Original Article

Effects of sevoflurane and desflurane on microcirculation during non-cardiac surgery

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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: Patients with American Society of Anesthesiologists (ASA) score of I-II who underwent ≥2 hours of 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 (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, the proportion of perfused vessel (PPV) was slightly increased at the second hour intraoperatively compared to the post-induction period in small vessels (94.7% vs 93%, *P*=.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 PPV 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.

KEY WORDS: 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 decreases in any of the measured parameters (proportion of perfused vessels (PPV), microvascular flow index (MFI), total vascular density (TVD), perfused vascular density (PVD)) 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

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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 by using orthogonal polarization spectral imaging were investigated and the authors concluded that sevoflurane, but not desflurane, had a negative effect on 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 patients with American Society of Anesthesiologists (ASA) score of I-II 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, 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 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 and 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 MFI score, TVD, PVD and PPV results of small, medium and all vessels with a report. MFI is the average of the flow in four 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, is

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

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 <.05 was accepted as statistically significant

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
Blood urea nitrogen (mg/dl)	13.4 ± 4.5	17.8 ± 19.5	0.331

RESULTS

Patient characteristics, laboratory and hemodynamic parameters

There were no significant differences in the patients' characteristics and operative parameters between the groups (Table 1). During surgery, none of the patients received any vasodilator and/or vasoconstrictor drugs. 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 <.05). Mean arterial pressure and heart rate were similar in both groups during all time points (Table 3).

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

Hemodynamics	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 <.05; compared to after induction; # P-values among sevoflurane and desflurane groups

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 >.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=.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=.037), and the changes in MFI, TVD or PVD were not significant (P >.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

Table 4: SDF values in small, medium-large sized and all vessels in sevoflurane and desflurane groups (mean ± standard deviation)

Vessel type and measurement time	MFI (AU)		TVD (mm/mm²)		PVD (mm/mm²)		PPV (%)	
	Sevoflurane	Desflurane	Sevoflurane	Desflurane	Sevoflurane	Desflurane	Sevoflurane	Desflurane
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								
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<.05 compared to after induction, P >.05 for all other comparison, SDF: sidestream dark field; MFI: microvascular flow index; TVD: total vessel density; PVD: perfused vessel density; PPV: proportion of perfused vessels.

small and medium-large vessels are analyzed separately or together (P >.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 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 and that the agent of choice 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. Therefore, they concluded that cardiac surgery alters microcirculation independent from CPB usage and the effects of anesthesia on microcirculation are transient[10]. Ozarslan *et al* investigated the effects of sevoflurane, isoflurane and desflurane on microcirculation in coronary artery bypass graft surgery. 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%) and 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. Landsverk *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 that 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[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 orthogonal polarization spectral. 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, and that survivors have improvement in small vessel perfusion, whereas those that 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 by surgery type could not be done, which can potentially affect microcirculation. Whether microcirculation is affected by the type of minor surgery requires further investigation. Also, none of our patients had post-surgical organ failure. As a result, 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

REFERENCES

1. Ince C. The microcirculation is the motor of sepsis. Critical Care 2005; 9 (Suppl 4):S13-S19.
2. De Backer D, Donadello K, Cortes DO. Monitoring the microcirculation. J Clin Monit Comput 2012; 26(5):361-366.
3. Donati A, Domizi R, Damiani E, Adrario E, Pelaia P, Ince C. From macrohemodynamic to the microcirculation. Crit Care Res Pract 2013; 2013:892710.
4. van Elteren HA, Ince C, Tibboel D, Reiss IKM, de Jonge RCJ. Cutaneous microcirculation in preterm neonates: comparison between sidestream dark field (SDF) and incident dark field (IDF) imaging. J Clin Monit Comput 2015; 29(5):543-548.
5. Brookes ZL, Brown NJ, Reilly CS. Intravenous anaesthesia and the rat microcirculation: the dorsal microcirculatory chamber. Br J Anaesth 2000; 85(6):901-903.
6. Schumacher J, Porksen M, Klotz KF. Effects of isoflurane, enflurane, and halothane on skeletal muscle microcirculation in the endotoxemic rat. J Crit Care 2001; 16(1):1-7.
7. Brioni JD, Varughese S, Ahmed R, Bein B. A clinical review of inhalation anesthesia with sevoflurane: from early research to emerging topics. J Anesth 2017; 31(5):764-778.
8. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, *et al*. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. Anesthesiology 2013; 119(3):507-515.
9. Ozarslan NG, Ayhan B, Kanbak M, Celebioglu B, Demircin M, Ince C, *et al*. Comparison of the effects of sevoflurane, isoflurane, and desflurane on microcirculation in coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 2012; 26(5):791-798.
10. De Backer D, Dubois MJ, Schmartz D, Koch M, Ducart A, Barvais L, *et al*. Microcirculatory alterations in cardiac surgery: effects of cardiopulmonary bypass and anesthesia. Ann Thorac Surg 2009; 88(5):1396-1403.
11. Ocak I, Kara A, Ince C. Monitoring microcirculation. Best Pract Res Clin Anaesthesiol 2016; 30(4):407-418.
12. Dan M. J. Milstein RB, Can Ince. Sidestream dark-field (SDF) video microscopy for clinical imaging of the microcirculation. In: Leahy MJ, editor. Microcirculation imaging. Weinheim: Wiley-Blackwell; 2012. p. 32-52.
13. De Backer D, Hollenberg S, Boerma C, Goedhart P, Buchele G, Ospina-Tascon G, *et al*. How to evaluate the microcirculation: report of a round table conference. Crit Care 2007; 11(5):R101.
14. Dobbe JGG, Streekstra GJ, Atasever B, van Zijderveld R, Ince C. Measurement of functional microcirculatory geometry and velocity distributions using automated image analysis. Med Biol Eng Comput 2008; 46(7):659-670.
15. De Backer D, Creteur J, Preiser JC, Dubois MJ, Vincent JL. Microvascular blood flow is altered in patients with sepsis. Am J Respir Crit Care Med 2002; 166(1):98-104.
16. Sakr Y, Dubois MJ, De Backer D, Creteur J, Vincent JL. Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. Crit Care Med 2004; 32(9):1825-1831.
17. Bauer A, Kofler S, Thiel M, Eifert S, Christ F. Monitoring of the sublingual microcirculation in cardiac surgery using orthogonal polarization spectral imaging: preliminary results. Anesthesiology 2007; 107(6):939-945.
18. den Uil CA, Lagrand WK, Spronk PE, van Domburg RT, Hofland J, Luthen C, *et al*. Impaired sublingual microvascular perfusion during surgery with cardiopulmonary bypass: a pilot study. J Thorac Cardiovasc Surg 2008; 136(1):129-134.
19. Landsverk SA, Kvandal P, Bernjak A, Stefanovska A, Kirkeboen KA. The effects of general anesthesia on human skin microcirculation evaluated by wavelet transform. Anesth Analg 2007; 105(4):1012-1019, table of contents.
20. Koch M, De Backer D, Vincent JL, Barvais L, Hennart D, Schmartz D. Effects of propofol on human microcirculation. Br J Anaesth 2008; 101(4):473-478.

21. De Blasi RA, Palmisani S, Boezi M, Arcioni R, Collini S, Troisi F, *et al*. Effects of remifentanil-based general anaesthesia with propofol or sevoflurane on muscle microcirculation as assessed by near-infrared spectroscopy. Br J Anaesth 2008; 101(2):171-177.
22. De Backer D, Orbegozo Cortes D, Donadello K, Vincent JL. Pathophysiology of microcirculatory dysfunction and the pathogenesis of septic shock. Virulence 2014; 5(1):73-79.
23. De Backer D, Creteur J, Dubois MJ, Sakr Y, Vincent JL. Microvascular alterations in patients with acute severe heart failure and cardiogenic shock. Am Heart J 2004; 147(1):91-99.