Příloha č. 3

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Oxygen consumption in awake cardiac surgical patients

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Disertační práce bude nejméně pět pracovních dnů před konáním obhajoby zveřejněna k nahlížení veřejnosti v tištěné podobě na Oddělení pro vědeckou činnost a zahraniční styky Děkanátu 1. lékařské fakulty.

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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 a 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.

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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.

1. 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 AWCS and evaluated the impact of awake TEA technique on major parameters of postoperative complications with comparison to patients with GA and TEA-GA.

2. HYPOTHESIS AND STUDY AIMS

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.

Thus, the aim of the study was to test 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

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

Thus, the aim of the study was to evaluate 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.

3. 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. A central venous catheter was placed via right internal jugular vein

into superior caval vein to measure central venous pressure (CVP) and to obtain blood samples. Another catheter 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. 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 and 7 ml of 0.5% bupivacaine + 10 ug of sufentanil were administered as a bolus into the space. Afterwards, an epidural catheter was inserted 2-4 cm into epidural space and continuous epidural infusion using mixture of 15 ml of 0.5% bupivacaine + 50 μg of sufentanil and 15 ml of saline was applied with a rate of 7-10 mL/hr till the end of surgery. 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. In combined anesthesia group (TEA-GA group), after epidural puncture general anesthesia was induced and maintained using isoflurane in the same dosage as in GA group.

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.

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 and right atrium 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 (ICU).

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, mean arterial pressure (MAP) and central venous pressure (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.

4. 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 of 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 - presented in table 1A, 1B and 2.

TABLE 1A. Demographic 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

TEA, thoracic epidural anesthesia group; TEA-GA combined thoracic epidural anesthesia and general anesthesia group; GA, general anesthesia group; BMI, body mass index; BSA, body surface area.

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

TABLE 1B. Preoperative data

	TEA (n=15)	TEA-GA (n=15)	GA (n=15)	P-value
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 I.	7%	0%	0%	0.624
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; 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
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
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. * P <0.05 vs. TEA, † P <0.05 vs. TEA-GA.

Hemodynamics

All the hemodynamic data are included in Table 3.

TABLE 3. Hemodynamic data, glycemia and oxygen delivery

	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	
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.

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

Arterial acid base parameters, venous saturations and oxygen delivery – all data are presented in figure 1-8 and table 3.

Figure 1

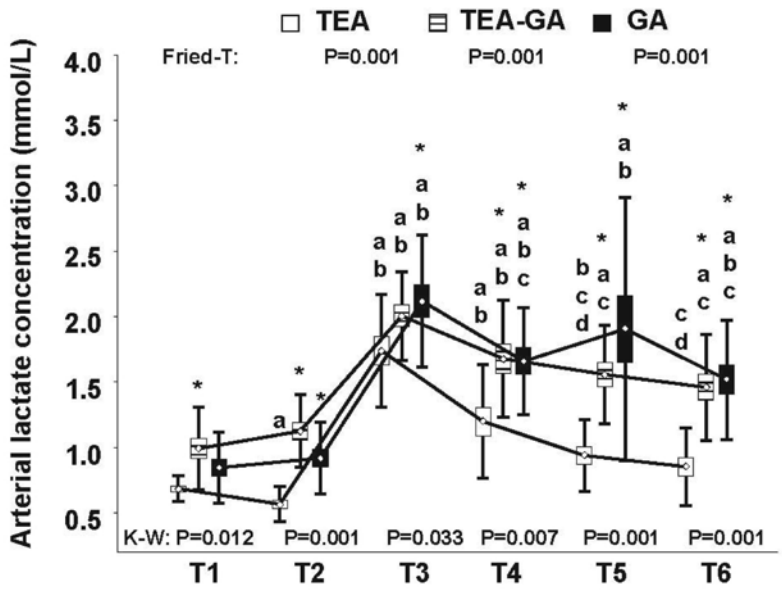


Figure 2

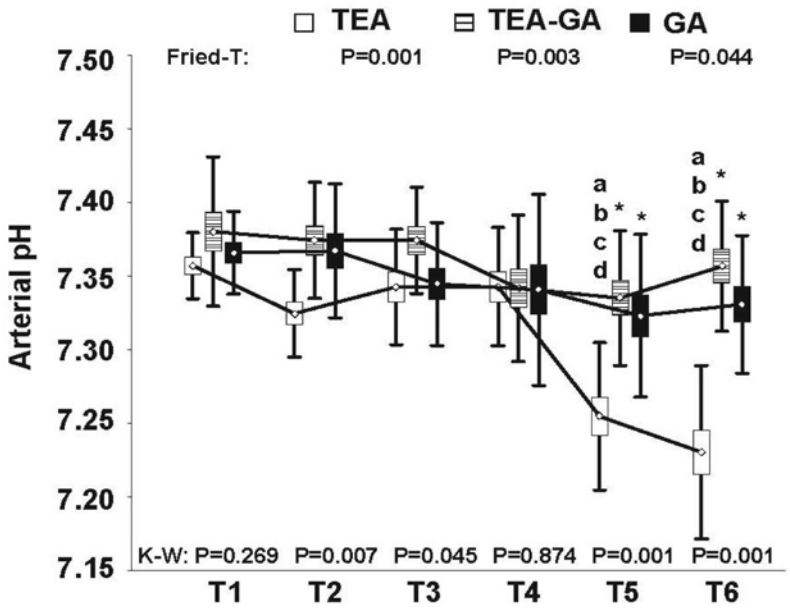


Figure 3

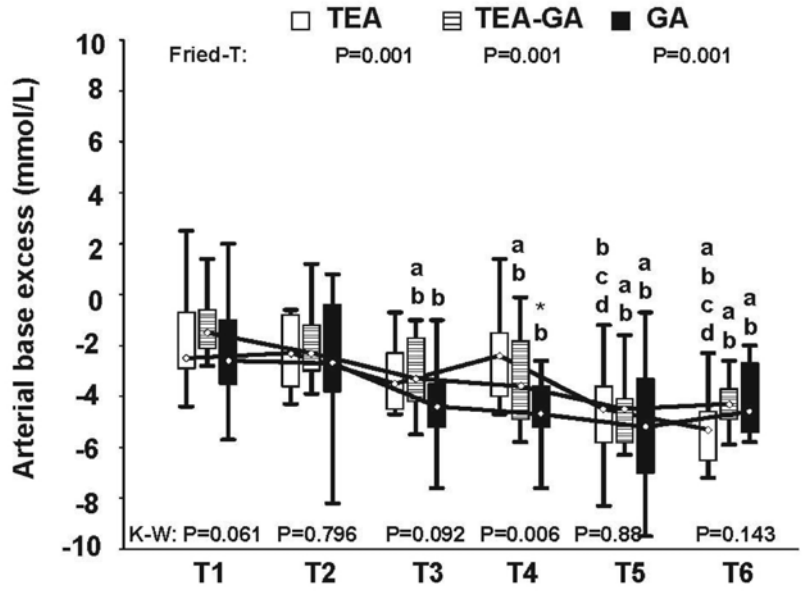
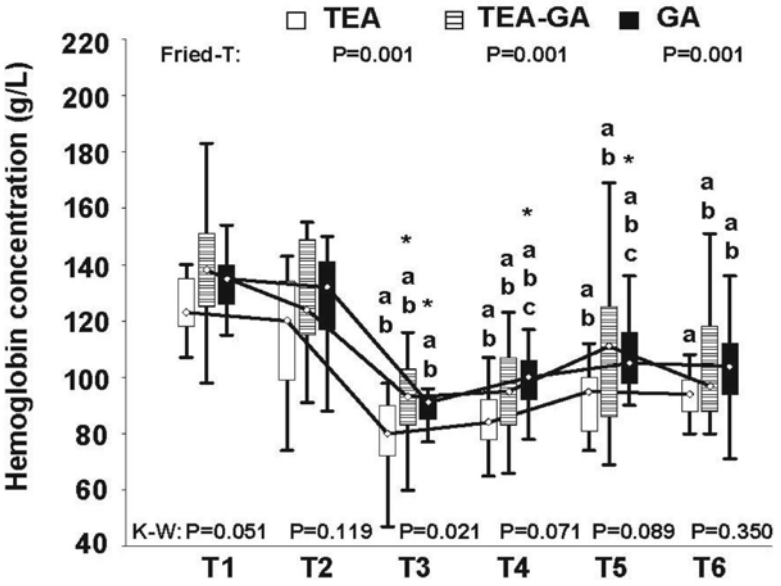


Figure 4



Figures 1-4 depict time course and comparisons of four parameters including arterial lactate concentration (1), arterial pH (2), arterial base excess (3) and hemoglobin concentration (4) at six consecutive time points . TEA, thoracic epidural anesthesia group; TEA-GA combined thoracic epidural anesthesia and general anesthesia group; GA, general anesthesia group. 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.

Figure 5

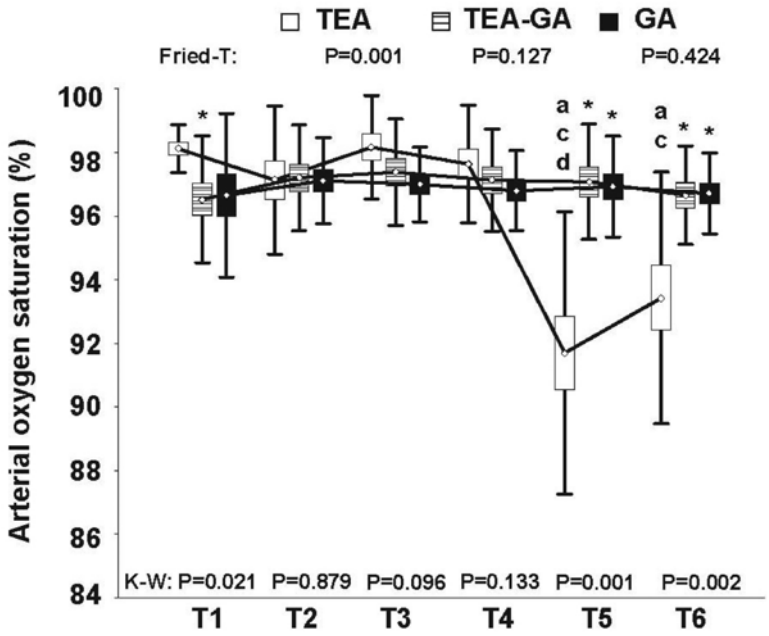
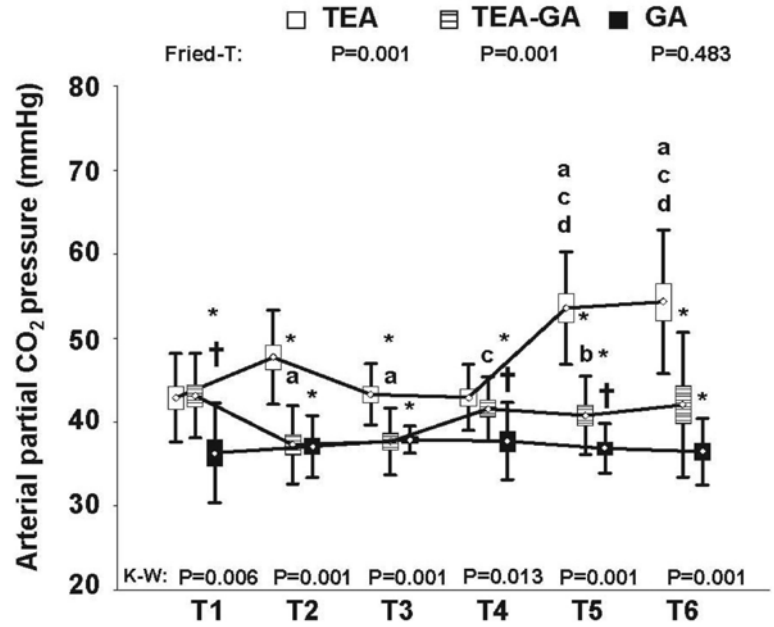


Figure 6



Figures 5-6 depict time course and comparisons of two parameters including arterial arterial oxygen saturation (5) and arterial partial CO_2 pressure (6) at six consecutive time points . TEA, thoracic epidural anesthesia group; TEA-GA combined thoracic epidural anesthesia and general anesthesia group; GA, general anesthesia group. 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.

Figure 7

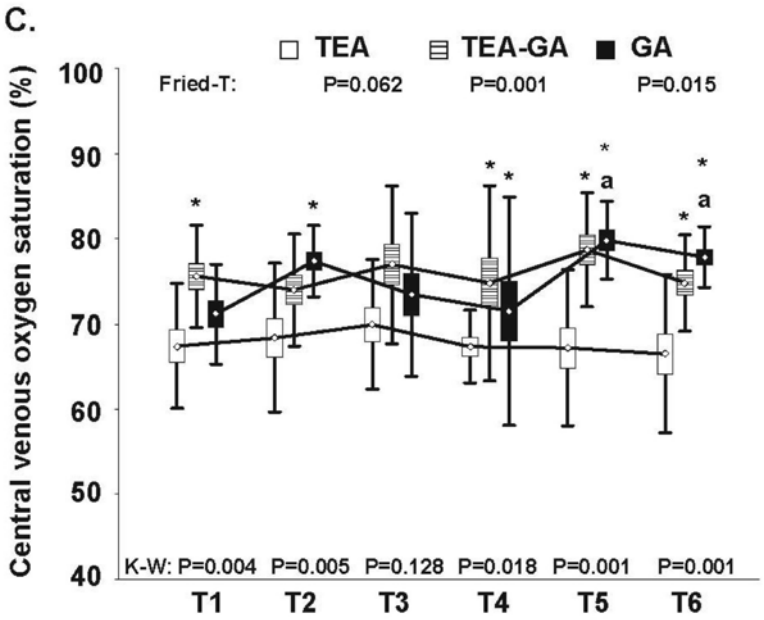
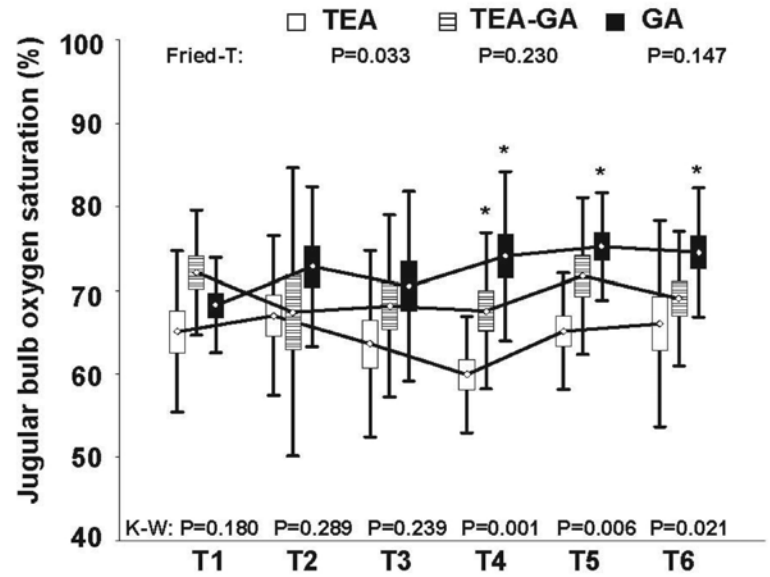


Figure 8



Figures 7-8 depict time course and comparisons of two parameters including central venous oxygen saturation (7) and jugular bulb oxygen saturation (8) at six consecutive time points . TEA, thoracic epidural anesthesia group; TEA-GA combined thoracic epidural anesthesia and general anesthesia group; GA, general anesthesia group. 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.

Příloha č. 3

Postoperative outcome in awake 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 4, 5 and 6. 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 4). The incidence of atrial fibrillation was higher in the GA group as compared to TEA group (Table 4).

TABLE 4. 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	0	0	0	
Intra-aortic balloon pump	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). * $P<0.05$ vs. TEA, † $P<0.05$ vs. TEA-GA.

TABLE 5. 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 6. 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.

5. DISCUSSION

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 [13]. 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]. However, BFRs as low as 1.2 L/min/m^2 have been used during hypothermic bypass with acceptable clinical outcomes [14] 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 [13]. On the other hand, low BFRs during CPB have been identified as an independent risk factor for development of hyperlactatemia [15|] due to inadequate DO_2 to peripheral tissues [16]. 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 [11,16]. However, the minimal safe or optimal BFRs during CPB have not yet been established [13].

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 [13, 17], which was observed also in our study (Table 3). 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 4). 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 [13]. 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 [18]. 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 [19]. $ScvO_2$ below 50% predicts poor outcome in patients in septic shock [20]. 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 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 providing luxurious DO_2. In this case, even significantly increased VO_2 in awake 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 [21] 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 [22]. 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.

5.2 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 [23]. 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 [24]. In our study, there was a lower incidence of atrial fibrillation in the TEA group, which corresponds to previously reported effects of TEA [7,23]. 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 [24]. Although our patients underwent various types of on-pump surgical procedures, their incidence did not differ among the study groups (Table 4).

Furthermore, the hypotensive effect of TEA as a result of excessive sympathetic blockade with its possible consequences has been described in the literature [25]. However, our

results show the opposite findings compared to the published data (Table 4). 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 [26]. 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 4).

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].

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 [27].

5.3 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 [18], 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.

6. CONCLUSIONS

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

Our study shows 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.

Postoperative outcome in awake cardiac surgery (Phase 2 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.

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8. LIST OF PUBLICATIONS

1. Publications *in extenso*, which the dissertation is based upon (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)

Porizka M, Stritesky M, Semrad M, Dobias M, Dohnalova A. Postoperative outcome in awake cardiac surgery. J Anesth. 2011 May 11. [Epub ahead of print]. **(IF 0.84)**