications. However, the sparsity of events precluded conclusions about mortality, myocardial infarction, and stroke, but the estimates suggested a reduced risk after TEA [7].

## 3.2 Awake cardiac surgery

Procedures to minimize surgical, anesthesiologic, or cardiopulmonary bypass trauma during cardiac operations have been in continuous development in an effort to reduce perioperative mortality and morbidity. Awake cardiac surgery technique with the use of sole thoracic epidural anesthesia without endotracheal intubation has recently emerged as an alternative to classic general anesthesia and combined anesthesia, following the introduction of minimally invasive cardiac surgical procedures. The use TEA alone has been initially published by Karagoz [1], desciribing the use of this method in patients undergoing mycoardial revascularization (CABG) without the use of cardiopulmonary bypass (off-pump CABG). More reports on awake cardiac surgery technique followed shortly, mostly including low-risk off-pump [2], and on-pump [3] procedures. Recently, this technique has been also used in high risk on-pump procedures [4].

The principle of awake technique is the use of high TEA without endotracheal intubation and mechanical ventilation in patients undergoing cardiac surgery. The anesthesia for the surgical field is only provided by TEA, covering dermatomes Th1-Th10. A slight sedation is often administered as an adjunct to TEA to yield more comfort to the patients, especially when the surgery lasts for a longer period of time.

Due to its nature, awake TEA may offer several advantages over general anesthesia including spontaneous ventilation without tracheal intubation [9], reduced stress response [5], reduced incidence of postoperative arrhythmias [5] and myocardial infarction [6] and improved pulmonary outcome [7,8]. All these factors may participate in the reduction of postoperative complications and morbidity [5,7,8].

With awake cardiac surgery risk of postoperative pulmonary failure and long-term ventilation may also be reduced because mechanical ventilation is avoided. This might have a clinical impact in patients with severe COPD, who represent very high-risk patient´s cohort with increased perioperative morbidity and mortality [29]. Some patients have hemodynamic compromise as a result of general anesthetic medication before intubation, which may increase the risk of preoperative myocardial ischemia in patients with severe coronary artery disease [30]. This also may be avoided in the conscious setting. In addition to these advantages, postoperative pain management is facilitated by continuous epidural application of analgesics.

In comparison with clinical data of patients with combined anesthesia undergoing cardiac surgery, there is very limited evidence on detailed analysis of early and late

postoperative outcome in awake cardiac surgical patients. Studies published so far focused more on description of the awake technique and peroperative course with very sparse comments on postoperative results [1,3,4]. Except for one study [2], none of these reports used controlled study design [1,3,4].

## 3.3 General anesthesia and oxygen consumption

General anesthesia is a state of unconsciousness and loss of protective reflexes resulting from the administration of one or more general anesthetic agents. A variety of medications may be administered, with the overall aim to ensure hypnosis, amnesia, analgesia, relaxation of skeletal muscles, and loss of control of reflexes of the autonomic nervous system.

There are basically three types of general anesthesia techniques. These include balanced anesthesia, solely inhalation aneshesia and total intravenous anesthesia.The most commonly used technique is a balanced anesthesia, which is based on the concept that administration of a mixture of different anesthetic components (including volatile anesthetics, intravenous anesthetics, opioids and muscle relaxants) summates the advantages but not the disadvantages of the individual components of the mixture. Every component of general anesthesia has its own effect on $VO_2$, which is described in detail below. Also many other physiological parameters affect $VO_2$ during general anaesthesia including body temperature [31], skeletal muscle activity [32] and passive hyperventilation [33].

### 3.3.1 Intravenous anesthetics and opioids

It is believed that the effects of intravenous anesthetics on total $VO_2$ are caused mainly by a decrease in cerebral oxygen consumption (cerebral metabolic rate – $CMRO_2$) and in myocardial oxygen consumption, while the other organs are involved in contributing to the overall decrease in $VO_2$ to a lesser extent. A decrease in $CMRO_2$ with thiopental infusion in man has been reported by several investigators [34,35]. In these studies the decrease $CMRO_2$ following thiopental varied from 30 to 55 % and was somewhat related to the total dose. As $CMRO_2$ accounts for approximately 20 % of the total $VO_2$ in man [36], 40 % fall in $CMRO_2$ results in 8% reduction in total $VO_2$. Similar to thiopental, propofol reduces $CMRO_2$ by 36% [37]. With a background of 0.5% enflurane, propofol still reduces $CMRO_2$ by 18%, whereas lactate and glucose metabolism remains unchanged [37]. It has been also reported that opioids

show the similar effects on $VO_2$ as intravenous anesthetics. The reduction of $VO_2$ may be as high as 10%, dependent on the dose used [10].

### 3.3.2 Volatile anesthetics

Similar to intravenous general anesthetics, volatile anesthetics also decrease oxygen consumption predominantly by decreasing cerebral and myocardial metabolic rate. Volatile anesthetics decrease $CMRO_2$ in a dosed dependent manner in animals and humans [38,39] with the magnitude of $CMRO_2$ reduction as high as 45%. In analogy to the effects of most other anesthetics, the reduction in $CMRO_2$ is caused primarily by the reduction in cerebral activity associated with the anesthetic effect of volatile anesthetics. An intrinsic effect on cellular metabolism seems unlikely at commonly used concentrations of MAC 1-1.5. However, other studies show that volatile anesthetics do not additionally decrease $CMRO_2$ when used as a supplement to deep intravenous anesthesia [40]. This observation was subsequently confirmed by Heath et al. [41], who found no decrease in $VO_2$ during propofol anesthesia supplemented by 0.5 MAC sevoflurane but a reduction in the cerebral arterial-venous oxygen content difference of 25% by 1.5 MAC sevoflurane [41].

Hemodynamic effects of changes in $CMRO_2$, which are represented by cerebral blood flow reduction, are partially counterbalanced by an intrinsic cerebral vasodilatory effect of volatile anesthetics [43]. Cerebrovascular $CO_2$ reactivity is not impaired by the administration of commonly used concentrations of volatile anesthetics [42]. There are not significant differences in cerebral blood flow and $CMRO_2$ between different volatile anesthetics [43]. A mild myorelaxant effect may also contribute to the decrease of whole body $VO_2$ by reducing the basal muscle tone.

### 3.3.3 Muscle relaxants

It has been suggested that neuromuscular blockade reduces whole body $VO_2$ by minimizing muscle activity and tone [44,45]. Study by Irish et al. demonstrated that in the unconscious and unmoving patient during CPB, administration of muscle relaxants to achieve complete neuromuscular blockade significantly reduced systemic $VO_2$ by rate of 30% with a concomitant increase in mixed venous oxygen saturation from 73% ± 18% to 83% ± 14%. Choice of muscle relaxant did not influence the change in $VO_2$ [46]. Subsequent studies also confirmed that neuromuscular blockade significantly reduces oxygen consumption and energy expenditure in critically ill patients who are sedated and mechanically ventilated [47]. However, another study provided contradictory results when neuromuscular blockade did not decrease

oxygen consumption. As authors speculated, this was possibly caused by sufficient anesthetic depth that prevented subclinical muscular activity [48].

## 3.4 Cardiopulmonary bypass

Cardiopulmonary bypass is indispensable to the current practice of cardiac surgery. Ideally, CPB should achieve several goals including maintaining systemic perfusion with oxygenation and carbon dioxide elimination, facilitating performance of the surgery and preserving systemic homeostasis during surgery.

### 3.4.1 CPB blood flow rates and systemic oxygen delivery

The CPB blood flow rates (BFR) required to provide adequate tissue perfusion are influenced by several variables including whole body oxygen consumption ($VO_2$), depth of anesthesia and muscle relaxation, degree of hypothermia, oxygen content of blood and individual organ ischemia tolerance.

So called "standard" CPB BFRs of 2.2-2.5 l/min*$m^2$ have been commonly used during normothermic CPB [49]. It has been recommended to set BFRs within this range for patients under general anesthesia [12], whose whole body $VO_2$ is decreased by 15-30% depending on the type and amount of anesthetics and muscle relaxants used [10,36,38,46]. The original studies that calculated these values were conducted in 1950' s [12] in cardiac surgical patients, who were deeply anesthetized using high doses of opioids in comparison with today's low dose opioid anesthetic practice.

Systemic oxygen delivery has been identified as the more precise determinant of optimal perfusion during CPB [49]. $DO_2$ is calculated by multiplying BFR by the arterial oxygen content:

$DO_2$ = BFR * ((hemoglobin concentration*hemoglobin oxyegen saturation* 1.36) + (0.003* arterial oxygen tension)).

The $DO_2$ calculation comprises of two significant perfusion parameters that determine tissue oxygenation: hematocrit values and BFR into a single measure. In the clinical setting, $DO_2$ can be improved by increasing BFR, increasing hematocrit concentrations, or by increasing hemoglobin saturation and the amount of dissolved oxygen (increasing the inspired oxygen concentration [$FiO_2$]).

$DO_2$ values observed during CPB are typically less than those measured in awake and anesthetized subjects. During CPB, if BFRs of 2.2 to 2.4 l/min*$m^2$ are maintained and

hemoglobin values decrease to 7 o 8 g/dL, $DO_2$ will be reduced to 200–300 ml $O_2$/ min*$m^2$. The reduction in $DO_2$ that is observed on CPB is due primarily to a decrease in arterial oxygen content that occurs from hemodilution at the onset of bypass. If whole-body $VO_2$ is unchanged, an increase in the oxygen extraction ratio is required to compensate for the reduced $DO_2$. The minimal safe $DO_2$ during bypass, termed the critical $DO_2$, has been assessed in several investigations. As $DO_2$ decreases, $VO_2$ initially remains stable via increases in tissue oxygen extraction ("flow independent oxygen consumption"). At the point when maximal oxygen extraction is reached, whole body $VO_2$ and tissue oxygenation begin to decrease and metabolic (lactic) acidosis begins to develop ("flow dependent oxygen consumption") [49]. Hyperlactatemia is a well-recognized marker of tissue hypoxia and its severity has been associated with increased morbidity and mortality of patients undergoing CPB [11]. The critical $DO_2$ in anesthetized humans without CPB has been claimed to be approximately 330 mL $O_2$/min*$m^2$ [50]. However, critical $DO_2$ values during CPB have not been definitively established [49]. Studies in cardiac surgical patients, which examined the relationship between $DO_2$ and $VO_2$, have so far provided contradictory results [51,52].

In addition, low BFR during CPB itself has been also identified as an independent risk factor for development of hyperlactatemia [53] due to inadequate oxygen delivery to peripheral tissues [54]. However, the optimal BFRs during normothermic CBP have not yet been established [49] as discussed above and institutional perfusion practices are largely based on empirical experience.

### 3.4.2 Awake cardiac surgery and oxygen consumption/delivery during CPB

Contrary to awake cardiac surgery, anesthetics and muscle relaxants used for GA and TEA-GA decrease whole body oxygen consumption [10,36,38,46]. However, usually only mild sedation or no anesthetics at all have been used in awake patients with TEA, therefore $VO_2$ may be increased and standard blood flow rates during CPB may not be sufficient enough for these patients. This could lead to inadequate oxygen delivery, increased tissue oxygen extraction with venous desaturation and eventually result in lactic metabolic acidosis which has been previously related to poor patient's outcome [11]. Moreover, lower doses of anesthetics are used in TEA-GA as compared to GA which may affect $VO_2$, tissue oxygen extraction and venous saturations.

It has been assumed that the standard BFRs of CPB, which were validated only for GA [12], have been sufficient and have been used in all studies with awake patients with

TEA [3,4] as well as patients with combined anesthesia. Nevertheless, it remains unknown, whether or not the use of standard BFRs in awake patients with TEA is associated with detrimental lactic acidosis and other possible consequences of inadequate BFRs mentioned above.

# 6. HYPOTHESIS

Our study comprised of two phases. The first phase focused on peroperative period with cardiopulmonary bypass and examined the impact of awake TEA technique on sufficiency of oxygen delivery. In the second phase, we evaluated clinical outcomes of these patients in postoperative period. Therefore, we stated two hypotheses:

**Study phase 1 – Oxygen consumption in awake cardiac surgical patients**

We hypothesized, that in awake patiens with TEA undergoing cardiac surgery, the use of standard blood flow rates of 2.4 L/min*$m^2$ during cardiopulmonary bypass may lead to insufficiency of oxygen delivery with metabolic acidosis which would require a further increase of blood flow rates.

**Study phase 2 – Postoperative outcome in awake cardiac surgery**

We hypothesized, that awake technique with TEA reduces postoperative complications because of sympathetic blockade and avoidance of tracheal intubation with mechanical ventilation.

# 7. AIMS OF THE STUDY

**Study phase 1 – Oxygen consumption in awake cardiac surgical patients**

In the first study, we tested the adequacy of standard blood flow rates of 2.4 l/min*$m^2$ in awake TEA patients during cardiac surgery with cardiopulmonary bypass by monitoring and comparing of lactate levels, acid-base parameters (pH, base excess, $PaO_2$, $PaCO_2$), $DO_2$ and venous desaturations with groups of patients under sole general anesthesia and with combined anesthesia at six time points (before, during and after CPB) during surgery.

**Study phase 2 – Postoperative outcome in awake cardiac surgery**

In the second study, we evaluated the impact of awake TEA technique on major parameters of postoperative outcome, including early and late three-year mortality in comparison with patients undergoing cardiac surgery under combined and sole general anesthesia.

# 8. MATERIALS AND METHODS

The study included 47 consecutive patients undergoing on-pump cardiac surgery referred for aortic valve replacement, coronary artery bypass grafting or combined procedures after obtaining approval from the Local Ethics Committee and informed patient consent. Inclusion criteria were: planned on-pump cardiac surgery, age above 18 years. Exclusion criteria were: severe peripheral vascular disease, left ventricular systolic dysfunction (ejection fraction < 50%), allergy to local anesthetics, intraoperative conversion to GA, intraoperative myocardial infarction, stroke, pulmonary embolism, aortic dissection, pneumothorax.

Ethical and medical considerations did not allow a randomized study design. All advantages and disadvantages of each type of anesthesia were discussed in detail with every patient. Patients freely chose the most comfortable type of anesthesia for themselves. There were three study groups. The first group (TEA group) comprised of 17 patients undergoing AWCS with only TEA supported by a light sedation. The second group (TEA-GA group) consisted of 15 patients undergoing combined TEA and GA. The third group consisted of 15 patients undergoing sole GA (GA group).

**Premedication, cannulation sites and patient monitoring (TEA, TEA-GA, GA group)**

All patients received 7.5-15 mg of midazolam orally one hour prior to arrival at the operating room. Before the induction of anesthesia, hemodynamic monitoring was established via radial artery catheter (Arteriofix art.-Kath.-Set 22G/80mm, B.Braun, Melsungen, Germany). A central venous catheter (Central Venous Catheter Set with AMC THROMBOSIELD, Edwards Lifesciences, California, USA) was placed via right internal jugular vein into superior caval vein to measure central venous pressure (CVP) and to obtain blood samples. Another catheter (Arteriofix art.-Kath.-SET 22G/80mm, B.Braun, Melsungen, Germany) was inserted via internal jugular vein into right jugular bulb in order to obtain blood samples. An epidural space puncture was performed in the TEA group and the TEA-GA group before induction of anesthesia. During cannulation, patients ventilated via face mask with fresh gas flow of 6 L/min. Monitoring of all patients included 5-lead electrocardiography, intra-arterial blood pressure, central venous pressure, pulse oximetry, capnography, diuresis, nasopharyngeal (not in group TEA) and rectal temperature.

**Epidural puncture and thoracic epidural anesthesia (TEA and TEA-GA group)**

The epidural puncture was performed in the TEA and TEA-GA group at the level Th1/2 - Th2/3 using 18-gauge Tuohy epidural needle (Perican, B.Braun, Melsungen, Germany) under local anesthesia. Coagulation profiles of all patients were normal before epidural puncture. The epidural space was identified using hanging drop technique and 7 ml of 0.5% bupivacaine + 10 ug (2 ml) of sufentanil were administered as a bolus into the space. Afterwards, an epidural catheter (Perifix – Katheter, B.Braun, Melsungen, Germany) was inserted 2-4 cm into epidural space. The level of anesthesia was determined by loss of pinprick sensation (Th1-Th10). Then, continuous epidural infusion using mixture of 15 ml of 0.5% bupivacaine + 50 μg of sufentanil (10 ml) and 15 ml of saline was applied with a rate of 7-10 mL/hr till the end of surgery.

**Management of awake patients (TEA group)**

In awake patients group (TEA group), after epidural puncture, slight sedation was used by administering dexmedetomidine starting with 1 μg/kg dose infused over 10 minutes and continuing with infusion of 0.2-0.4 μg/kg/hr. Richmond agitation and sedation score scale was used targeting minus 1 grade in all patients (not fully alert, but with sustained awakening for more than 10 seconds, with eye contact, to voice) [37]. In order to monitor patients comfort and anesthesia sufficiency, patients were regularly questioned every 15 minutes about their status and sedation was adjusted if needed. Additional local anesthesia with 0.5% bupivacaine was used in patients in whom saphenous vein graft harvesting was required.

**General anesthesia (GA group)**

General anesthesia (GA group) was induced with intravenous bolus of thiopental (0.3-0.5 mg/kg), sufentanil (0.5 μg/kg) and rocuronium (0.4-0.6 mg/kg). General anesthesia was maintained using isoflurane of minimal alveolar concentration 0.7-1.0 in a gas mixture of oxygen and air. Total amount of sufentanil was 2.5-5 μg/kg according to the individual pain response. No other myorelaxation was needed throughout the procedure.

**Combined thoracic epidural and general anesthesia (TEA-GA group)**

In combined anesthesia group (TEA-GA group), epidural puncture was performed as described above. Then general anesthesia was induced and maintained using isoflurane in the same dosage as in GA group. Two patients required additional administration of sufentanil (they received 25 and 60 μg as a bolus, respectively).

**Pre and Post-CPB hemodynamic management (TEA, TEA-GA and GA group)**

Intraoperative hemodynamic management was identical for all groups and aimed to maintain mean arterial pressure (MAP) pre- and post-CPB between 65-80 mmHg. All patients received an infusion of 1000 ml of Ringer's solution, before CPB was commenced. Transient hypotension (defined as MAP < 65 mmHg) was managed with intravenous boluses of norepinephrine. Persistent hypotension required continuous infusion of norepinephrine. An infusion of more than 0.05 µg/kg/min of norepinephrine was considered as clinically significant vasopressor support.

**Surgery and CPB management (TEA, TEA-GA and GA group)**

Median sternotomy was used in all patients (TEA, TEA-GA and GA group). After administration of 300 IU/kg of unfractionated heparin to achieve activated clotting time > 480 seconds, cannulation of the aorta (24F x 20 cm aortic perfusion cannula, Edwards Lifesciences, California, USA) and right atrium (36F/46F x 40 cm Thin-Flex $^{TM}$ Dual Stage Venous Drainage Cannula , Edwards Lifesciences, California, USA) was performed and CPB was commenced. The time interval between epidural puncture and heparin administration was between 60 and 90 minutes. The CPB circuit was primed by 1500 ml of Hartmann's solution and 200 ml of 20% mannitol. CPB BFRs were kept at 2.4 L/min * $m^2$. Triggers for increasing BFRs were arterial lactate level >3 mmol/L or central venous oxygen saturations ScvO2 < 55%. MAP was maintained between 45 and 70 mmHg with boluses or continuous infusion of norepinephrine. A Stockert roller pump CPB and hollow-fiber oxygenator (Medos Hilite 7000 Rheoparin coated, MEDOS Medizintechnik, AG, Germany) was used. Fresh gas flow was initially set to 2 L/min and in-flow oxygen concentration to 60% and subsequently adjusted to maintain blood gases in physiological ranges ($PaO_2$ above 100 mmHg, $PaCO_2$ 35-45 mmHg). During CPB, all patients were kept normothermic (36-37 degrees of Celsius) and received blood cardioplegia. Transfusion trigger was set to 70 g/L of hemoglobin concentration. In the TEA-GA and GA group, isoflurane concentrations were not changed and no other intravenous anesthetics including propofol were used during CPB. The time interval between aortic cross clamp release and CPB discontinuation was 30% of the total aortic cross clamp time. Before weaning from CPB epicardial stimulation was used when needed. The effects of heparin were reversed with 3 mg/kg of protamine after discontinuation of CPB. Then chest closure was performed and patients were transferred to postoperative intensive care unit.

**Postoperative management (TEA, TEA-GA and GA group)**

After the transfer to ICU, patient´s monitoring included hemodynamic parameters (HR, MAP, and CVP), laboratory parameters (arterial and central venous acid base and blood gases parameters, hemoglobin concentration and glycemia in regular intervals), diuresis and blood loss. Patients in the TEA group breathed via face mask using fresh gas flow of 4-12 L/min according to their arterial oxygen parameters. Triggers for any kind of ventilatory support were $PaO_2 < 60$ mmHg and $PaCO_2 > 60$ mmHg.

Intubated patients (TEA-GA and GA group) were weaned off the ventilator and extubated according to local extubation protocol. This included fully awake, cooperative patient with stable hemodynamic parameters, without significant blood loss (< 200 ml/2 Hr) and with acceptable arterial blood gases parameters (i.e. $PaO_2 > 60$ mmHg and $PaCO_2 < 60$ mmHg) on non-aggressive ventilation (pressure support ventilation, PEEP ≤ 5 cm H20, $FiO_2$ ≤ 0.4, pressure support ≤ 6 cm $H_20$ and respiration frequency ≥ 10/min). In the GA group, postoperative pain management was conducted by a nurse-driven intravenous morphine protocol. Patients with visual analogue scale (VAS) scores < 50 received 1 mg of intravenous morphine and 2 mg of morphine were admininistered to patients with VAS scores >50. The minimal time interval between 2 morphine injections was 5 minutes and the maximal hourly dose was 10 mg.

After 24 hours an analgesic therapy continued with oral morphine-sulphate. Postoperative analgesia in the TEA and TEA-GA group was provided by continuous infusion of local anesthetics to epidural catheter (a mixture of 15 ml of 0.5% bupivacaine + 50 μg of sufentanil + 25 ml of saline infused by rate of 3-7 mL/hr), which was removed on the fourth postoperative day. In case of insuficciency of epidural analgesia, opioids were administered in the same way as in the GA group.

Criteria for intensive care unit discharge were as follows: fully alert and cooperative patient without significant neurological impairment, hemodynamic stability without inotropic or vasopressor therapy, no hemodynamically significant arrhytmias, spontaneous breathing with arterial oxygen saturation > 90% at FiO2 ≤50% via a facemask, urine output > 0.5 ml/kg/hr, chest tube drainage < 20 ml/hr. Criteria for the hospital discharge were as follows: hemodynamically stable with controlled arrhythmias, independent in ambulation and feeding, afebrile with no infections and clean wound , normal voiding and bowel movements, full oral diet, pain controlled on oral medication.

**Study protocol (Group TEA, TEA-GA and GA)**

**Phase 1** (Oxygen consumption in awake cardiac surgical patients):

The study protocol consisted of hemodynamic measurements and blood samples draws performed at six consecutive time points throughout the study, before, during and after CPB. The time points (T) included T1 (early pre-CPB period; baseline prior to induction of anesthesia), T2 (late pre-CPB period; beginning of cardiac surgery after sternotomy), T3 (early-CPB period; initiation of CPB, after aortic cross clamping and prior to cardiac surgery), T4 (late- CPB period; end of CPB, after the cardiac surgery procedure and release of aortic cross clamp), T5 (early post-CPB; 10 minutes after discontinuation of CPB and protamine sulfate administration) and T6 (late post-CPB period; after chest closure).

Hemodynamic measurements consisted of heart rate, MAP and CVP. Blood samples from all 3 cannulation sites were drawn and analyzed in blood gas analyzer (ABL 700 Series, Radiometer Copenhagen, Denmark). Blood parameters included arterial oxygen saturation ($SaO_2$), arterial partial pressure of carbon dioxide ($PaCO_2$), arterial lactate, arterial pH, arterial base excess (BE), arterial hemoglobin concentration, central venous oxygen saturation ($ScvO_2$) and jugular bulb oxygen saturation ($SjbO_2$).

Oxygen delivery was calculated only for CPB period (T3 and T4) using following formula: $DO_2 = 2.4\ l/min*m^2 \times (1.36 \times Hb \times SaO_2/100 + 0.003 \times PaO_2)$.

**Phase 2** (Postoperative outcome in awake cardiac surgery):

We recorded and compared early postoperative outcome data including all major organ systems outcome parameters and early (ICU and hospital) mortality among the groups. The quality of analgesia was evaluated using VAS scoring that was recorded every 4 hours and compared at 24 hours postoperatively among the study groups. Additionally, morphine requirements during the first 24 hours postoperatively were compared among the study groups.

Follow up data for each patient were collected after a three-year period via telephone interviews or correspondence and included an inquiry on overall satisfaction with perioperative course and anesthesia, mortality and cause of death. The response rate was 100%.

**Statistical analysis**

Data are presented as mean ± standard deviation. SPSS 13.0 software was used for statistical analysis. Chi-square test was used for comparisons of preoperative qualitative parameters. Normal distribution was tested for all quantitative parameters. Kruskal-Wallis non-parametric analyses with Mann-Whitney tests were used for comparisons of quantitative parameters among the study groups. Friedman non-parametric tests with Wilcoxon tests were used to assess the differences of quantitative parameters at different time points in a single study group. Bonferrroni corrections were used for the multiple comparisons. P values $<0.05$ were considered statistically significant.

# 9. RESULTS

Forty-seven consecutive patients were enrolled in the study from 2005 to 2008. Two patients in the TEA group were excluded from the final analysis the phase 1 study (Oxygen consumption in wake cardiac surgical patients) because of conversion to GA. The first patient suffered from a severe embolic stroke after discontinuation of CPB. He had to be intubated and subsequently died on the third postoperative day due to cerebral edema. The second patient suffered from aortic dissection after decannulation of aorta and had to be intubated. After surgical correction, he had an uneventful postoperative course. The rest of the patients had uneventful perioperative course and there were no serious complications, including those related to epidural puncture and use of epidural catheter (epidural hematoma, abscess, spinal cord or nerve injury, accidental dural puncture, high spread of epidural anesthesia).

**Demographic, preoperative and perioperative data**

There was no difference in demographic, preoperative and perioperative data across all study groups, except for lower weight in the TEA group as compared to the TEA-GA group (Table 1) and a mildly longer aortic cross clamp time in TEA-GA group as compared to the TEA and the GA groups (Table 2). Other inotropes except for norepinephrine (Table 2) including dobutamine, dopamine and epinephrine were not needed during the procedures.

**TABLE 1. Demographic and preoperative data**

| | TEA (n=15) | TEA-GA (n=15) | GA (n=15) | P-value |
|---|---|---|---|---|
| Age (years) | 67 ± 10 | 64 ± 11 | 67 ± 7 | 0.451 |
| Weight (kg) | 67 ± 7 | **82 ± 15**[*] | 79 ± 15 | **0.025** |
| Height (cm) | 174 ± 9 | 173 ± 11 | 173 ± 9 | 0.948 |
| BMI ($kg/m^2$) | 26 ± 5 | 28 ± 5 | 27 ± 4 | 0.454 |
| BSA ($m^2$) | 1.9 ± 0.2 | 2 ± 0.2 | 2 ± 0.2 | 0.702 |
| Male (female) | 9(6) | 10(5) | 10(5) | 0.908 |
| CAD | 6/15 | 8/15 | 7/15 | 0.765 |
| Hypertension | 12/15 | 11/15 | 12/15 | 0.879 |
| LV EF (%) | 63 ± 5 | 62 ± 7 | 58 ± 7 | 0.147 |
| COPD | 4/15 | 4/15 | 2/15 | 0.598 |
| Diabetes mellitus | 6/15 | 5/15 | 6/15 | 0.910 |
| Stroke/TIA | 1/15 | 1/15 | 0/15 | 0.593 |
| NYHA: | | | | 0.624 |
| I. | 7% | 0% | 0% | |
| II. | 40% | 47% | 53% | |
| III. | 40 % | 40% | 47% | |
| IV. | 13% | 13% | 0% | |
| EUROSCORE ad. | 4.7 ± 2.3 | 4.3 ± 1.5 | 4.4 ± 21 | 0.689 |
| Serum creatinine (umol/l) | 95 ± 21 | 100± 26 | 99 ± 30 | 0.624 |
| Type of surgery: | | | | 0.914 |
| AVR | 67% | 60% | 60% | |
| CABG | 20% | 33% | 27% | |
| AVR + CABG | 13% | 7% | 13% | |

TEA, thoracic epidural anesthesia group; TEA-GA combined thoracic epidural anesthesia and general anesthesia group; GA, general anesthesia group; CAD, coronary artery disease; LV EF, left ventricular ejection fraction; COPD, chronic obstructive pulmonary disease; TIA, transitory ischemic attack; NYHA, New York Heart Association heart failure classification; EUROSCORE ad., European System for Cardiac Operative Risk Evaluation, additive score; BMI, body mass index; BSA, body surface area; AVR, aortic valve replacement; CABG, coronary artery bypass grafting. [*] $P<0.05$ vs. TEA, [†] $P<0.05$ vs. TEA-GA.

**TABLE 2. Peroperative data**

| | TEA (n=15) | TEA-GA (n=15) | GA (n=15) | P-value |
|---|---|---|---|---|
| Blood loss (mL) | 490 ± 90 | 560 ± 190 | 520 ± 160 | 0.408 |
| Transfusion (PRBC units) | 1.5 ±1.4 | 2.3 ± 2.5 | 1.1 ± 1.8 | 0.248 |
| Duration of surgery (minutes) | 280 ± 32 | 270 ± 42 | 263 ± 45 | 0.450 |
| Duration of CPB (minutes) | 92 ± 11 | 87 ± 15 | 86 ± 19 | 0.167 |
| Aortic cross clamp time (minutes) | 52 ± 10 | **61 ± 10** * | **51 ± 18** † | 0.048 |
| Surgical revision due to ischemia | 0 | 0 | 0 | |
| Surgical revision due to bleeding | 0 | 1 | 0 | 0.406 |
| Norepinephrine > 0,05 μg/kg/min | 20% | 47% | 53% | 0.143 |

TEA, thoracic epidural anesthesia group; TEA-GA combined thoracic epidural anesthesia and general anesthesia group; GA, general anesthesia group; CPB, cardiopulmonary bypass; PRBC, packed red blood cells.

* $P < 0.05$ vs. TEA, † $P < 0.05$ vs. TEA-GA.

## Hemodynamics

All the hemodynamic data are included in Table 3. Heart rates in the post-CPB (T5 and T6) period were higher then in the pre-CPB period (T1 and T2) in all groups. As compared to the TEA-GA and GA groups, the TEA group had significantly higher heart rates in the pre-CPB period. As expected, MAP significantly dropped during the CPB period (T3 and T4) in all groups. No significant difference in MAP was found among the groups at any time point except for T2 and T5 when MAP was or tended to be higher in the TEA group in comparison with the other two groups. CVP increased significantly in the post-CPB period in all groups. No significant difference in CVP was noted among the groups at any time point.

**TABLE 3. Hemodynamic data**

| | **T1** | **T2** | **T3** | **T4** | **T5** | **T6** | Fried-T |
|---|---|---|---|---|---|---|---|
| **HR (bpm)** | | | | | | | |
| TEA | 80 ± 9 | 75 ± 8 | --- | --- | 86 ± 7 [b] | 86 ± 6 [b] | **P=0.001** |
| TEA-GA | **64 ± 7** [*] | **63 ± 6** [*] | --- | --- | 87 ± 5 [ab] | 86 ± 5 [ab] | **P=0.001** |
| GA | **68 ± 11** [*] | **61 ± 8** [* a] | --- | --- | 89 ± 3 [ab] | 88 ± 4 [ab] | **P=0.001** |
| K-W test | **P=0.001** | **P=0.001** | --- | --- | P=0.276 | P=0.312 | |
| **MAP (mmHg)** | | | | | | | |
| TEA | 93 ± 7 | 88 ± 9 | 56 ± 5 [ab] | 59 ± 4 [ab] | 85 ± 6 [cd] | 82 ± 8 [cd] | **P=0.001** |
| TEA-GA | 89 ± 11 | 82 ± 8 | 63 ± 8 [ab] | 62 ± 11 [ab] | **78 ± 6** [* acd] | 78 ± 4 [acd] | **P=0.001** |
| GA | 86 ± 11 | **76 ± 7** [*] | 61 ± 9 [ab] | 61 ± 9 [ab] | **76 ± 7** [* acd] | 77 ± 8 [cd] | **P=0.001** |
| K-W test | P=0.120 | **P=0.001** | P=0.107 | P=0.846 | **P=0.001** | P=0.302 | |
| **CVP (mmHg)** | | | | | | | |
| TEA | 8 ± 4 | 9 ± 3 | --- | --- | 10 ± 3 | 11 ± 4 [ab] | **P=0.001** |
| TEA-GA | 8 ± 2 | 9 ± 2 | --- | --- | 8 ± 3 | 11 ± 3 [ae] | **P=0.004** |
| GA | 7 ± 3 | 8 ± 3 | --- | --- | 9 ± 2 | 10 ± 3 [ab] | **P=0.001** |
| K-W test | P=0.466 | P=0.697 | --- | --- | P=0.371 | P=0.665 | |

TEA, thoracic epidural anesthesia group; TEA-GA combined thoracic epidural anesthesia and general anesthesia group; GA, general anesthesia group; HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; bpm, beats per minute; K-W, Kruskal-Wallis analyses. Fried-T, Friedman non-parametric tests).

[*] *P*<0,0 vs. TEA, [†] P <0.05 vs. TEA-GA, [a] *P* <0,05 vs. T1, [b] *P* <0,05 vs. T2, [c] *P* <0,05 vs. T3, [d] *P* <0,05 vs. T4, [e] *P* <0,05 vs. T5.

## 9.1 Oxygen consumption in awake cardiac sugerical patients (Phase 1 study)

### Arterial acid base parameters

In all groups, arterial lactate level increased from baseline (T1 and T2), peaking during the CPB period at T3, and then slowly decreased at T4 and during the post CPB period (Figure 1). In the TEA group the lactate levels were comparable to baseline values, while in the TEA-GA and GA groups, arterial lactate levels remained higher at the end of the study (T6) as compared to baseline (T1). Arterial lactate levels varied among the groups and never exceeded 3 mmol/L. Arterial lactate levels were significantly lower in the TEA group as compared to the other two groups throughout the study (T1-T6), except for T1 (TEA vs. GA, P=NS) and T3 (TEA vs. GA, P=NS).

**Figure 1**

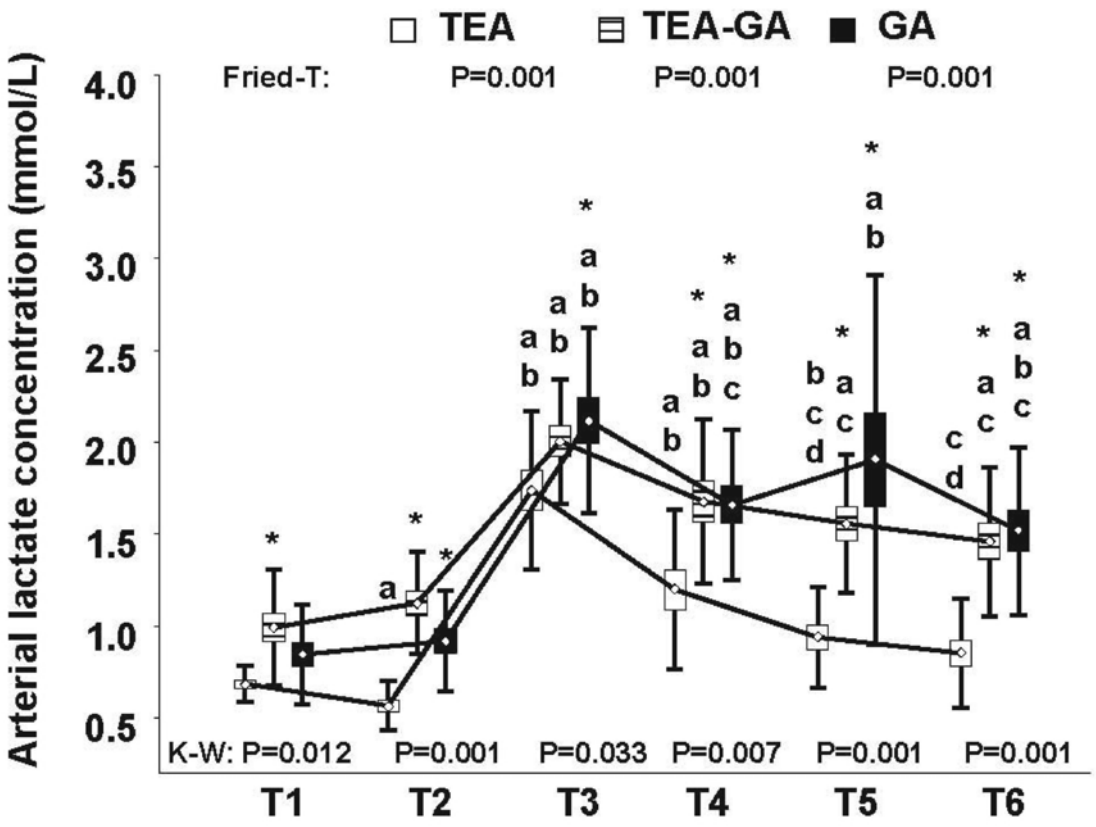


Figure 1: Arterial lactate concentration. The means are depicted as rhomboids within boxes indicating standard errors. Whiskers indicate standard deviations. K-W, Kruskal-Wallis analyses, Fried-T, Friedman non-parametric tests .$^{*}$ $P < 0,05$ vs. TEA. $^{\dagger}$ $P < 0,05$ vs. TEA-GA. $^{a}$ $P = 0,05$ vs. T1. $^{b}$ $P = 0,05$ vs. T2. $^{c}$ $P = 0,05$ vs. T3. $^{d}$ $P = 0,05$ vs. T4. $^{e}$ $P = 0,05$ vs. T5.

Arterial pH decreased significantly in the TEA group in the post CPB period (T5 and T6) as compared to the pre CPB and CPB periods (T1-T4) (Figure 2). In the other two groups, there was a trend towards a decrease in the post CPB periods. Arterial pH varied among the groups, being lower in the TEA group as compared to the other groups in the post CPB period (T5 and T6).

**Figure 2**

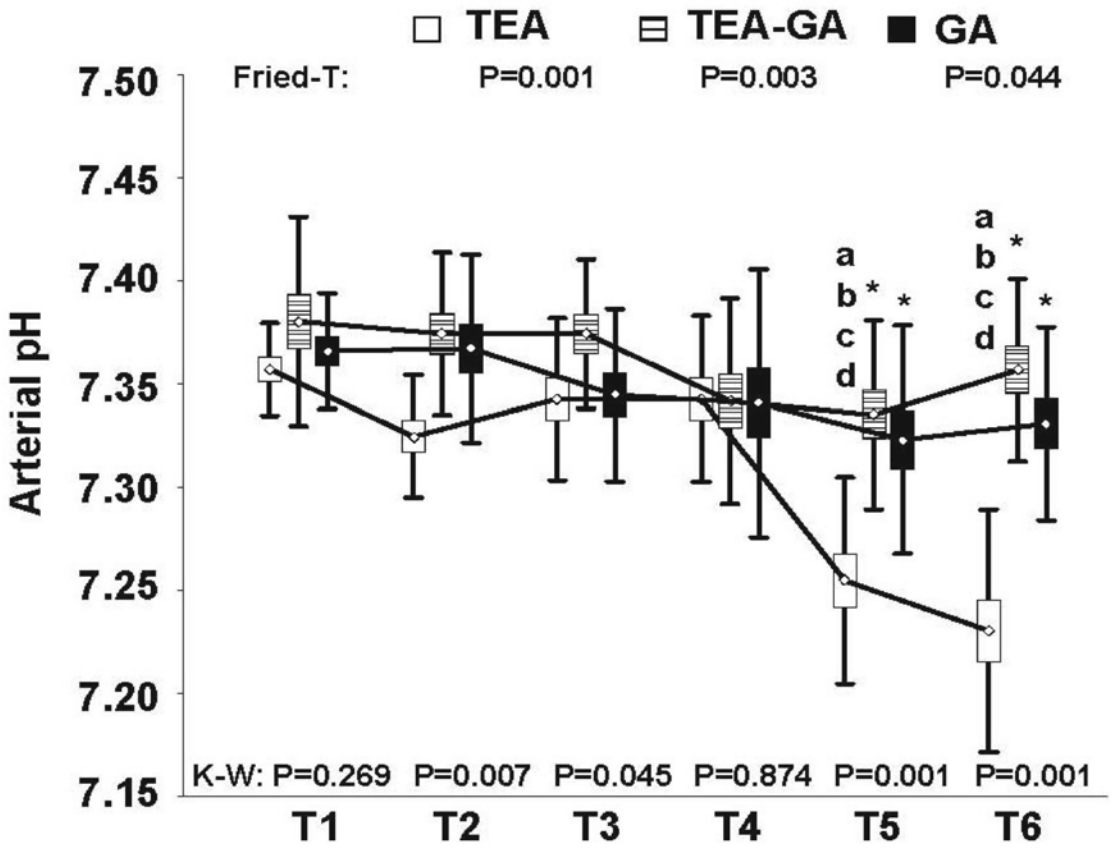


Figure 2: Arterial pH. The means are depicted as rhomboids within boxes indicating standard errors. Whiskers indicate standard deviations. K-W, Kruskal-Wallis analyses, Fried-T, Friedman non-parametric tests.[*] $P < 0,05$ vs. TEA. [†] $P < 0,05$ vs. TEA-GA. [a] $P = 0,05$ vs. T1. [b] $P = 0,05$ vs. T2. [c] $P = 0,05$ vs. T3. [d] $P = 0,05$ vs. T4. [e] $P = 0,05$ vs. T5.

Arterial BE decreased significantly during the procedure in all groups, reaching the highest values in the post CBP period (T5 and T6) (Figure 3). There was no difference among the groups in arterial BE, except for T4 when BE was higher in group GA as compared to the TEA group.

**Figure 3**

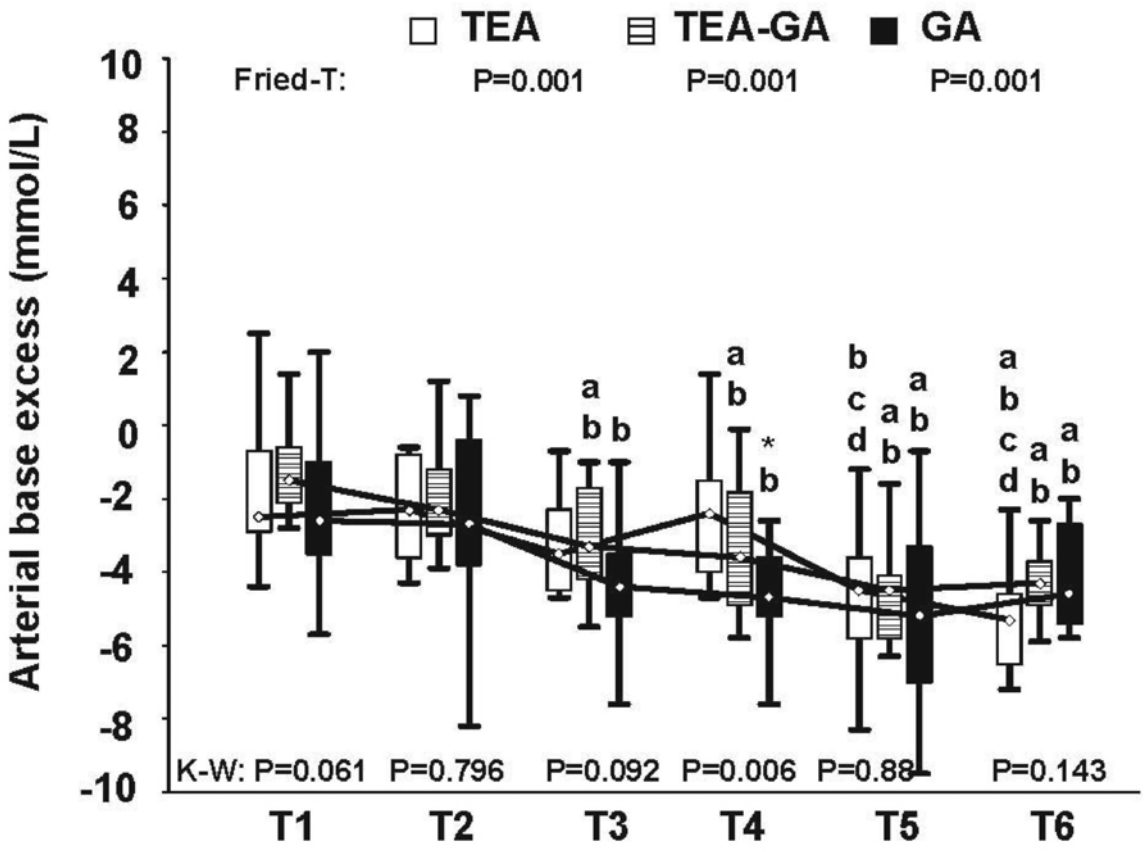


Figure 3: Arterial base excess. The means are depicted as rhomboids within boxes indicating standard errors. Whiskers indicate standard deviations. K-W, Kruskal-Wallis analyses, Fried-T, Friedman non-parametric tests . * $P < 0,05$ vs. TEA. † $P < 0,05$ vs. TEA-GA. [a] $P = 0,05$ vs. T1. [b] $P = 0,05$ vs. T2. [c] $P = 0,05$ vs. T3. [d] $P = 0,05$ vs. T4. [e] $P = 0,05$ vs. T5.

Arterial oxygen saturation decreased significantly in the TEA group in the post CPB period (T5 and T6) as compared to baseline (T1) and the CPB period (T3 and T4), but not in the other groups. Arterial oxygen saturation varied among the groups, being lower in the TEA group as compared to the TEA-GA and GA groups in the post CPB (T5 and T6) period (Figure 4).

**Figure 4**

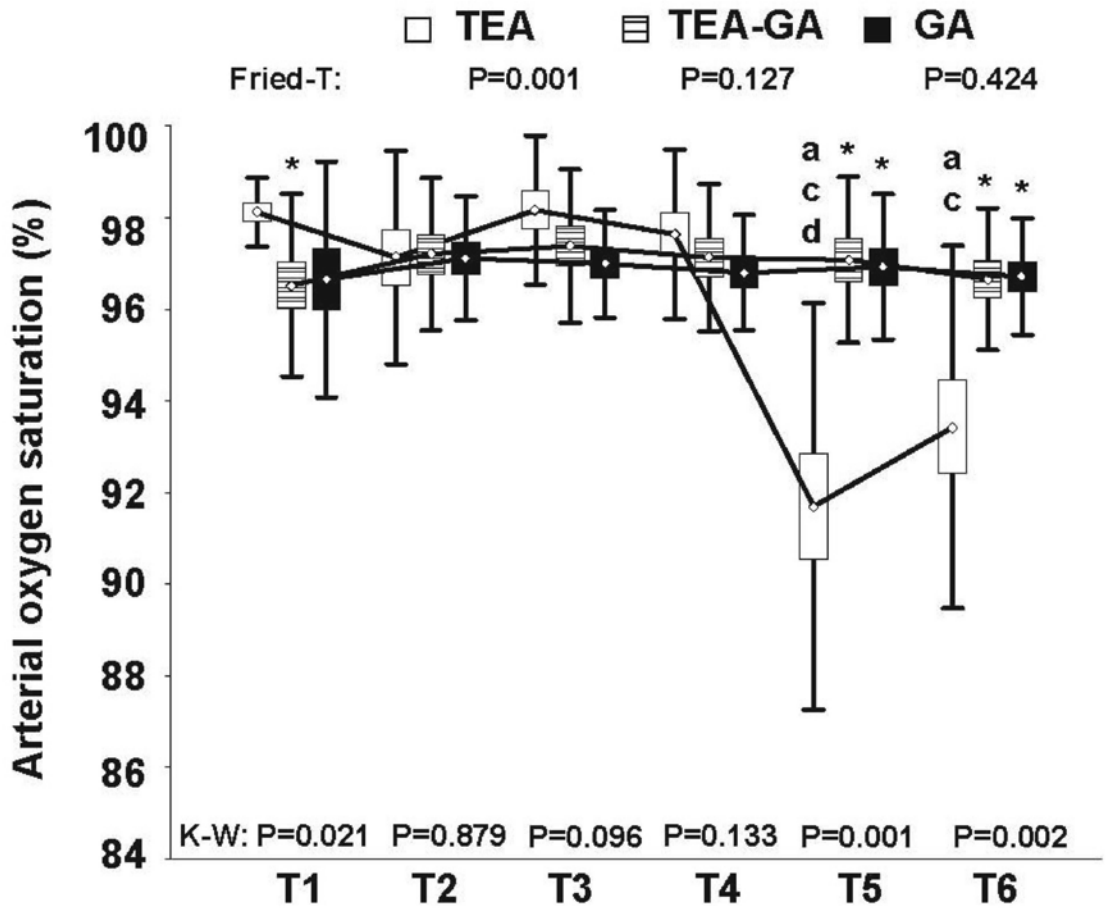


Figure 4: Arterial oxygen saturation. The means are depicted as rhomboids within boxes indicating standard errors. Whiskers indicate standard deviations. K-W, Kruskal-Wallis analyses, Fried-T, Friedman non-parametric tests .* $P < 0,05$ vs. TEA. † $P < 0,05$ vs. TEA-GA. [a] $P = 0,05$ vs. T1. [b] $P = 0,05$ vs. T2. [c] $P = 0,05$ vs. T3. [d] $P = 0,05$ vs. T4. [e] $P = 0,05$ vs. T5.

Arterial $PaCO_2$ increased significantly in the post CPB period (T5 and T6) in the TEA group (Figure 5). In the TEA-GA group, $PaCO_2$ continually decreased significantly from the baseline during the late pre CPB (T2) and early CPB periods (T3), then increased (T4) and remained stabile during the post CPB period (T5-6). In the GA group, PaCO2 did not change significantly during the procedure. $PaCO_2$ varied significantly among the groups, being higher in the TEA group at all time points as compared to the GA group and higher at T2, 3, 5 and 6 in comparison with the TEA-GA group.

**Figure 5**

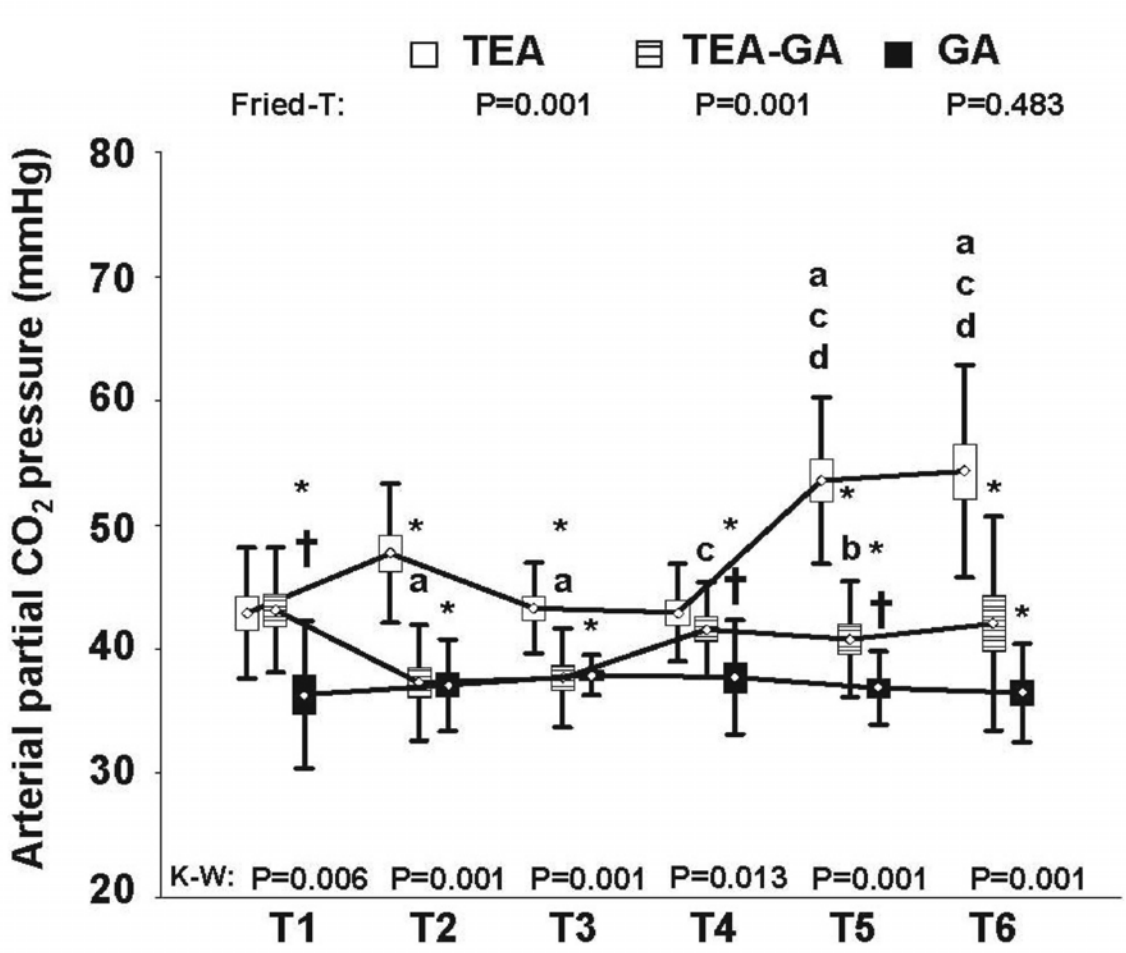


Figure 5: Arterial partial $CO_2$ pressure. The means are depicted as rhomboids within boxes indicating standard errors. Whiskers indicate standard deviations. K-W, Kruskal-Wallis analyses, Fried-T, Friedman non-parametric tests .$^{*}$ $P < 0,05$ vs. TEA. $^{\dagger}$ $P < 0,05$ vs. TEA-GA. $^{a}$ $P = 0,05$ vs. T1. $^{b}$ $P = 0,05$ vs. T2. $^{c}$ $P = 0,05$ vs. T3. $^{d}$ $P = 0,05$ vs. T4. $^{e}$ $P = 0,05$ vs. T5.

**Venous saturations**

$ScvO_2$ did not change significantly during the procedure in the TEA and TEA-GA groups. In group GA, $ScvO_2$ was significantly higher in the post CBP period (T5 and T6) as compared to the baseline (T6) (Figure 6). $ScvO_2$ varied among the groups, being lower in the TEA group compared with the TEA-GA group at baseline (T1). $ScvO_2$ was also lower in the TEA group compared with the GA group in the pre CPB period (T2), and compared with the TEA-GA and GA groups in the late CPB (T4) and post CPB periods (T5 and 6).

**Figure 6**

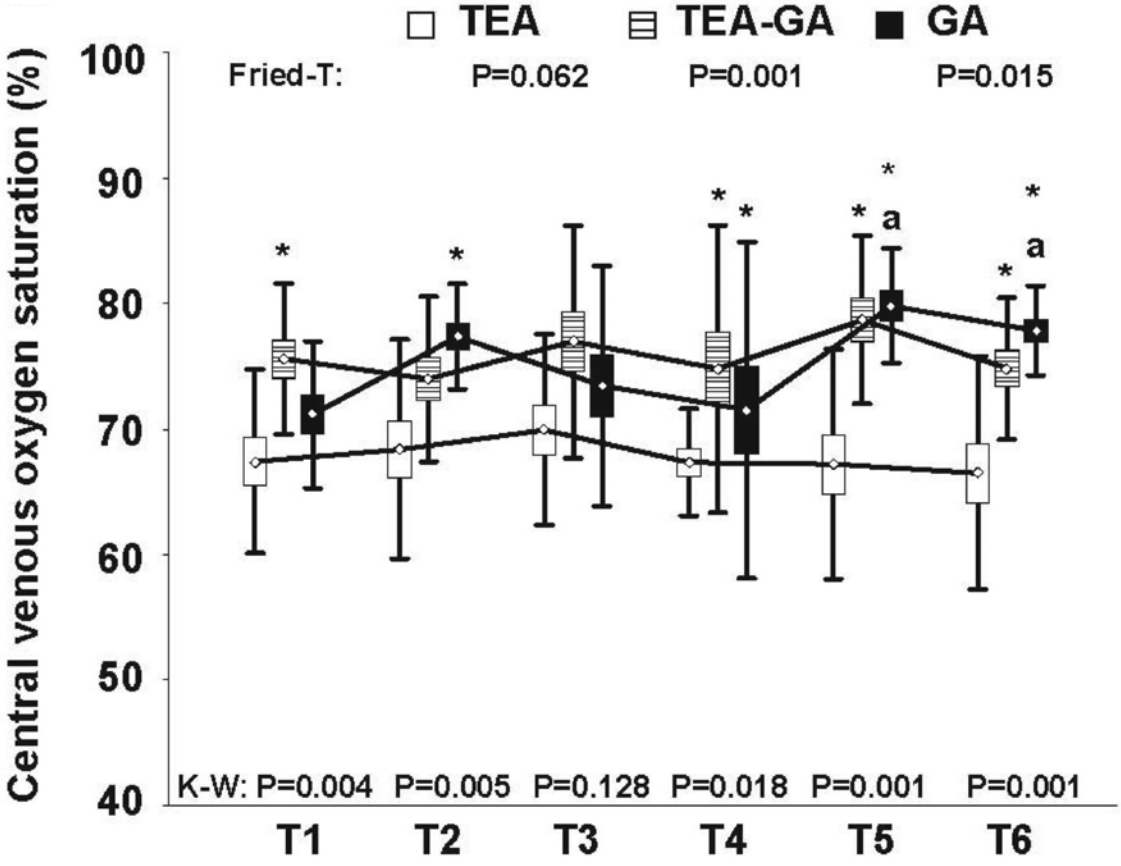


Figure 6: Central venous oxygen saturation. The means are depicted as rhomboids within boxes indicating standard errors. Whiskers indicate standard deviations. K-W, Kruskal-Wallis analyses, Fried-T, Friedman non-parametric tests .[*] $P < 0,05$ vs. TEA. [†] $P < 0,05$ vs. TEA-GA. [a] $P = 0,05$ vs. T1. [b] $P = 0,05$ vs. T2. [c] $P = 0,05$ vs. T3. [d] $P = 0,05$ vs. T4. [e] $P = 0,05$ vs. T5.

$SjbO_2$ did not change significantly during the procedure in any study group (Figure 7). $SjbO_2$ varied among the groups, being lower in the TEA group compared with the TEA-GA or GA groups at the end of the CPB period (T4) and compared with the GA group at the CPB periods (T5 and T6).

**Figure 7**

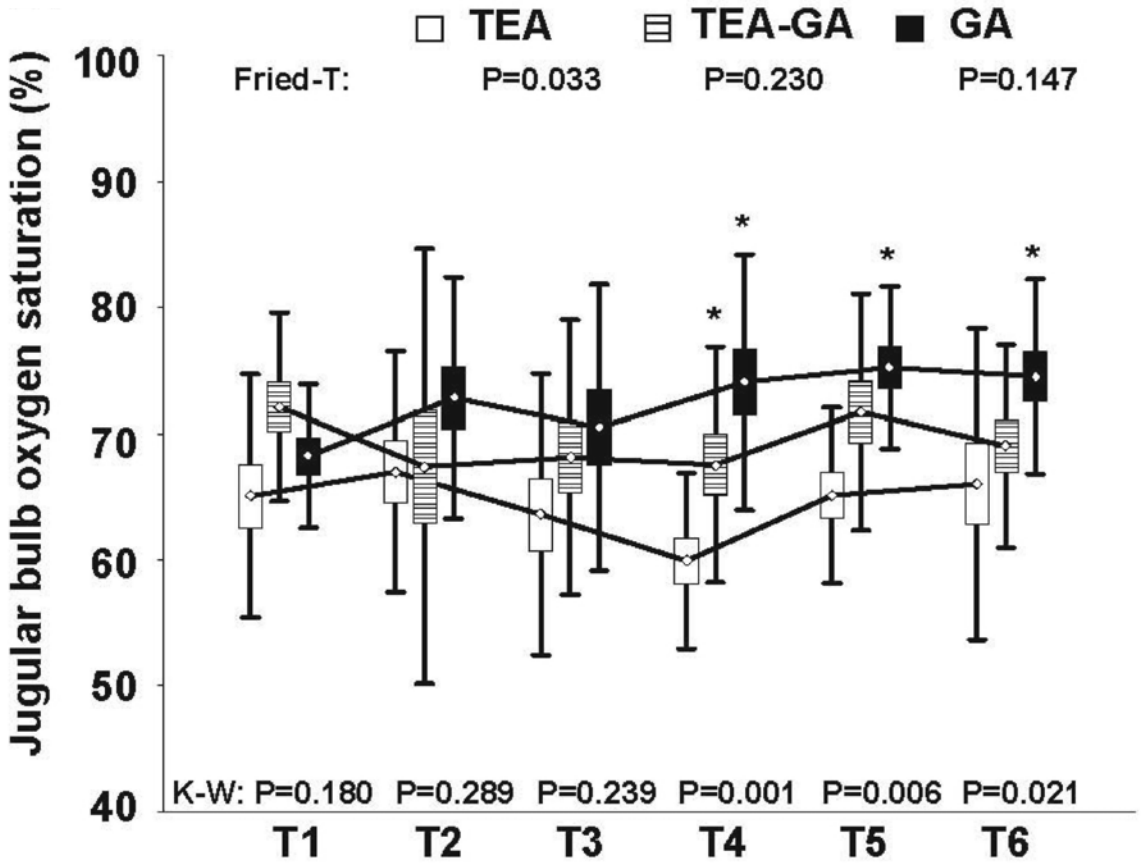


Figure 7: Jugular bulb oxygen saturation. The means are depicted as rhomboids within boxes indicating standard errors. Whiskers indicate standard deviations. K-W, Kruskal-Wallis analyses, Fried-T, Friedman non-parametric tests .$^{*}$ $P < 0{,}05$ vs. TEA. $^{\dagger}$ $P < 0{,}05$ vs. TEA-GA. $^{a}$ $P = 0{,}05$ vs. T1. $^{b}$ $P = 0{,}05$ vs. T2. $^{c}$ $P = 0{,}05$ vs. T3. $^{d}$ $P = 0{,}05$ vs. T4. $^{e}$ $P = 0{,}05$ vs. T5.

**Arterial hemoglobin level and glycemia**

As expected, hemoglobin level decreased significantly during the CPB period (T3 and T4) and then the level tended to increase in the post CPB period (T5 and 6) in all study groups (Figure 8). Hemoglobin levels varied significantly among the groups, being lower in the TEA group compared with the GA group during the CPB and early post CPB periods (T3-5). Hemoglobin levels were lower at T3 in the TEA group compared with the TEA-GA group.

**Figure 8**

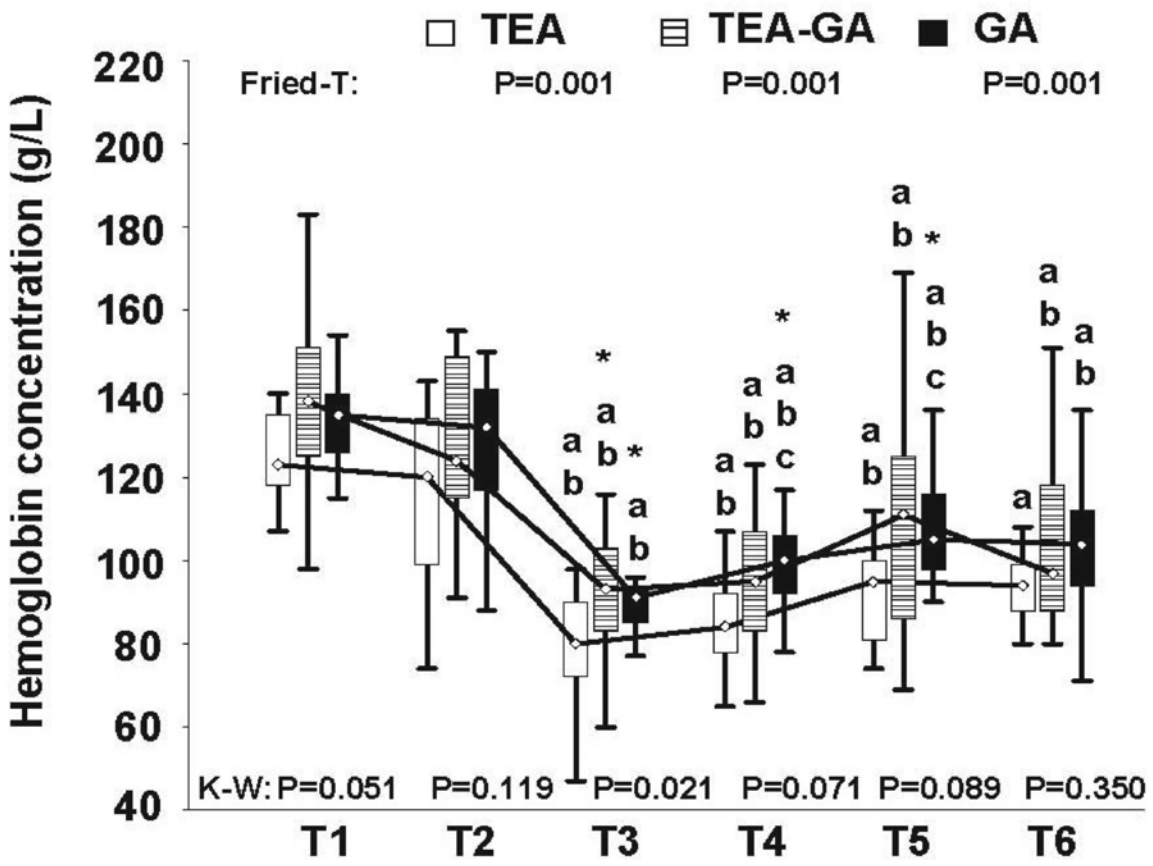


Figure 8: Hemoglobin concentration. The means are depicted as rhomboids within boxes indicating standard errors. Whiskers indicate standard deviations. K-W, Kruskal-Wallis analyses, Fried-T, Friedman non-parametric tests .[*] $P < 0,05$ vs. TEA. [†] $P < 0,05$ vs. TEA-GA. [a] $P = 0,05$ vs. T1. [b] $P = 0,05$ vs. T2. [c] $P = 0,05$ vs. T3. [d] $P = 0,05$ vs. T4. [e] $P = 0,05$ vs. T5.

$DO_2$ was calculated only during the CPB period. $DO_2$ was higher in the TEA and TEA-GA groups in the late CPB period (T4) as compared to the early CPB period (T3) and tended to increase in the GA group (Table 4). $DO_2$ varied among the groups, being significantly lower in the TEA group than the GA group at T3 and the TEA than the TEA-GA group at T4.

Arterial glucose level tended to mildly increase during the procedure in all groups, being significantly higher at T4 (as compared to T1,2 and 3) and T5 (as compared to T2 and T3) in the TEA-GA group and T4 (as compared to T3) in the GA group (Table 4). There was no difference in arterial glucose levels among the groups at any time point.

**TABLE 4.** Glycemia and oxygen delivery

| | T1 | T2 | T3 | T4 | T5 | T6 | Fried-T |
|---|---|---|---|---|---|---|---|
| **Arterial glucose level (mmol/l)** | | | | | | | |
| TEA | 6.5 ± 1,7 | 6.8 ± 1.0 | 7.3 ± 0.9 | 8.3 ± 1.7 | 7.6 ± 1.7 | 7.4 ± 1.8 | **P=0.001** |
| TEA-GA | 6.7 ± 0,9 | 6.6 ± 0.9 | 6.6 ± 0.9 | 8.4 ± 1.5 [a bc] | 8.0 ± 1.1 [bc] | 7.4 ± 1.3 | **P=0.001** |
| GA | 6.3 ± 1,3 | 6.6 ± 1.3 | 6.4 ± 0.8 | 7.7 ± 1.0 [c] | 7.8 ± 1.3 | 6.9 ± 1.3 | **P=0.002** |
| Kruskal-Wallis | P=0.286 | P=0.705 | P=0.061 | P=0.319 | P=0.564 | P=0.390 | |
| **Oxygen delivery (ml O2/m2*min)** | | | | | | | |
| TEA | --- | --- | 254 ± 40 | 274 ± 32 | --- | --- | P=0.061 |
| TEA-GA | --- | --- | 281 ± 18 | **319 ± 38 *** [c] | --- | --- | **P=0.02** |
| GA | --- | --- | **292 ± 47*** | 303 ± 49 [c] | --- | --- | **P=0.027** |
| K-W test | --- | --- | **P=0.001** | **P=0.001** | --- | --- | |

TEA, thoracic epidural anesthesia group; TEA-GA combined thoracic epidural anesthesia and general anesthesia group; GA, general anesthesia group; K-W, Kruskal-Wallis analyses. Fried-T, Friedman non-parametric tests).

[*] *P*<0,0 vs. TEA, [†] P <0.05 vs. TEA-GA, [a] *P* <0,05 vs. T1, [b] *P* <0,05 vs. T2, [c] *P* <0,05 vs. T3, [d] *P* <0,05 vs. T4, [e] *P* <0,05 vs. T5.

## BFRs adjustments and ventilatory support

As no lactic acidosis developed and no venous saturation fell below 55%, there was no need to increase BFRs in any study group. As $PaCO_2$ increased mildly only in the TEA group resulting in post-CPB mild respiratory acidosis, no ventilatory support was necessary in TEA group.

## 9.2 Postoperative outcome in cardiac surgery (Phase 2 study)

### Postoperative outcome data

All patients in the TEA group were included in this analysis. All postoperative outcome data are listed in tables 5, 6 and 7. There was no difference in postoperative outcome data except for higher pain VAS scores and higher morphine requirements in GA group as compared to TEA and TEA-GA group (Table 5). The incidence of atrial fibrillation was higher in the GA group as compared to TEA group (Table 5). Total dose of norepinephrine and duration of vasopressor support tended to be lower in TEA group compared to TEA-GA and GA group, but did not reach a statistical significance (Table 5). The overall satisfaction with perioperative course and type of anesthesia did not differ among the groups (86%, 91%, 83%, respectively, P=0.864). The patients, who were satisfied on the inquiry, would choose the same type of anesthesia for the procedure again.

**TABLE 5. Postoperative data - pain management, pulmonary and cardiovascular outcome data**

| | TEA (n=17) | TEA-GA (n=15) | GA (n=15) | P-value |
|---|---|---|---|---|
| Pain VAS score - at 24 hours postoperatively | 4 ± 7 | 6 ± 7 | **14.7 ± 11 *†** | **0.004** |
| Morphine requirements - first 24 hours (μg/kg) | 30 ± 6 | 30 ± 6 | **250 ± 140 *†** | **0.001** |
| Pulmonary outcome | | | | |
| Reintubation | 0 | 0 | 1 (6.7%) | 0.360 |
| Time to extubation (hours) | 0.2 ± 1.2 | **7.3 ± 3.8 *** | **6,7 ± 3.5 *** | **0.001** |
| Mechanical ventilation > 48 hours | 1 (5.9%) | 0 | 1 (6.7%) | 0.609 |
| Pneumonia | 0 | 0 | 1 (6.7%) | 0.406 |
| Pneumothorax | 0 | 0 | 0 | |
| Atelectasis | 0 | 0 | 0 | |
| Cardiovascular outcome | | | | |
| Myocadial infarction | 0 | 0 | 0 | |
| Ionotropic support/IABP | 0 | 0 | 0 | |
| Atrial fibrillation | 4 (23.5%) | 8 (53.3%) | **10 (66.7%) *** | **0.028** |
| Total norepinephrine dose (μg/kg) | 36 ± 62 | 43 ± 85 | 69 ± 72 | 0.231 |
| Norepinephrine support > 48 hours | 1 (5.9%) | 3 (20%) | 4 (26.7%) | 0.111 |

TEA, thoracic epidural anesthesia group; TEA-GA combined thoracic epidural anesthesia and general anesthesia group; GA, general anesthesia group; VAS, visual analogue scale (0-100) ; IABP, Intra-aortic balloon pump. * P <0.05 vs. TEA, † P <0.05 vs. TEA-GA.

**Length of hospital stay and early mortality**

There was no difference in either ICU or hospital length of stay across the study groups (Table 6). Also no difference in ICU, hospital or early 30-day mortality was noted across the study groups (Table 6).

**Late mortality**

The overall three-year mortality did not differ among the study groups (Table 6). There was no difference in the incidence of deaths related to cardiovascular causes (myocardial infarction, heart failure and sudden cardiac death) in these patients (66.7%, 50% and 66.7%, respectively, P=0.678).

**TABLE 6. Postoperative data -length of ICU/hospital stay and mortality**

| | TEA (n=17) | TEA-GA (n=15) | GA (n=15) | P-value |
|---|---|---|---|---|
| Length of stay (days) | | | | |
| ICU | 5 ± 2 | 5 ± 2 | 8 ± 12 | 0.516 |
| Hospital | 10 ± 5 | 12 ± 6 | 16 ± 15 | 0.339 |
| Mortality | | | | |
| ICU | 1 (5.9%) | 0 | 0 | 0.406 |
| Hospital | 1 (5.9%) | 0 | 0 | 0.406 |
| 30-day | 1 (5.9%) | 0 | 0 | 0.406 |
| 3-year | 3 (17.6%) | 4 (26.7 %) | 3 (20%) | 0.678 |

TEA, thoracic epidural anesthesia group; TEA-GA combined thoracic epidural anesthesia and general anesthesia group; GA, general anesthesia group; ICU, intensive care unit.

* P <0.05 vs. TEA, † P <0.05 vs. TEA-GA.

**TABLE 7. Postoperative data - neurological, renal and infections outcome data**

| | TEA (n=17) | TEA-GA (n=15) | GA (n=15) | P-value |
|---|---|---|---|---|
| Neurological outcome | | | | |
| ICU delirium | 3 (17.6%) | 4 (26.7%) | 4 (26.7%) | 0.887 |
| Stroke/TIA | 1 (5.9%) | 1 (6.7%) | 0 | 0.593 |
| Renal outcome | | | | |
| Peak postoperative serum creatinine (μmol/L) | 124 ± 46 | 110 ± 33 | 102 ± 23 | 0.355 |
| RIFLE risk | 2 (11.8%) | 2 (13.3%) | 1 (6.7%) | 0.799 |
| RIFLE injury | 0 | 0 | 0 | |
| RIFLE failure | 0 | 0 | 0 | |
| CRRT | 0 | 0 | 0 | |
| Infection | | | | |
| Catheter-related | 0 | 2 (13.3%) | 0 | 0.483 |
| Sternum dehiscence | 0 | 1 (6.7%) | 3 (20%) | 0.598 |
| Urinary tract | 1 (5.9%) | 0 | 0 | 0.406 |

TEA, thoracic epidural anesthesia group; TEA-GA combined thoracic epidural anesthesia and general anesthesia group; GA, general anesthesia group; ICU, intensive care unit; TIA, transient ischemic attack; RIFLE – risk, injury, failure, loss, end stage renal disease (Acute Dialysis Quality Initiative workgroup classification system); CRRT, continuous renal replacement therapy.

* $P < 0.05$ vs. TEA, † $P < 0.05$ vs. TEA-GA.

# 10. DISCUSSION

## 10.1 Oxygen consumption in awake cardiac surgical patients (Phase 1 study)

In our study, metabolic lactic acidosis did not develop in any study group at any time point. Moreover, jugular bulb and central venous desaturation did not fall bellow 55% in any study group at any time point either. Based on these results and our study protocol, an increase of BFRs was not required in any study group. As expected, however, $PaCO_2$ gradually increased in the TEA group, which resulted in post-CPB mild respiratory acidosis with concomitant slight decrease of $SaO_2$ . Thus, no ventilatory support was necessary to use in the TEA group. These findings indicate that the use of standard BFRs is adequate for patients undergoing awake on-pump cardiac surgery.

The CPB BFRs of 2.4 L/min*$m^2$ used in all our patients were within the limits of "standard" blood flow rates of 2.2-2.5 L/min*$m^2$ that have been commonly used during normothermic CPB [49]. It has been recommended to set BFRs within this range for patients under general anesthesia [12], whose whole body $VO_2$ is decreased by 15-30% depending on the type and amount of anesthetics used [10,36,38,46]. However, BFRs as low as 1.2 L/min/$m^2$ have been used during hypothermic bypass with acceptable clinical outcomes [56] but data for normothermic perfusion are not available. The potential advantages of lower than standard BFRs include improved intracardiac exposure due to less bronchial blood flow returning to the left heart, reduced warming of the myocardium via noncoronary collateral vessels and reduced destruction of blood elements [49]. On the other hand, low BFRs during CPB have been identified as an independent risk factor for development of hyperlactatemia [53] due to inadequate $DO_2$ to peripheral tissues [54]. Hyperlactatemia is a well-recognized marker of circulatory failure with tissue hypoxia and its severity has been associated with increased morbidity and mortality of patients undergoing CPB [11,54]. However, the minimal safe or optimal BFRs during CPB have not yet been established [49].

It is conceivable that awake TEA patients as well as TEA-GA patients could require higher than standard BFRs compared with GA patients, as the awake TEA patients lack the decreasing effects of general anesthesia on oxygen consumption and the dose of anesthetics used in TEA-GA patients is lower than in GA patients. Possible increases in oxygen consumption in the TEA patients could raise requirements for oxygen delivery above critical level associated with the development of metabolic lactic acidosis.

Nevertheless, to our knowledge, no study has been performed before to test the adequacy of standard BFRs in awake TEA patients or combined TEA-GA patients. In our study, for the first time, we show that despite significantly lower $DO_2$ in TEA patients (254 and 274 mL/m$^2$*min) at the beginning and end of CPB as compared to TEA-GA (281 and 320 mL/m$^2$*min) and GA (290 and 302 mL/m$^2$*min) patients, no metabolic acidosis has developed and lactate remained in the normal range in all groups at all time points. After initiation of CPB, $DO_2$ values are typically reduced into the range of 200-300 mL/m$^2$*min [49, 52], which was observed also in our study (Table 4). The decrease of $DO_2$ has been previously related to hemodilution and decreased hemoglobin level [49]. In our study, we observed hemodilution in all groups (Figure 8). However, the TEA group tended to have lower hemoglobin at baseline which was likely responsible for lower $DO_2$ during the CPB period when compared with the other groups. The minimal safe $DO_2$ value during CPB, below which metabolic lactic acidosis develops, has not yet been established [49]. We speculate that the critical level of $DO_2$ was not reached in any of our patient because no lactic acidosis has developed in any group. Therefore, based on lactate monitoring no BFR adjustments were required in any study group.

In clinical practice, BFRs are being adjusted according to actual lactate levels as well as to degree of venous desaturations, specifically CPB venous effluent, $ScvO_2$, $SjbO_2$ and potentially mixed venous oxygen saturation ($SvO_2$). Measurements of $SvO_2$ allow calculations of other parameters including of whole body oxygen consumption and oxygen extraction ratio, however, this requires an insertion of a pulmonary artery catheter. Pulmonary artery catheter placement bears substantial risks for the patient (including serious arrhythmias and pulmonary artery perforation) and its yield for patient anesthesia management remains highly controversial [57]. The benefits (measurements of $VO_2$) for our patients would be very limited and would not outweigh the risks. Moreover, the measurement of precise value of oxygen consumption was not the primary aim of the study.

On the other hand, $SjbO_2$ level (which reflects the global brain oxygen metabolism) below 50% has been associated with adverse neurological outcome in patients undergoing normothermic CPB [58]. $ScvO_2$ below 50% predicts poor outcome in patients in septic shock [59]. However, critical value of $ScvO_2$ or $SvO_2$ for patients undergoing CPB has not been identified yet. In our study, all values of $ScvO_2$ and $SjbO_2$ were above 50%. It is generally accepted that these values without lactic acidosis are well tolerated by patients and not harmful. Therefore, no adjustments of BFRs were needed as there were no severe venous desaturations (below 50%).

Although all $ScvO_2$ and $SjbO_2$ values in the TEA group were above 50%, they were mildly but significantly lower at the end of CPB and after CPB as compared to patients with GA or TEA-GA. There are a few factors that might be related to this phenomenon.

First, tissue oxygen extraction could be increased due to the increase of $VO_2$ caused by the lack of effect of general anesthesia in the TEA group, which was stated in our hypothesis. However, venous oxygen desaturations in awake TEA patients were of a mild degree, without concomitant lactic acidosis, therefore the increase of $VO_2$ could have been of a lesser extent than we originally expected. On the other hand, we also must take into account a possibility that original studies calculated BFRs that provide luxurious $DO_2$ during CPB. In this case, even significantly increased $VO_2$ in awake TEA patients would not have to lead to profoundly increased oxygen extraction and severe venous oxygen desaturations.

Second, we observed decreased $DO_2$ level caused by lower level of hemoglobin in the TEA group, which could lead to higher oxygen extraction and subsequently to lower venous saturations.

Additionally, two other factors including the use of dexmedetomidine and the effect of hypercapnia may have increased venous saturation either in the whole body or solely in the jugular bulb. The whole body venous saturations might have been affected by use of central sympathetic α2-agonist dexmedetomidine in the TEA group. Dexmedetomidine decreases whole body $VO_2$ in a dose dependent manner [60] and could increase venous saturations in the TEA group. In our study, however, we used the lowest dose of dexmedetomidine sufficient for sedation to maximally diminish possible increase of venous saturations. We speculate that the effect of dexmedetomidine was minimal in our study, because, despite using the drug, we observed slightly but significantly lower values of venous saturations in awake TEA patients. Increased levels of $PaCO_2$ observed in the TEA group could have an impact on $SjbO_2$ values as well. It has been shown that hypercapnia-induced cerebral vasodilatation increases cerebral blood flow and decreases cerebral oxygen extraction [61]. Nevertheless, $SjbO_2$ remained lower in the TEA group compared to other groups at the end of CPB, thus the effect of $PaCO_2$ was likely minimal.

Therefore, based on these results, it is impossible to state, whether $VO_2$ of awake TEA patients was potentially increased compared to the other groups, as several variables could have affected this parameter, as noted above. Nevertheless, standard BFRs provided sufficient $DO_2$ in these patients, which was documented by lack of metabolic lactic acidosis and significant venous oxygen desaturations. It would certainly be beneficial to employ methods that measure the regional level of oxygen metabolism (i.e. tissue oximetry, near infrared

spectroscopy or microdialysis) to specifically assess oxygen consumption at organ level. More studies are warranted to elucidate this topic to a greater extent.

Additionally, all the above mentioned parameters including $DO_2$ did not differ between the GA and TEA-GA groups. We speculate that despite lower dosage of anesthetics used in TEA-GA as compared to GA group, the decrease of $VO_2$ was similar in both groups and thus there was no requirement for further adjustment of BFRs in TEA-GA group either.

In awake TEA patients, mild hypercapnia has been previously reported [1,2] which is consistent with our data. Hypercapnia may cause respiratory acidosis, arterial vasodilatation and induce tachycardia followed by impaired consciousness at high level CO2 [61]. In our study, the hypercapnia was only of mild degree and none of the detrimental effects of hypercapnia were observed. Hypercapnia in the TEA group was more obvious in the post-CPB period and was accompanied by mild respiratory acidosis. In the TEA group, MAPs in the post-CPB period were only mildly but non-significantly lower as compared to the pre-CPB period and tachycardia was not observed. Faster heart rates (but within normal range) in the TEA group in the pre-CPB period were likely induced by psychic stress of patients.

We also observed mild $SaO_2$ reductions (92-93%) in the post-CPB period in the TEA group but without concomitant metabolic lactic acidosis or excessive venous desaturations. Thus, no patient had to be intubated in the TEA group because of severe hypercapnia or arterial hypoxemia. The $SaO_2$ reductions and increased $PaCO_2$ levels in spontaneously breathing conscious patients during post-CPB period, likely correspond to a mild degree of hypoventilation due to paralysis of intercostal muscles.

Interestingly, twelve patients in the TEA group stopped breathing when CPB was commenced. They restored their respiratory effort when they were asked to. This phenomenon was observed in a previous study as well [3], however the etiopathogenesis remains unclear.

### 10.2 Postoperative outcome in awake cardiac surgery (Phase 2 study)

In the second phase of the study, focusing on clinical outcomes, we found out that there was not a major difference in early and late postoperative outcome data among the three study groups, except for a higher incidence of atrial fibrillation in the GA group compared to TEA group. Also pain relief was more efficient and analgesic requirements were lower in the TEA and TEA-GA group compared to GA group.

It has been reported that TEA improves coronary blood flow distribution, caused by thoracic sympathicolysis, and was proposed to decrease the incidence of postoperative myocardial infarction [6], however this is not supported by the most recent meta-analysis [7]. There were no cases of perioperative myocardial ischemia, and no inotropic support except for norepinephrine was used in any of the study groups. Postoperative myocardial ischemia is a relatively common complication after surgical coronary revascularization with the incidence as high as 10-25%, significantly affecting postoperative morbidity and mortality [62]. In the present study, myocardial revascularization procedures represented about 35-40% of operations in each group, which were relatively small-sized. Thus, our results are certainly influenced by this limitation.

Atrial fibrillation is the most common arrhythmia after cardiac surgery that leads to increased risk for thromboembolism and excessive health care resource utilization [63]. In our study, there was a lower incidence of atrial fibrillation in the TEA group, which corresponds to previously reported effects of TEA [7,62]. This effect is most likely a consequence of sympathetic blockade and blunted stress response. Catecholamine response, reflected by epinephrine and norepinephrine release, is abolished or attenuated under TEA [5]. It is well known that the incidence of atrial fibrillation increases with procedure complexity in cardiac surgery [63]. Although our patients underwent various types of on-pump surgical procedures, their incidence did not differ among the study groups (Table 5).

Furthermore, the hypotensive effect of TEA as a result of excessive sympathetic blockade with its possible consequences has been described in the literature [64]. However, our results show the opposite findings compared to the published data (Table 5). There was a trend towards lower total dose of norepinephrine used and shorter time of vasopressor support in the TEA and TEA-GA group compared to GA group, but the statistical significance was not reach in any of these parameters. The etiology of this remains unknown. It has been shown that atrial fibrillation represents a risk factor for hypotension and increased use of iontropic medications after cardiac surgery [65]. Thus, we speculate that the higher incidence of atrial fibrillation in the GA group could prolong vasopressor support in these patients.

Although there is a considerable body of evidence that TEA may improve pulmonary outcome in patients undergoing cardiothoracic or abdominal surgery [7,8], there was not a difference in pulmonary outcome data among the groups in our study. The overall incidence of these complications was very low in all groups (Table 5).

It has been proposed that awake TEA may be more beneficial and safer than GA in patients with chronic obstructive pulmonary disease (COPD) [4,66]. Patients with asthma or

COPD have a high incidence of bronchial hyperreactivity [67]. Therefore, general anesthesia with tracheal intubation can induce bronchospasm, which, in some cases, can be life-threatening in these patiens [68]. Awake TEA providing superior analgesia, improved diaphragmatic function and preservation of spontaneous ventilation without mechanical ventilation may contribute to improved pulmonary outcome in these patients [4,9,66,69]. On the other hand, thoracic sympathicolysis may increase airway resistance, and motor blockade of intercostal muscles [27] could lead to respiratory insufficiency in COPD patients. However, currently published data support the safety of TEA in COPD patients, when none of the above mentioned risks have been proven to be of clinical significance [70,71].

Severe COPD patients represent a high risk surgical population with extremely high percentage of postoperative pulmonary complications [72]. Thus, severe COPD patients have been frequently contraindicated for cardiac surgery. In our study, two patients suffered from severe COPD (FEV1 < 30% of normal values). Both patients preferred sole TEA and had uneventful perioperative courses. These data support the hypothesis that the TEA method could represent an alternative to the GA or conservative approach in COPD patients. However, other specifically designed studies are warranted to confirm this hypothesis.

The quality of analgesia was evaluated using visual analogue scale scores in our study. VAS scores and morphine requirements were significantly lower in patients with TEA (TEA and TEA-GA group). That corresponds to previously reported results of TEA and represents the beneficial effect of TEA that is supported by the largest body of evidence, compared to its other effects [5,9]. Inadequate analgesia during the postoperative period may increase morbidity by causing adverse hemodynamic, metabolic, immunologic,and hemostatic alterations [73]. Thus, aggressive pain control could have potential to improve outcome in these patients [5]. Additionally, avoidance of parenteral opioids in TEA patients reduces the incidence of opioid-related side-effects [5].

There has been a trend toward more rapid recovery after cardiac surgery, with earlier extubation and shorter stays in ICU and in hospital (fast-track anesthesia) [74]. TEA represents one of the methods of fast-track anesthesia and many studies reported shorter length of hospital stay when using TEA [5]. In contrast to this data, there was not a difference in duration of ICU or hospital stay among our study groups. Nevertheless, length of hospital stay is also influenced by other factors unrelated to anesthetic method used . The local protocol of patient discharge represents the crucial factor. We simply were unable to influence the final surgeons' decisions regarding discharge from hospital.

On the whole, contrary to combined anesthesia technique there is still a lack of good quality evidence on postoperative outcome in awake cardiac surgical patients. Studies published so far concentrated more on description of the awake technique and actual perioperative course with sparse comments on postoperative outcome [1,3,4]. Moreover, only one of these studies used controlled study design [2]. Our current study for the first time examines the detailed postoperative outcome results of awake patients in controlled manner, however not randomized. Our study failed to prove an improvement in any of the major morbidity outcome measures except for lower incidence of postoperative atrial fibrillation and better pain relief. This corresponds to the results of latest meta-analysis of postoperative outcome in combined TEA-GA patients. [7]. However, we believe, that in specific high-risk cohorts of patients, especially those with COPD, avoidance of tracheal intubation and mechanical ventilation could improve postoperative morbidity as discussed above.

Also, only limited data exist on early in-hospital [1-4,9] or late mortality [4] of awake TEA patients, which seems to be low (~ 4%) [4]. This corresponds to our early in-hospital mortality 5.9%. There was only one study reporting two-year mortality of awake TEA patients [4]. This is the first study to date reporting long-term outcome of awake TEA patients compared to other types of anesthesia. In the present study, three-year mortality and the incidence of deaths related to cardiovascular causes (myocardial infarction, heart failure, sudden cardiac death), which represented 50-66.7%, did not differ among the study groups. However, it is still a matter of debate if the early or late mortality is related to type of anesthesia itself or the complications of surgery [4].

The risk of epidural hematoma formation related to the use of TEA still represents the major argument against the wide-spread use of TEA technique. New cases of epidural hematoma related to epidural anesthesia in cardiac surgery have been reported recently [75,76]. Epidural hematoma formation may lead to catastrophic neurologic consequences. Prompt diagnosis and urgent decompressive laminectomy with hematoma evacuation are crucial in minimizing the neurological damage [77].

However, the latest estimation of the risk of epidural hematoma formation in cardiac surgery was calculated to be 1:12000 [78]. Such a risk is similar to the risk of epidural hematoma in non-obstetrical surgery. On the other hand, this analysis contains data from on-pump as well as off-pump procedures. Therefore, the risk for solely on-pump procedures may be increased due to higher level of heparinization. Although the overall risk is considered to be relatively low, all possible precautions must be undertaken to minimize it. Normal coagulation parameters and safe withdrawal intervals of antithrombotic drugs are mandatory

[60]. The time interval between epidural catheter placement and full heparinization in on-pump cardiac surgery should be at least one hour [5,79]. We did not experience any of the above described inadvertent effects in our TEA patients.

We also did not have any other of previously described side effects of TEA, such as incomplete anesthesia, pneumothorax, phrenic nerve palsy or severe hemodynamic instability requiring intubation [2]. Two of our awake TEA patients had to be switched to GA because of embolic stroke and aortic dissection. However, these two complications are not caused by anesthetic technique but are typically related to surgical procedure [80].

Awake cardiac surgery with TEA requires a perfect patient's understanding and collaboration. Close collaboration between anesthetist and surgeon is necessary. Moreover, this technique is demanding for a surgeon, who needs to be experienced and able to promptly manage potential complications. Awake cardiac surgery also bears a certain amount of psychic stress for the patients, therefore it should be restricted to selected patients who have excellent compliance to the technique. The final decision as to which method should be chosen should be made on an individual basis after careful evaluation of the procedure risks and the advantages and disadvantages of each anesthetic technique with regard to the patient´s personality and cooperation.

### 10.3 Study limitations

Ethical and medical considerations did not allow a randomized study design. Therefore, after a thorough explanation of advantages and disadvantages of each anesthetic method, the patient chose the type of anesthesia on their own.

As discussed above, we did not use pulmonary artery catheter in any of our patients to avoid all possible confounding factors [47], which would compromise our patient's outcome. Thus, precise calculation of $VO_2$ was not possible. Moreover, information about $VO_2$ would not affect already clinically established management of BFRs, which is based on monitoring of lactate levels and venous saturations.

We did not compare different levels of BFRs (higher or lower than the standard BFRs) and their effect on blood gasses and acid-base parameters. However, the main objective of the study was to evaluate adequacy of standard BFRs which have been used in awake patients. In our protocol, an increase of BFRs under conditions of lactic acidosis and severe decrease of venous saturations has been implemented, however, no adjustments were needed during the study. Future studies are warranted to test if other settings of BFRs in awake patients would be more favorable for the patient's management than the use of standard BFRs values.

The transesophageal echocardiography was not used during CPB for evaluation of cardiac output because it would cause severe discomfort in the awake TEA patients.

# 11. CONCLUSIONS

## 11.1 Oxygen consumption in awake cardiac surgical patients (Phase 1 study)

In the first study, we tested the oxygen delivery sufficiency of standard blood flow rates of 2.4 l/min*$m^2$ in awake TEA patients during cardiac surgery with cardiopulmonary bypass by monitoring and comparing of lactate levels, acid-base parameters and venous desaturations and compared these results with groups of patients under sole general anesthesia and with combined anesthesia. As original blood flow rates values during cardiopulmonary bypass were calculated for patients under general anesthesia, concerns about its sufficiency exist in awake TEA patients, who may have increased oxygen consumption due to the missing effect of general anesthesia. Our study showed that under careful monitoring the use of standard blood flow rates is adequate in patients undergoing awake on-pump normothermic cardiac surgery as well as is sufficient for combined anesthesia. Neither lactic acidosis nor severe venous desaturations were observed in awake TEA patients, thus no adjustments of BFRs were needed. Only a mild hypercapnia and a mild decrease of arterial oxygen saturation developed in the post-CPB period; therefore no conversion from awake TEA to GA was required due to anesthesiologic indications.

## 11.2 Postoperative outcome in awake cardiac surgery (Phase 2 study)

In the second study, we evaluated the impact of awake TEA technique on major parameters of postoperative outcome in comparison with patients undergoing cardiac surgery under combined and sole general anesthesia. The beneficial effect of thoracic epdiural anesthesia with sympathetic blockade and stress response attenuation has been proven to improve postoperative outcome in patients with combined anesthesia. However, very limited data exist on postoperative outcome in awake TEA patients, in whom avoidance of tracheal intubation and mechanical ventilation may represent another factor for reducing postoperative morbidity. In our study, there was no major difference in early and late postoperative outcome data including hospital and three-year mortality among the three study groups, except for the lower incidence of atrial fibrillation in awake TEA patients as compared to patients under general anesthesia. Also, methods using postoperative epidural analgesia provided superior pain relief. Future studies are warranted to elucidate the potential profit of awake technique in cardiac surgery in specific patient cohorts such as high risk patients with COPD.

# 12. REFERENCES

[1] Karagoz HY, Sönmez B, Bakkaloglu B, Kurtoglu M, Erdinc M, Türkeli A, Bayazit K. Coronary artery bypass grafting in the conscious patient without endotracheal general anesthesia. Ann Thorac Surg 2000;70(1):91-6.

[2] Kessler P, Aybek T, Neidhart G, Dogan S, Lischke V, Bremerich DH, Byhahn C. Comparison of three anesthetic techniques for off-pump coronary artery bypass grafting: general anesthesia, combined general and high thoracic epidural anesthesia, or high thoracic epidural anesthesia alone. J Cardiothorac Vasc Anesth 2005;19(1):32-9.

[3] Chakravarthy M, Jawali V, Patil TA, Jayaprakash K, Kolar S, Joseph G, Das JK, Maheswari U, Sudhakar N. Cardiopulmonary bypass in conscious patients undergoing cardiac surgery. J Extra Corpor Technol 2000;37(2):213-8.16.

[4] Bottio T, Bisleri G, Piccoli P, Negri A, Manzato A, Muneretto C. Heart valve surgery in a very high-risk population: a preliminary experience in awake patients. J Heart Valve Dis 2007;16(2):187-94.

[5] Chaney MA. Intrathecal and epidural anesthesia and analgesia for cardiac surgery. Anesth Analg 2006;102(1):45-64.

[6] Beattie WS, Badner NH, Choi P. Epidural analgesia reduces postoperative myocardial infarction: a meta-analysis. Anesth Analg 2001;93(4):853-8.

[7] Svircevic V, van Dijk D, Nierich AP, Passier MP, Kalkman CJ, van der Heijden GJ, Bax L. Meta-analysis of thoracic epidural anesthesia versus general anesthesia for cardiac surgery. Anesthesiology. 2011;114:271-82.

[8] Ballantyne JC, Carr DB, deFerranti S, Suarez T, Lau J, Chalmers TC, Angelillo IF, Mosteller F. The comparative effects of postoperative analgesic therapies on pulmonary outcome: cumulative meta-analyses of randomized, controlled trials. Anesth Analg 1998;86(3):598-612.

[9] Mineo TC. Epidural anesthesia in awake thoracic surgery. Eur J Cardiothorac Surg 2007;32:13-19.

[10] Westenskow DR, Jordan WS. Changes in Oxygen Consumption Induced by Fentanyl and Thiopentone During Balanced Anaesthesia. Can Anaesth Soc J 1978;25:18-21.

[11] Maillet JM, Le Besnerais P, Cantoni M, Nataf P, Ruffenach A, Lessana A, Brodaty D. Frequency, risk factors, and outcome of hyperlactatemia after cardiac surgery. Chest 2003;123(5):1361-6.

[12] Kirklin JW, Dushane JW, Patrick RT, Donald DE, Hetzel PS, Harshbarger HG, Wood EH. Intracardiac surgery with the aid of a mechanical pump-oxygenator system (gibbon type): report of eight cases. Proc Staff Meet Mayo Clin 1955;30(10):201-6.
[13] Clowes GHA, Neville WE, Hopkins A, et al. Factors contributing to success or failure in the use of a pump oxygenator for complete by-pass of the heart and lung, experimental and clinical. Surgery 1954;36:557–79.
[14] Hoar PF, Hickey RF, Ullyot DJ. Systemic hypertension following myocardial revascularization: a method of treatment using epidural anesthesia. J Thorac Cardiovasc Surg 1976;71:859–64.
[15] El-Baz N, Goldin M. Continuous epidural infusion of morphine for pain relief after cardiac operations. J Thorac Cardiovasc Surg 1987;93:878–83.
[16] Basse L, Raskow HH, Jacobsen DH, Sonne E, Billesbolle P, Hendel HW, Rosemberg J, Kehlet H. Accelerated postoperative recovery programmeafter colonic resection improves physical performance, pulmonary function and body composition. Br J Surg 2002;89:446—53.
[17] Loick HM, Schmidt C, Van Aken H, Junker R, Erren M, Berendes E, Rolf N, Meissner A, Schmid C, Scheld HH, Mo¨lhoff T. High thoracic epidural anesthesia, but not clonidine, attenuates the perioperative stress response via sympatholysis and reduces the release of troponin T in patients undergoing coronary artery bypass grafting. Anesth Analg 1999;88:701—9.
[18] Olausson K, Magnusdottir H, Lurje L, Wennerblom B, Emanuelsson H, Ricksten SE. Anti-ischemic and anti-anginal effects of thoracic epidural anesthesia versus those of conventional medical therapy in the treatment of severe refractory unstable angina pectoris. Circulation 1997;96:2178—82.
[19] Rutberg H, Hakanson E, Anderberg B, Jorfeldt L, Martensson J, Schildt B. Effects of the extradural administration of morphine or bupivacaine on the endocrine response to upper abdominal surgery. Br J Anaesth 1984;56:233—8.
[20] Blomberg S, Emanuelsson H, Ricksten SE. Thoracic epidural anesthesia and central hemodynamics in patients with unstable angina pectoris. Anesth Analg 1989;69:558—62.
[21] Davis RF, DeBoer LWV, Maroko PR. Thoracic epidural anesthesia reduces myocardial infarct size after coronary occlusion in dogs. Anesth Analg 1986;65:711—7.
[22] Klassen GA, Bramwell RS, Bromage PR, Zborowska-Sluis DT. Effect on acute sympathectomy by epidural anesthesia on the canine coronary circulation. Anesthesiology 1980;52:8—15.

[23] Kock M, Blomberg S, Emanuelsson H, Lomsky M, Stromblad SO, Ricksten SE. Thoracic epidural anesthesia improves global and regional left ventricular function during stress-induced myocardial ischemia in patients with coronary artery disease. Anesth Analg 1990;71:625—30.

[24] Williams JP, Sullivan EA, Ramakrishna H. Effects of thoracic epidural anesthesia on the coagulation system. Clin Anesth 1999;13:31—56; Jacobaeus H. The practical importance of thoracoscopy in surgery of thechest. Surg Gynecol Obstet 1922;34:289—96.

[25] Mark DB, Lam LC, Lee KI, Johns RH, Pryor DB, Stack RS, Williams RB, Clapp-Channing NE, Califf RM, Hlatky MA. Effects of coronary angioplasty, coronary bypass surgery, and medical therapy on employment in patients with coronary artery disease. A prospective comparison study. Ann Intern Med 1994;120:111—7.

[26] Ribakove GH, Miller JS, Anderson RV, Grossi EA, Applebaum RM, Cutler WM, Buttenheim PM, Baumann FG, Galloway AC, Colvin SB. Minimally invasive port-access coronary artery bypass grafting with early angiographic follow-up: initial clinical experience. J Thorac Cardiovasc Surg 1998;115:1101—10.

[27] Clemente A, Carli F. The physiological effects of thoracic epidural anesthesia and analgesia on the cardiovascular, respiratory and gastrointestinal systems. Minerva Anestesiol. 2008 Oct;74(10):549-63.

[28] Liu SS, Block BM, Wu CL. Effects of perioperative central neuraxial analgesia on outcome after coronary artery bypass surgery: a meta-analysis. Anesthesiology 2004;101:153–61.

[29] Samuels LE, Kaufman MS, Morris RJ, Promisloff R, Brockman SK. Coronary artery bypass grafting in patients with COPD. Chest. 1998;113:878-82.

[30] Tarhan S, Moffitt EA, Taylor WF, Giuliani ER. Myocardial infarction after general anesthesia. JAMA. 1972;220:1451-4.

[31] Spurr GB, Hutt BK, Horath SM. Responses of dogs to hypothermia. Amer. J. Physiol. 179: 139(1954).

[32] Wilson RS,Sullivan SF, Malm JR. The oxygen cost of breathing following anesthesia and cardiac surgery. Anesthesiology 39: 387.(1973).

[33] Cain SM. Increased oxygen uptake with passive hyperventilation of dogs. J. of Appl. Phys. 28: 4(1970).

[34] Theye RA. Thiopental and oxygen consumption. Anesth. and Analg. 49: 69 (1970).

[35] Wechsler RL, Dripps RD, Kety SS Blood flow and oxygen consumption of the human brain during anesthesia produced by thiopental. Anesthesiology 12: 308(1951).

[36] Wade OL, Bishop JM. Cardiac output and regional blood flow. Oxford, Blackwell Scientific Publications, p. 268 (1962).
[37] Stephan H, Sonntag H, Schenk HD, Kohlhausen S: Effect of Disoprivan (propofol) on the circulation and oxygen consumption of the brain and CO2 reactivity of brain vessels in the human. Anaesthesist. 36:60–65, 1987.
[38] Algotsson L, Messeter K, Nordstro¨m CH, Ryding E. Cerebral blood flow and oxygen consumption during isoflurane and halothane anesthesia in man. Acta Anaesthesiol Scand. 1988;32: 15–20.
[39] Young WL, Prohovnik I, Correll JW, et al. Cerebral blood flow and metabolism in patients undergoing anesthesia for carotid endarterectomy: a comparison of isoflurane, halothane, and fentanyl. Anesth Analg 1989;68:712–7.
[40] Weyland A, Grune F, Stephan H, et al. Cerebrovascular effects of 0.8% halothane in man. J Cereb Blood Flow Metab 1995;15(Suppl 1):S521.
[41] Heath KJ, Gupta S, Matta BF. The effects of sevoflurane on cerebral hemodynamics during propofol anesthesia. Anesth Analg. 1997;85:1284 –7.
[42] Mielck F,Heidrun S, Weyland A, Sonntag H. Effects of One Minimum Alveolar Anesthetic Concentration Sevoflurane on Cerebral Metabolism, Blood Flow, and CO2 Reactivity in Cardiac Patients. Anesth Analg 1999;89:364 –9.
[43] Oshima T, Karasawa F, Okazaki Y, Wada H, Satoh T. Effects of sevoflurane on cerebral blood flow and cerebral metabolic rate of oxygen in human beings: a comparison with isoflurane. Eur J Anaesthesiol. 2003 Jul;20(7):543-7.
[44] Sharpe MD: The use of muscle relaxants in the intensive care unit. Can J Anaesth 1992; 39:949-962.
[45] Bion JF, Oh TE. Sedation in intensive care. In: Oh TE ed. Intensive Care Manual, 4th edition. Butterworth Heinemann; 675-676.
[46] Irish CL, Murkin JM, Cleland A, MacDonald JL, Mayer R. Neuromuscular blockade significantly decreases systemic oxygen consumption during hypothermic cardiopulmonary bypass.J Cardiothorac Vasc Anesth. 1991 Apr;5(2):132-4.
[47] Vernon DD, Witte MK. Effect of neuromuscular blockade on oxygen consumption and energy expenditure in sedated, mechanically ventilated children. Crit Care Med. 2000 May;28(5):1569-71.
[48] Werlhof V, Sessler DI. Pancuronium Does Not Decrease Oxygen Consumption During Hypothermic or Normothermic Cardiopulmonary Bypass. Anesth Analg. 1995;81:465-8

[49] Murphy GS, Hessel EA 2nd, Groom RC. Optimal perfusion during cardiopulmonary bypass: an evidence-based approach. Anesth Analg 2009;108(5):1394-417.
[50] Shibutani K, Komatsu T, Kubal K, Sanchala V, Kumar V, Bizzarri DV. Critical level of oxygen delivery in anesthetized man. Crit Care Med 1983;11:640–3
[51] Komatsu T, Shibutani K, Okamoto K, Kumar V, Kubal K, Sanchala V, Lees DE. Critical levels of oxygen delivery after cardiopulmonary bypass. Crit Care Med 1987;15:194–7
[52] Parolari A, Alamanni F, Gherli T, Bertera A, Dainese L, Costa C, Schena M, Sisillo E, Spirito R, Porqueddu M, Rona P, Biglioli. Cardiopulmonary bypass and oxygen consumption: oxygen delivery and hemodynamics. Ann Thorac Surg 1999;
67:1320–7
[53] Abraham, B. P., P. Prodhan, et al. "Cardiopulmonary bypass flow rate: a risk factor for hyperlactatemia after surgical repair of secundum atrial septal defect in children." J Thorac Cardiovasc Surg 139(1): 170-3.
[54] Ranucci, M., B. De Toffol, et al. (2006). "Hyperlactatemia during cardiopulmonary bypass: determinants and impact on postoperative outcome." Crit Care 10(6): R167.
[55] Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, Tesoro EP, Elswick RK. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002;166(10):1338-44.
[56] Rogers AT, Prough DS, Roy RC, Gravlee GP, Stump DA, Cordell AR, Phipps J, Taylor CL. Cerebrovascular and cerebral metabolic effects of alterations in perfusion flow rate during hypothermic cardiopulmonary bypass in man. J Thorac Cardiovasc Surg 1992;103:363–8.
[57] Peters SG, Afessa B, Decker PA, Schroeder DR, Offord KP, Scott JP. Increased risk associated with pulmonary artery catheterization in the medical intensive care unit. J Crit Care 2003;18(3):171-72.
[58] Croughwell ND, Newman MF, Blumenthal JA, White WD, Lewis JB, Frasco PE, Smith LR, Hurwitz BJ, Leone BJ. Jugular bulb saturation and cognitive dysfunction after cardiopulmonary bypass. Ann Thorac Surg 1994;58(6):1702-8.
[59] Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M. Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345(19):1368-77.

[60] Taittonen MT, Kirvelä OA, Aantaa R, Kanto JH. Effect of clonidine and dexmedetomidine premedication on perioperative oxygen consumption and haemodynamic state. Br J Anaesth 1997;78(4):400-6.
[61] Kavanagh BP, Laffey JG. Hypercapnia: permissive and therapeutic. Minerva Anestesiol 2006;72(6):567-76.
[62] Scott NB, Turfrey DJ, Ray DA, Nzewi O, Sutcliffe NP, Lal AB, Norrie J, Nagels WJ, Ramayya GP. A prospective randomized study of the potential benefits of thoracic epidural anesthesia and analgesia in patients undergoing coronary artery bypass grafting. Anesth Analg. 2001;93:528–35.
[63] Nair SG. Atrial fibrillation after cardiac surgery. Ann Card Anaesth. 2010;13:196-205
[64] Casalino S, Mangia F, Stelian E, Novelli E, Diena M, Tesler UF. High thoracic epidural anesthesia in cardiac surgery: risk factors for arterial hypotension. Tex Heart Inst J. 2006;33:148-53.
[65] Shantsila E, Watson T, Lip GY. Atrial fibrillation post-cardiac surgery: changing perspectives. Curr Med Res Opin. 2006;22:1437-41.
[66] Aoki K, Kanazawa H, Okamoto T, Takahashi Y, Nakazawa S, Yamazaki Y. Awake partial sternotomy pacemaker implantation under thoracic epidural anesthesia. Gen Thorac Cardiovascular Surg. 2009;57:418-20.
[67] Guerra S. Asthma and chronic obstructive pulmonary disease. Curr Opin Allergy Clin Immunol. 2009;9:409-16.
[68] Warner DO, Warner MA, Offord KP, Schroeder DR, Maxson RN, Scanlon PD. Airway obstruction and perioperative complications in smokers undergoing abdominal surgery. Anesthesiology. 1999;90:372–9.
[69] Knapik P, Przybylski R, Nadziakiewicz P, Zembala M. Awake heart valve surgery in a patient with severe pulmonary disease. Ann Thorac Surg. 2008;86:293-5.
[70] Groeben H, Schäfer B, Pavlakovic G, Silvanus MT, Peters J. Lung function under high thoracic segmental epidural anesthesia with ropivacaine or bupivacaine in patients with severe obstructive pulmonary disease undergoing breast surgery. Anesthesiology. 2002;96:536-41.
[71] Gruber EM, Tschernko EM, Kritzinger M, Deviatko E, Wisser W, Zurakowski D, Haider W. The effects of thoracic epidural analgesia with bupivacaine 0.25% on ventilatory mechanics in patients with severe chronic obstructive pulmonary disease. Anesth Analg. 2001;92:1015-9.

[72] Samuels LE, Kaufman MS, Morris RJ, Romisloff R Brockman SK. Coronary artery bypass grafting in patients with COPD. Chest 1998;113:878-882.

[73] Ulke ZS, Sentürk M. Non-analgesic effects of thoracic epidural anesthesia. Agri. 2007;19:6-12.

[74] Myles PS, Daly DJ, Djaiani G, Lee A, Cheng DC. A systematic review of the safety and effectiveness of fast-track cardiac anesthesia. Anesthesiology. 2003;99:982-7.

[75] Rosen DA, Hawkinberry DW 2nd, Rosen KR, Gustafson RA, Hogg JP, Broadman LM. An epidural hematoma in an adolescent patient after cardiac surgery. Anesth Analg. 2004;98:966–9.

[76] Sharma S, Kapoor MC, Sharma VK, Dubey AK. Epidural hematoma complicating high thoracic epidural catheter placement intended for cardiac surgery. J Cardiothorac Vasc Anesth. 2004;18:759-62.

[77] Morse K, Weight M, Molinari R. Extensive postoperative epidural hematoma after full anticoagulation: case report and review of the literature. J Spinal Cord Med. 2007;30:282-7.

[78] Bracco D, Hemmerling T. Epidural analgesia in cardiac surgery: an updated risk assessment. Heart Surg Forum. 2007;10:E334-7.

[79] Gogarten W, Vandermeulen E, Van Aken H, Kozek S, Llau JV, Samama CM. Regional anaesthesia and antithrombotic agents: recommendations of the European Society of Anaesthesiology. Eur J Anaesthesiol. 2010;27:999-1015.

[80] Bucerius J, Gummert JF, Borger MA, Walther T, Doll N, Onnasch JF, Metz S, Falk V, Mohr FW. Stroke after cardiac surgery: a risk factor analysis of 16,184 consecutive adult patients. Ann Thorac Surg 2004;78(2):755-6.

# 13. APPENDICES

**List of publications with impact factor**

**Porizka M**, Stritesky M, Semrad M, Dobias M, Dohnalova A, Korinek J. Standard blood flow rates of cardiopulmonary bypass are adequate in awake on-pump cardiac surgery. Eur J Cardiothorac Surg. 2011 Apr;39(4):442-50. Epub 2011 Jan 14. **(IF 2.39)**

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