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Original Article

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ABSTRACT

Objectives: Assessment of microcirculation is thought to be a surrogate of tissue perfusion, and anesthetic drugs are known to alter the microcirculation in cardiac surgery patients, but their effects in less complicated non-cardiac surgery remain unknown. Our aim is to investigate the effects of sevoflurane and desflurane on the microcirculation parameters during non-cardiac surgery.

Design: Prospective cohort study

Setting: Hacettepe University Medical Faculty and Hospital

Subjects: ASA I-II patients who underwent ≥ 2 hours non-cardiac surgery were randomly divided into two groups: sevoflurane (n = 20) and desflurane (n = 19).

Intervention: Sevoflurane or desflurane

Main outcome measures: Demographic, hemodynamic variables (heart rate, mean arterial pressure) and laboratory parameters (hematocrit, hemoglobin, urea and creatinine) were measured. Microcirculation imaging was performed by using side stream dark field imaging.

Results: There were no statistical differences in demographic, hemodynamic and laboratory parameters between groups. In the sevoflurane group, proportion of perfused vessel was slightly increased at the second hour intraoperatively compared to the post-induction period in small vessels (94.7% vs 93%, p = 0.036), but other parameters (microvascular flow index, total vascular density and perfused vascular density) were comparable in both measurement periods. In the desflurane group, all microcirculation parameters were comparable between post-induction period and second hour intraoperatively.

Conclusions: Sevoflurane anesthesia slightly increases the proportion of perfused vessel in small vessels, whereas desflurane has no effect on microcirculation parameters in ASA I-II non-cardiac surgery patients. Neither sevoflurane nor desflurane have major effects on microcirculation in this patient population.

KEYWORDS: anesthesia; desflurane; microcirculation; non-cardiac surgery; sevoflurane

INTRODUCTION

Microcirculation is a blood vessels network consisting of <100 µm diameter arterioles, capillaries and venules. Microcirculation is essential for adequate tissue oxygenation and important for organ function. Alterations in microcirculation can cause inadequate tissue oxygenation and may lead to organ failure[1].

Microcircular oxygen delivery cannot be predicted from global hemodynamic measurements and thus microcirculation provides a novel way of assessing tissue perfusion. Sidestream dark field (SDF) is a new microcirculation imaging technique that allows bedside in vivo microcirculation imaging[2,3]. It is one of the most commonly used devices for assessing tissue perfusion, and a decrease in any of the measured parameters (proportion of perfused vessels, microvascular flow index, total vascular density, perfused vascular density) reflect tissue hypoperfusion[4].

Previous animal studies showed that various injectable and inhalation anesthetic agents can cause microcirculatory alterations[5,6] and there are various reports about microcirculatory alterations in humans with sepsis, shock and cardiac failure; however it is unknown whether anesthetics have a direct effect on microcirculation or their effects become evident in the presence of severe hemodynamic changes in these

serious conditions. To our knowledge there are no reports about microcirculatory alterations in humans during non-severe conditions or minor surgery.

Sevoflurane and desflurane are among the most commonly used inhalation anesthetics. Volatile anesthetics may cause global hemodynamic changes including hypotension and tachycardia through their effects on the myocardium and by decreasing systemic vascular resistance[7] and this hypotension may be associated with acute kidney injury and myocardial injury in patients undergoing non-cardiac surgery[8]. The effects of general anesthetics on microcirculation during coronary artery bypass graft surgery (CABG) by using orthogonal polarization spectral (OPS) imaging were investigated and the authors concluded that sevoflurane but not desflurane, had a negative effect on the microcirculation during cardiac surgery[9]. It has also been shown that cardiopulmonary bypass caused significant microvascular alterations during cardiac surgery[10], which was thought to be due to increased prevalance of hypothermia, surgical trauma, hemodilution, and inflammatory reaction in this patient population. We hypothesized that inhalation anesthetics might have a direct effect on microcirculation and aimed to investigate microcirculatory alterations in non-cardiac surgery patients, in whom the confounding effects of hemodynamic alterations are minimal, and also investigate whether a differential effect between sevoflurane and desflurane exists in this low-risk patient population.

SUBJECTS AND METHODS

Patients and procedures

The Institutional Ethical Committee approved the study protocol (approval number: 04-116-12) and informed consent was obtained from each patient. This prospective study was performed in a tertiary university hospital. All patients were evaluated preoperatively by the study team and patients who have end-stage organ failure, obstructive/restrictive respiratory disease, sepsis, shock, and multi organ failure were excluded. A total of 39 ASA I-II patients who underwent elective non-cardiac surgery (general surgery, urology, plastic surgery, gynecology, orthopedics and non-cardiac vascular surgery) were included. Patients were randomly divided into two groups and groups were named according to the inhalation agents used: sevoflurane (n = 20) and desflurane (n = 19).

In the operating room, patients were routinely monitored with electrocardiogram (ECG), pulse oximetry, non-invasive blood pressure and capnography. Anesthesia induction was performed using intravenous propofol (2 mg/kg), fentanyl (1 mcg/kg) and rocuronium (0.6 mg/kg). For anesthesia maintenance, inhalation agents were given at 1 MAC (sevoflurane 2% and desflurane 6%) in 50%-50% oxygen-air mixture. Inhalation agents were used in these patients during the entire surgery period. All patients were ventilated with synchronized intermittent mandatory ventilation (SIMV) mode. The ventilation parameters were tidal volume 6-8 ml/kg, ventilator frequency 10-12/min and all these parameters were adjusted to maintain an end-tidal CO_2 level between 35-45 mmHg.

The patients' demographic and clinical characteristics (age, sex, body weight, duration of anesthesia, comorbidities, drugs, fluid infusion) were recorded. The heart rate and blood pressure were also recorded after induction and at the 2nd hour of surgery. Laboratory parameters (hematocrit, hemoglobin, creatinine, blood urea nitrogen) were measured in the preoperative period.

Microcirculation analysis

Sublingual microcirculation was imaged using SDF method and recorded after induction and at the 2nd hour of surgery. A hand-held microscope was held steadily and perpendicular to the tissue surface without pressure to record the images from a mix of large and small vessels[11]. The video clips were taken for longer than 5 seconds from 5 different sublingual sites in each patient. The imaging output is red blood cell flowing as dark globules against a white/grayish background[12]. The analysis was performed as previously described by an investigator blinded to the inhalation agent used[9]. The SDF (MicroVision Medical, Amsterdam, the Netherlands) probe, covered by a sterile cap, was placed on a sublingual tissue surface to avoid pressure according to consensus report[13]. Image analysis was performed blindly in the recorded video clips by using the computer software (AVA 3.1; MicroVision Medical BV, Amsterdam, the Netherlands)[14]. The vessels were automatically detected by the program, then corrected by hand with a computer mouse. After the vessels were identified through analysis, the flow of every vessel was determined as absent (0), intermittent (1), sluggish (2), or continuous (3). The software provided the results of Microvascular flow index (MFI) score, total vessel density (TVD), perfused vessel density (PVD) and proportion of perfused vessel (PPV) results of small, medium and all vessels with a report. MFI is the average of the flow in 4 quadrants. The PPV (%) is calculated with 100 * (total number of vessels – (no flow + intermittent flow))/ total number of vessels. PVD, an estimate of functional capillary density (FCD), is calculated by multiplying vessel density by the proportion of perfused vessels[13].

Statistical analysis

Statistical analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, IL). All values are expressed as mean ± standard deviation. The variables were analyzed using Kolmogorov-Smirnov/Shapiro-Wilks test to determine whether they were distributed normally. Statistical significance was tested using one-way ANOVA for parametric variables and Mann-Whitney U test for nonparametric variables. P-value <0.05 was accepted as statistically significant

RESULTS

Patient characteristics, laboratory and hemodynamic parameters

There were no significant differences in the patients' characteristics and operative parameters between the groups (Table 1). None of the patients received any vasodilator and/or vasoconstrictor drugs during surgery. Preoperative hematocrit, hemoglobin, creatinine and blood urea nitrogen values were similar among groups (Table 2). At the 2nd hour of surgery, heart rate significantly decreased in both groups compared to after induction values ($p < 0.05$). Mean arterial pressure and heart rate were similar in both groups during all time points (Table 3).

SDF parameters of small, medium-large and all vessels

In the sevoflurane group at the second hour, MFI, TVD or PVD remained unchanged compared to post-induction period in small vessels ($p > 0.05$, Table 4). PPV of small vessels increased slightly (93% to 94.7%) at the second hour compared to post-induction period, and this increase was statistically significant

(p = 0.036). When medium-large vessels are analyzed, there were no changes in MFI, TVD, PVD or PPV in sevoflurane group at the second hour compared to post-induction period. When all vessels are analyzed together, there was a slight but statistically significant increase in PPV at the second hour compared to post-induction period (p = 0.037), and the changes in MFI, TVD or PVD were not significant (p >0.05).

In the desflurane group, there were no significant changes in MFI, TVD, PVD and PPV at second hour of anesthesia compared to post-induction period when small and medium-large vessels are analyzed separately or together (p >0.05, Table 4).

There were no significant differences between sevoflurane and desflurane groups for MFI, TVD, PVD and PPV at any time points studied (Table 4).

DISCUSSION

Microcirculation is essential for adequate tissue perfusion and oxygenation. Imaging of microcirculation provides information about a novel aspect of circulation evaluation for patients. Previous studies investigated the role of microcirculation in serious medical conditions such as sepsis, shock and cardiac surgery[9,10,15,16] and showed sevoflurane, but not desflurane, had a negative effect on the microcirculation during cardiac surgery. Those patients have major hemodynamic alterations such as hypothermia, hypotension, surgical trauma and inflammatory reaction, which are known to directly affect microcirculation. In this study, we investigated microcirculation alterations in ASA I-II patients undergoing non-cardiac surgery in order to investigate the direct effects of anesthetic drugs in microcirculation, as this low-risk population has minimal hemodynamic alterations. Our results showed that sevoflurane and desflurane do not have substantial effects on microcirculatory parameters. The agent of choice also does not have any significant effects on these parameters in ASA I-II non-cardiac surgery patients.

The microcirculatory alterations during cardiac surgery have been well investigated. Cardiac surgery can alter microcirculation, especially during cardiopulmonary bypass (CPB) period, which causes significant changes in temperature, hematocrit, systemic blood pressure and arterial perfusion pressure that can affect systemic oxygen requirement[9]. Bauer *et al* showed that functional capillary density is decreased during cardiac surgery[17]. Uil *et al* compared sublingual microcirculation in CPB patients with sevoflurane anesthesia before and after surgery. They concluded that microvascular blood flow of medium and large vessels are decreased during CPB and this decrease was not associated with hemodynamic parameters[18]. De Backer *et al* compared microcirculation in off-pump and on-pump cardiac surgery patients. They showed that PPV is dramatically decreased during CPB and on admission to the recovery room, PPV is still decreased in both off-pump and CPB patients, but the decrease in the latter is slightly more severe (60% vs. 64% in off-pump group). They also showed that in their control group (thyroidectomy patients), use of similar anesthetic procedure (propofol + remifentanil) also impairs PPV during surgery, but it is normalized in the recovery room in these patients. They concluded that cardiac surgery alters microcirculation independent from CPB usage and the effects of anesthesia on microcirculation are transient[10]. Ozaslan *et al* investigated the effects of sevoflurane, isoflurane and desflurane on microcirculation in CABG. They showed that microcirculation is greatly altered during CPB period and sevoflurane use is associated with further decrease in TVD (14.7%), PVD (22%) and PPV (5.97%),

whereas desflurane use was associated with a slight but statistically significant decrease in PPV (1.4%) but no significant changes in TVD or PVD[9]. In our study, sevoflurane slightly increased the PPV of small vessels (~2%) while desflurane had no effect on microcirculation in non-cardiac surgery in ASA I-II patients.

The effects of injectable anesthetics on microcirculation have been widely studied using other techniques. Lanndsverk *et al* used laser Doppler to measure skin microcirculation and showed that propofol infusion impairs microcirculation in healthy subjects[19]. Koch *et al* investigated the effect of propofol on microcirculation in ASA I patients by using SDF and they concluded propofol decreased microcirculation transiently[20]. Blasi *et al* investigated effects of sevoflurane + remifentanil and propofol + remifentanil combination on microcirculation in healthy patients during maxillofacial surgery by using near infrared spectroscopy (NIRS)[21]. In both groups, microcirculation parameters increased during surgery. In our study, we used a more advanced and new technique, SDF, to quantify microcirculation and demonstrated that sevoflurane and desflurane do not induce substantial changes in microcirculatory parameters.

It is known that microcirculation is impaired in sepsis. De Backer *et al* compared sublingual microcirculation in 10 healthy volunteers, 16 patients who will undergo cardiac surgery, 10 acutely ill patients without sepsis and 50 patients with severe sepsis by using OPS. They showed that microvascular blood flow alterations are common in sepsis patients and there is no correlation between arterial blood pressure and microcirculation[15]. Sakr *et al* showed that impairment in microcirculation is associated with mortality in septic shock patients, also survivors have improvement in small vessel perfusion, whereas those who did not survive had no improvement[16]. Another study showed that severity of microcirculation impairment is correlated with organ dysfunction and mortality[22]. In addition, De Backer *et al* showed that microcirculatory alterations are frequent in acute severe cardiac failure patients[23].

The main limitation of our study is the small patient population who underwent different types of short-duration minor surgeries and due to limited number of patients, separate analysis for surgery type which can potentially affect microcirculation could not be done. Whether microcirculation is affected by the type of minor surgery requires further investigation. Also, none of our patients had post-surgical organ failure so we could not investigate whether there is a correlation between microcirculation and post-surgical organ failure development in this low-risk patient population. Future studies investigating effects of sevoflurane and desflurane in development of post-surgical organ failure in a larger group of patients or higher risk patients are warranted.

CONCLUSION

We showed that neither sevoflurane nor desflurane alter microcirculation substantially during non-cardiac surgery in ASA I-II patients. Our results suggest that anesthetic of choice is not of critical importance in this patient population in terms of tissue perfusion.

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Conflict of interest statement: None

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Table 1: Patient characteristics and operative values (mean ± standard deviation)

Patient characteristics	Sevoflurane (n = 20)	Desflurane (n = 19)	Total (n = 39)
Age (year)	47.9 ± 15.7	49.6 ± 14.5	48.7 ± 14.9
Female / Male (n/n)	11 / 9	10 / 9	21 / 18
Weight (kg)	71.6 ± 13.9	68.9 ± 18.2	70.3 ± 16
Anesthesia duration (min)	138.5 ± 57.4	152.1 ± 81.7	145.1 ± 69.7
Crystalloid fluid (ml)	1550 ± 705.2	1765.7 ± 858.3	1655.1 ± 780.7
Colloid fluid (ml)	282.5 ± 375.3	352.6 ± 367.2	316.6 ± 368.2
Blood transfusion (number of units)	1	2	3

Table 2: Preoperative laboratory values (mean ± standard deviation)

Lab values	Sevoflurane (n = 20)	Desflurane (n = 19)	p-value
Hematocrit (%)	40 ± 5.2	39.7 ±3.3	0.870
Hemoglobin (g/dl)	13.5 ± 1.9	13.5 ± 1.1	0.884
Creatinine (mg/dl)	0.79 ± 0.15	0.92 ± 0.47	0.252
BUN (mg/dl)	13.4 ± 4.5	17.8 ± 19.5	0.331

Table 3: Heart rate (beats/min) and mean arterial pressure (mmHg) in groups (mean ± standard deviation)

Hemodynamics	Time	Sevoflurane	Desflurane	p-values#
Heart Rate	**After induction**	82.45 ± 13.56	83.16 ± 12.58	0.867
	2nd hour	76.90 ±11.83*	70.26 ± 11.83*	0.065
	At the end of surgery	77.90 ± 15.65	76.00 ± 12.21	0.676
Mean Arterial Pressure	**After induction**	89.25 ± 19.91	85.02 ±10.81	0.418
	2nd hour	87.37 ± 13.25	83.05 ± 10.18	0.263
	At the end of surgery	86.85 ± 12.89	87.09 ± 11.58	0.952

* $p < 0.05$; compared to after induction; # p values among sevoflurane and desflurane groups

Table 4: SDF values in small, medium-large sized and all vessels in Sevoflurane and Desflurane groups (mean ± standard deviation). MFI: microvascular flow index, TVD: total vessel density, PVD: perfused vessel density, PPV: proportion of perfused vessels

Vessel type and measurement time		MFI (AU)		TVD (mm/mm^2)		PVD (mm/mm^2)		PPV (%)	
		Sevoflurane	Desflurane	Sevoflurane	Desfluran e	Sevoflurane	Desfluran e	Sevoflurane	Desfluran e
Small Vessels	After induction	2.63 ± 0.2	2.69 ± 0.3	16.01 ± 1.9	16.51 ± 1.7	14.90 ± 1.9	15.59 ± 1.9	93.05 ± 4.2	94.24 ± 3.8
	2nd hour	2.75 ± 0.3	2.73 ± 0.3	15.18 ± 2.0	16.17 ± 2.1	14.38 ± 2.1	15.16 ± 2.2	94.73 ± 3.7*	93.50 ± 5.2
Medium-Large Vessels	After induction	2.78 ± 0.3	2.88 ± 0.2	0.65 ± 0.4	0.56 ± 0.2	0.49 ± 0.4	0.46 ± 0.2	99.41 ± 2.6	97.96 ± 6.0
	2nd hour	2.82 ± 0.3	2.86 ± 0.2	0.69 ± 0.3	0.50 ± 0.4	0.51 ± 0.4	0.39 ± 0.4	100.0 ± 0.0	97.71 ± 9.3
All Vessels	After induction	2.71 ± 0.3	2.79 ± 0.2	16.50 ± 1.8	16.97 ± 1.7	15.39 ± 1.8	16.04 ± 1.9	93.23 ± 4.2	94.39 ± 3.7
	2nd hour	2.79 ± 0.2	2.81 ± 0.2	15.69 ± 2.0	16.57 ± 2.2	14.90 ± 2.2	15.55 ± 2.2	94.87 ± 3.6*	93.65 ± 5.1

*p <0.05 compared to after induction, p >0.05 for all other comparison