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ORIGINAL RESEARCH

Effects of propofol versus sevoflurane on cerebral circulation time in patients undergoing coiling for cerebral artery aneurysm: a prospective randomized crossover study

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Abstract

Many neuroendovascular treatments are supported by real-time anatomical and visual hemodynamic assessments through digital subtraction angiography (DSA). Here we used DSA in a single-center prospective randomized crossover study to assess the intracranial hemodynamics of patients undergoing coiling for cerebral aneurysm (n = 15) during sevoflurane- and propofol-based anesthesia. Color-coded DSA was used to define time to peak density of contrast medium (TTP) at several intravascular regions of interest (ROIs). Travel time at a particular ROI was defined as the TTP at the selected ROI minus TTP at baseline position on the internal carotid artery (ICA). Travel time at the jugular bulb on the anterior–posterior view was defined as the cerebral circulation time (CCT), which was divided into four segmental circulation times: ICA, middle cerebral artery (MCA), microvessel, and sinus. When bispectral index values were kept between 40 and 60, CCT (median [interquartile range]) was 10.91 (9.65–11.98) s under propofol-based anesthesia compared with 8.78 (8.32–9.45) s under sevoflurane-based anesthesia ($P < 0.001$). Circulation times for the ICA, MCA, and microvessel segments were longer under propofol-based anesthesia than under sevoflurane-based anesthesia ($P < 0.05$ for all). Our results suggest that, relative to sevoflurane, propofol decreases overall cerebral perfusion.

Keywords Cerebral circulation time · Digital subtraction angiography · Sevoflurane · Propofol

1 Introduction

Endovascular treatments for cerebrovascular disorders, such as cerebral aneurysm and cerebral artery stenosis or occlusion, have increased as devices and techniques have advanced [1–3]. These treatments often require general

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anesthesia. However, clinical doses of propofol and sevoflurane affect regional cerebral hemodynamics by decreasing cerebral blood flow (CBF) and CBF velocity (CBFV) in specific vessels. These anesthesia-induced changes in cerebral hemodynamics are greater under propofol-based anesthesia than sevoflurane-based [4–8]. Therefore, compared with sevoflurane-based anesthesia, propofol-based anesthesia may decrease cerebral perfusion in patients undergoing endovascular treatments.

Currently, cerebral endovascular treatments are planned and performed with the aid of not only anatomical assessment but also hemodynamic assessment through digital subtraction angiography (DSA), which has high spatial and temporal resolution. Cerebral hemodynamics can be evaluated quantitatively by parametric color coding in real-time within the angiography suite [9–12]. In parametric color coding, the temporal course of the density of the contrast medium during an entire two-dimensional DSA series is converted into a single, composite colored image, and the time to peak (TTP), which is the time point of maximal concentration of contrast medium along the time–density curve, is obtained for various regions of interests (ROIs). The difference in TTP between two ROIs indicates the time required for blood flow between the two ROIs (hereafter, 'travel time'); the travel time is an effective indicator of the characteristic hemodynamics associated with various cerebrovascular disorders [9, 12, 13]. Moreover, the difference in TTP between cerebral arteries and veins represents the time needed for blood to pass through the brain parenchyma (that is, the cerebral circulation time, CCT) [14, 15]; CCT is a robust method for monitoring intracranial hemodynamic changes and is a surrogate marker of CBF [15]. Therefore, travel time and CCT derived from DSA can serve as indicators of overall brain hemodynamics in patients undergoing endovascular treatment. However, although reference values for normal intracranial travel time and CCT in conscious subjects are available [9], the effects of general anesthetic agents on these parameters are unknown.

We hypothesized that if general anesthesia affects cerebral hemodynamics during cerebral angiography, then travel time and CCT as determined by DSA will differ between propofol- and sevoflurane-based anesthesia. To test our hypothesis, we used DSA to prospectively measure contrast material travel times from the internal carotid artery (ICA) to several cerebral arteries and veins in sevoflurane- and propofol-anesthetized patients undergoing endovascular treatment for cerebral aneurysm. We then assessed the effects of these anesthetics on travel time and CCT by comparing the values obtained from anesthetized patients with those determined during pre-operative diagnostic DSA of these same patients while they were conscious.

2 Methods

2.1 Study design

This prospective randomized crossover trial was registered with the University Hospital Medical Information Network Center (UMIN 000016551) on February 20, 2015. It was approved by the Medical Research Ethics Committee of Tokyo Medical and Dental University (Tokyo, Japan; reference number M2000-1985). Written informed consent was obtained from all patients before enrollment. This prospective study was conducted between March 9, 2015 and September 20, 2016.

2.2 Patients

Patients 20 years of age or older who were scheduled to undergo elective coiling at the Medical Hospital of Tokyo Medical and Dental University for cerebral aneurysm in the anterior cerebral circulation were eligible for inclusion in this observer-blinded crossover study (Fig. 1). All patients were of American Society of Anesthesiologists physical status class 2 or lower. The criteria for exclusion were allergy to study drugs, a history of malignant hyperthermia, pregnancy, refusal to participate in the present study, and mental illness.

Before the induction of anesthesia for endovascular treatment, patients were randomized by the envelope method to undergo one of two sequences. In those receiving the sevoflurane–propofol (SP) sequence, general anesthesia was induced and maintained with sevoflurane until the first DSA sequence (DSA_1), which was performed to check the primary condition before coiling, after which sevoflurane was stopped, and propofol was introduced until the second DSA (DSA_2), which was performed to check the final condition after coiling. The remaining patients received the propofol–sevoflurane (PS) sequence: general anesthesia was induced and maintained through propofol infusion until DSA_1, after which propofol infusion was stopped and sevoflurane was introduced until DSA_2. Anesthesia sequence assignment was concealed from the patients and the interventionists who performed the endovascular treatment.

In our hospital, all patients who are scheduled to undergo surgical or endovascular treatment for an unruptured cerebral aneurysm routinely receive diagnostic cerebral angiography while conscious before the treatment. Therefore, we likewise performed diagnostic cerebral angiography on patients enrolled in this study and measured the travel time during pre-operative DSA, which was performed in conscious patients ($DSA_{conscious}$). These

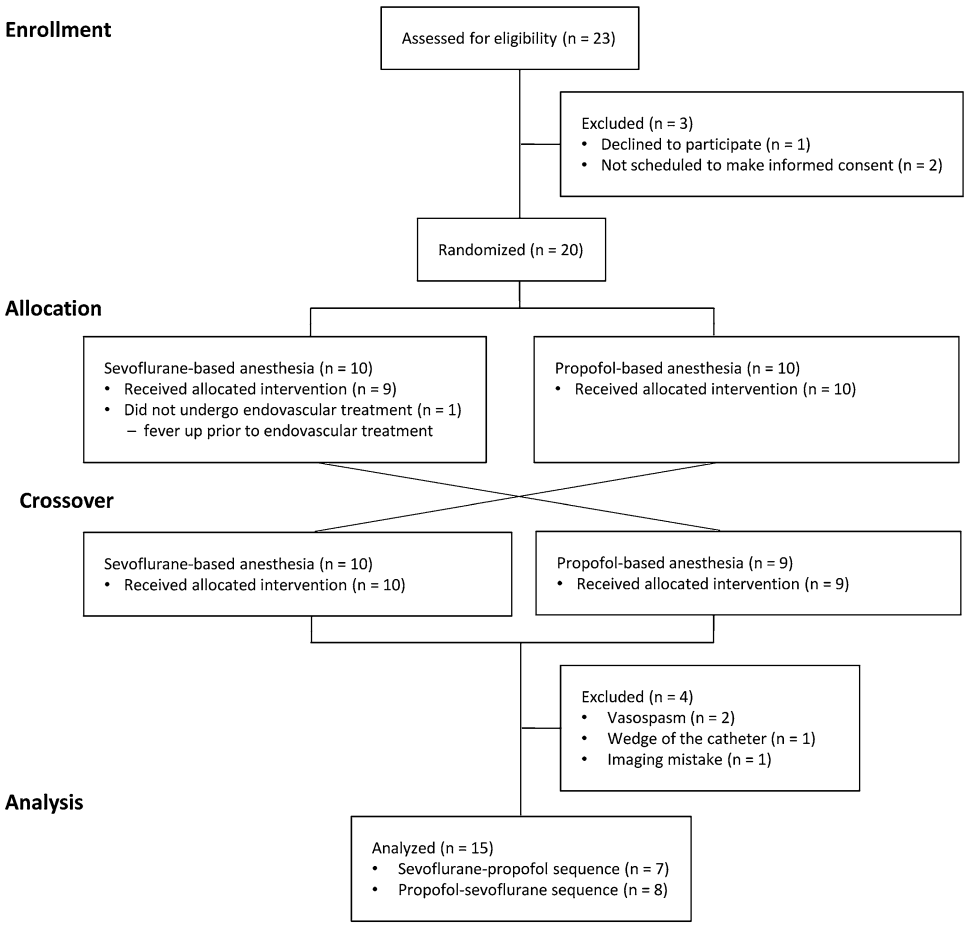

Fig. 1 CONSORT flow diagram for this study

pre-operative values were used as controls for assessing the effects of sevoflurane and propofol on travel time and CCT.

2.3 Anesthesia

On the morning of endovascular treatment, patients were allowed only to take their routine medication; they were not permitted to eat or drink anything. Anesthesia was induced with a continuous infusion of remifentanil at a rate of 0.3 μg kg^{-1} min^{-1} with 100% oxygen (with or without sevoflurane). After anesthesia induction, a radial arterial catheter was inserted and connected to a FloTrac sensor and Vigileo monitoring system (Edwards Lifesciences, Irvine, CA, USA) for measuring cardiac output, stroke volume variation (SVV), and arterial pressure throughout the procedure. The SP sequence included mask induction with 5–8% sevoflurane in 100% oxygen. In the PS sequence, propofol anesthesia was induced through intravenous target-controlled infusion (catalog no. TE-371, Diprifusor TCI system, Terumo, Tokyo, Japan) with a primary target venous plasma concentration of 3 μg mL^{-1}. In both sequences, the trachea was intubated after paralysis by intravenous administration of 0.9 mg kg^{-1} of rocuronium. The lungs were ventilated mechanically with oxygen-enriched air (fraction inspired oxygen, 0.5) adjusted to achieve an end-tidal carbon dioxide concentration ($ETCO_2$) of approximately 35 mmHg. In addition, the bispectral index (BIS) was monitored (model 2000, Aspect Medical System, Newton, MA, USA), and the doses of anesthetic agents were adjusted to achieve a BIS score of 40–60 throughout the procedure. To maintain the BIS score within the target range during the crossover between anesthetic agents, the second agent was introduced gradually as the effect of the initial anesthetic agent declined. The BIS sensor was removed during DSA. In both sequences, the remifentanil infusion was titrated to the patients' clinical requirement as judged by the anesthesiologist present, and rocuronium was infused at a rate of 7 μg kg^{-1} min^{-1} throughout the study. Systolic arterial pressure (SAP) was maintained within 20% of pre-induction values through the administration of phenylephrine or ephedrine.

2.4 Imaging protocol and angiographic analysis

All DSAs were performed in a biplanar flat-detector angiographic system (Artis Zee Biplane System, Siemens

Healthcare, Erlangen, Germany); for details refer to Supplemental File 1. An angiocatheter (4 Fr in conscious patients; 5 Fr [4 Fr at the tip] in anesthetized patients) was placed in the cervical ICA for DSA. In each patient, the amount of contrast medium and the injection speed were kept constant between DSA_1 and DSA_2 by using a power injector. Angiography acquisition was tailored for clinical diagnosis without additional series.

The baseline position and 5 ROIs on the anterior–posterior (AP) view of DSA were defined for measuring travel time along the middle cerebral artery (MCA) flow: BL_{AP} (baseline position on the AP view; the middle point of the horizontal segment of the ICA), M1 (the middle point of the first segment of the MCA), M2–3 (the transition region between the second and third segments of the MCA), M3–4 (the transition region between the third and fourth segments of the MCA), TS (the middle point of the transverse sinus), and JB (the jugular bulb) (Fig. 2a).

The baseline position and 5 ROIs on the lateral view of DSA were defined for measuring travel time at each branch of the anterior circulation: $BL_{lateral}$ (baseline position on the lateral view; the end of the cavernous portion in the ICA), OA (the edge of the first turn of the ophthalmic artery), A2 (the genu of the anterior cerebral artery), $MCA_{lateral}$ (the transition region between the third and fourth segments of the MCA), VG (the junction of the vein of Galen and the straight sinus), and PV (at the parietal vein) (Fig. 2b).

Travel time at each ROI (in seconds) was defined as TTP at each ROI (in seconds) minus the TTP at baseline position (in seconds). CCT was defined as the travel time from baseline position to JB on the AP view (i.e., TTP at JB), and was divided into four segmental circulation times, defined as the difference in TTP between two ROIs, according to vessel levels: ICA segment (from baseline to M1), MCA segment (from M1 to M3–4), microvessel segment (from M3–4 to TS), and sinus segment (from TS to JB).

All anonymized DSAs were assessed independently by an interventionist (KM) and an anesthesiologist (TI) who were trained in quantifying DSAs. Allocation was concealed from the interventionist and the anesthesiologist who analyzed the DSA data, and any disagreement in results was resolved by consensus between the two assessors. Images that showed vasospasms or wedges of the catheter or that involved imaging mistakes were excluded from the present study.

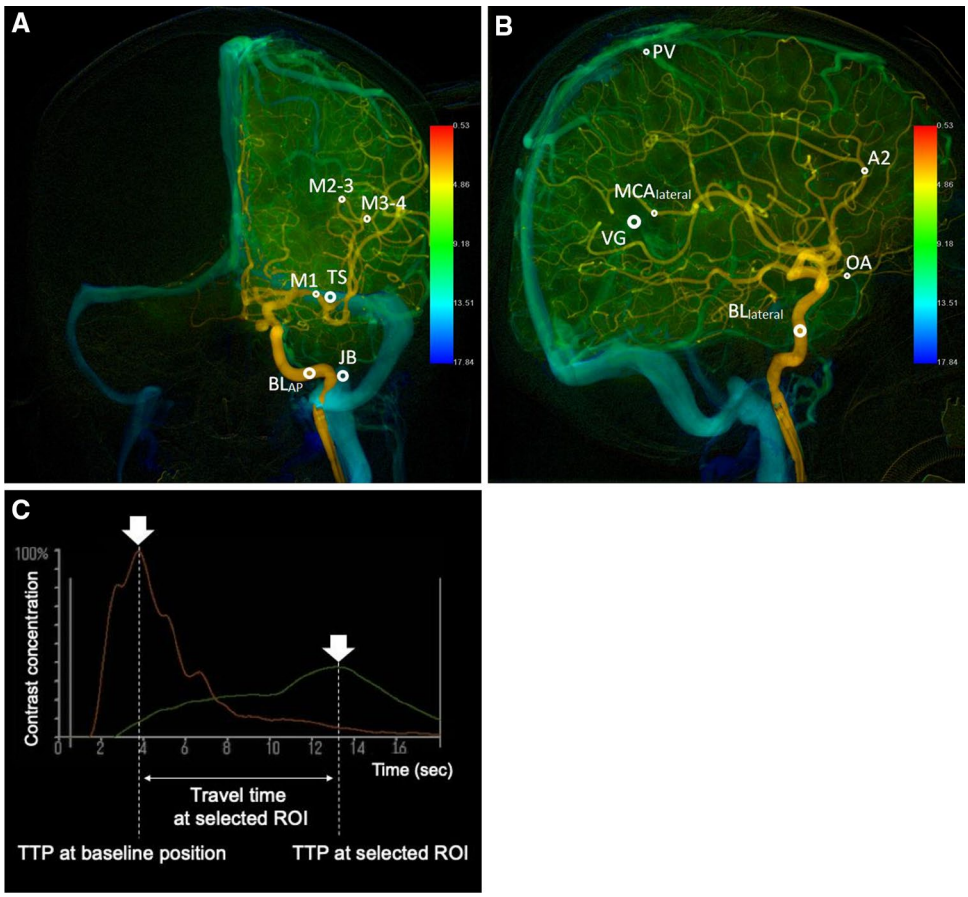

Fig. 2 DSA imaging. **a** Anterior–posterior view of color-coded left internal carotid artery DSA. **b** Lateral view of color-coded left internal carotid artery DSA. **c** Time–density curve. Horizontal axis represents imaging timeline of DSA (in seconds), and the vertical axis represents contrast medium opacity. Travel time at each ROI was defined as the difference between TTP at baseline position and TTP at each ROI

2.5 Intraoperative data collection

Heart rate (HR), SAP, mean arterial pressure (MAP), diastolic arterial pressure (DAP), cardiac output, SVV, percutaneous arterial oxygen saturation (SpO_2), $ETCO_2$, end-tidal sevoflurane concentration (ET_{SEV}), BIS, and bladder temperature were recorded every 5 min until the completion of the procedure. Comparison of intraoperative data (hemodynamic and respiratory parameters, hematocrit, and activated clotting time) between sevoflurane- and propofol-based anesthesia and the conscious state was performed around the time of DSA_1, DSA_2, and $DSA_{conscious}$. At diagnostic cerebral angiography, arterial pressure was obtained from non-invasive automated arterial pressure measurement, and several other parameters (cardiac output, SVV, $ETCO_2$, bladder temperature, hematocrit, activated clotting time, and BIS) were not measured.

2.6 Outcomes

The primary endpoint of this study was to evaluate whether CCT as determined by DSA differed significantly between sevoflurane- and propofol-based anesthesia, and the primary efficacy analysis consisted of a two-stage crossover analysis of CCT as determined by DSA. The secondary endpoint of this study was to explore the segments of cerebral vessels responsible for the difference in CCT between sevoflurane- and propofol-based anesthesia, and the effects of sevoflurane and propofol on travel time and CCT were assessed by comparison with travel time and CCT from conscious patients.

2.7 Statistical analysis

According to an earlier pilot study, a sample size of at least 14 patients is necessary to detect an expected mean difference of 1.2 s in CCT and an expected change in standard deviation of 1.0 s between sevoflurane- and propofol-based anesthesia, with a two-tailed α error of 0.01 and power of 90%. Considering possible dropouts and observational variation, we aimed to recruit 20 patients (10 patients per sequence).

Data are expressed as mean ± 1 SD, median [interquartile range], or number (percentage), as appropriate. The Shapiro–Wilk W test was used to test the normality of distribution of the data. Preoperative and intraoperative data from the SP and PS sequences were compared by using unpaired *t* test, Mann–Whitney *U* test, or Fisher's exact test, as appropriate. Intraoperative anesthesia-related data under sevoflurane- and propofol-based anesthesia were compared by using paired *t* test, Wilcoxon signed-rank test, or McNemar's test, as appropriate. Travel time at each ROI was compared between sevoflurane- and propofol-based anesthesia by using Wilcoxon signed-rank test, regardless of the type of variable distribution. Unpaired *t* tests or Mann–Whitney *U* tests were performed to evaluate differential carry-over effect, period effect, and treatment effect. After exclusion of carry-over and period effects, travel time at each ROI and circulation time in each segment were compared between sevoflurane- and propofol-based anesthesia and the conscious state by using the Friedman test, regardless of the type of variable distribution, and when differences were significant, the Wilcoxon signed-rank test with Bonferroni correction. Hemodynamic parameters (HR, SAP, MAP, and DAP) under sevoflurane- and propofol-based anesthesia and the conscious state were analyzed by using one-way repeated-measures analysis of variance with Bonferroni multiple-comparison tests. SpO_2 under sevoflurane- and propofol-based anesthesia and consciousness was analyzed by using the Friedman test, and when differences were significant, the Wilcoxon signed-rank test with Bonferroni correction. Pearson's correlation was used to assess the effect of hemodynamic covariates (MAP and cardiac output) on CCT during general anesthesia. To reduce interindividual variability unrelated to experimental manipulation, dependent variables (HR, MAP, and CCT) were expressed as a percentage change from the conscious value. A *P* value of 0.05 or less was considered statistically significant. All statistical analyses were performed by using the SigmaPlot statistical software package for Windows (version 11.2; Systat, San Jose, CA, USA).

3 Results

3.1 Patients

In this study, data analysis was performed on 15 patients, with 7 patients in the SP sequence and 8 patients in the PS sequence (Fig. 1). Intraoperative aneurysmal rupture did not occur in any patient.

3.2 Preoperative data

Preoperative data did not differ between the SP and PS sequences (Table 1). Three patients (42.9%) in the SP sequence and one patient (12.5%) in the PS sequence had a history of intracranial surgery ($P = 0.282$). In the SP sequence, one patient with previous intracranial surgery had undergone coiling for a ruptured cerebral aneurysm on the basilar artery, one had undergone clipping for an unruptured cerebral aneurysm on the contralateral MCA, and one had undergone resection of a cerebellopontine angle tumor; in the PS sequence, one patient had undergone coiling for an unruptured cerebral aneurysm on the same vessel that was to be treated in the current study. In all patients, the preoperative modified Rankin scale score [16] was zero.

Table 1 Preoperative data in the sevoflurane–propofol (SP) and propofol–sevoflurane (PS) sequences

Variables	SP sequence (n = 7)	PS sequence (n = 8)	*P*
Patient characteristics			
Age, year	60 ± 13	67 ± 13	0.338
Female, n	6 (85.7)	6 (75.0)	1.000
Body mass index, kg m^{-2}	23 [21–26]	22 [21–24]	0.613
Body weight, kg	54 [50–59]	58 [51–60]	0.613
ASA physical status, n			1.000
1	0 (0.0)	1 (12.5)	
2	7 (100.0)	7 (87.5)	
Comorbidities, n			
Hypertension	1 (14.3)	4 (50.0)	0.282
Hyperlipidemia	1 (14.3)	3 (37.5)	0.569
Ischemic heart disease	0 (0.0)	1 (12.5)	1.000
Respiratory complications	2 (28.6)	1 (12.5)	0.569
Ischemic stroke	0 (0.0)	1 (12.5)	1.000
Multiple cerebral aneurysm	3 (42.9)	0 (0.0)	0.077
Current smoker	1 (14.3)	0 (0.0)	0.467
Previous medical history, n			
Intracranial surgery	3 (42.9)	1 (12.5)	0.282
Subarachnoid hemorrhage	1 (14.3)	0 (0.0)	0.467
Former smoker	3 (42.9)	3 (37.5)	1.000
Family history, n			
Cerebral aneurysm, n	3 (42.9)	2 (25.0)	0.608
Preoperative medication, n			
Antiplatelet therapy[a]	7 (100.0)	8 (100.0)	–
Anticoagulation therapy	1 (14.3)	0 (0.0)	0.467
Antihypertensive therapy	2 (28.6)	3 (37.5)	1.000
Cerebral aneurysm			
Right side, n	4 (57.1)	4 (50.0)	1.000
Location, n			0.995
Internal carotid artery	5 (71.4)	6 (75.0)	
Middle cerebral artery	2 (28.6)	1 (12.5)	
Anterior cerebral artery	0 (0.0)	0 (0.0)	
Anterior communicating artery	0 (0.0)	1 (12.5)	
Maximum diameter, mm	8.4 ± 2.8	7.3 ± 2.1	0.413
Symptomatic, n	1 (14.3)	2 (25.0)	1.000

Continuous variables are presented as mean ± 1 SD or median [interquartile range], and categorical variables are presented as number (percentage)

[a]Prior to diagnostic cerebral angiography, two patients in the PS group received preoperative antiplatelet therapy, whereas prior to cerebral angiography for endovascular treatment, all patients in the SP and PS sequences received prophylactic antiplatelet therapy for 1 week before the procedure

3.3 Intraoperative anesthesia-related data

The duration between DSA_1 and DSA_2 was 111 ± 45 min in the SP sequence and 135 ± 67 min in the PS sequence ($P = 0.443$). This time was sufficient to allow complete washout of the initial anesthetic drug, as indicated by the ET_{SEV} of 0.0% immediately before DSA_2 in the SP sequence and the predicted effect-site concentration of propofol of 0.1 ± 0.1 μg mL^{-1} at immediately before DSA_2 in the PS sequence. The median injection speed of contrast media for DSA was 3 (2–3) mL s^{-1}, and the median amount of contrast media for DSA was 6 (5–6) mL.

Hemodynamic and respiratory parameters did not differ between sevoflurane- and propofol-based anesthesia (Table 2), and MAP during sevoflurane- and propofol-based anesthesia did not fall below 60 mmHg in any patient.

Table 2 Intraoperative anesthesia-related data

Variable	Sevoflurane-based anesthesia (n = 15)	Propofol-based anesthesia (n = 15)	*P*
HR, bpm	56 ± 9	54 ± 7	0.402
SAP, mmHg	108 ± 13	111 ± 11	0.311
MAP, mmHg	77 ± 9	79 ± 10	0.360
DAP, mmHg	59 ± 8	60 ± 9	0.341
Cardiac output, L min^{-1}	3.5 ± 1.0	3.3 ± 0.6	0.188
SVV, %	9.7 ± 2.9	10.3 ± 2.9	0.471
SpO_2, %	99 [99–100]	99 [99–100]	0.125
$ETCO_2$, mmHg	35 [34–36]	35 [34–36]	1.000
Remifentanil, μg kg^{-1} min^{-1}	0.3 [0.3–0.5]	0.3 [0.3–0.6]	0.688
Predicted effect-site concentration of propofol, μg mL^{-1}	0.1 ± 0.1	2.4 ± 0.4	< 0.001
ET_{SEV}, %	1.2 ± 0.1	0.0 ± 0.0	< 0.001
BIS value	46 ± 5	44 ± 5	0.109
Bladder temperature, °C	36.3 ± 0.4	36.1 ± 0.5	0.259
Activated clotting time, s	320 ± 40	308 ± 39	0.318
Hematocrit, %	38 ± 3	38 ± 2	0.760
Use of vasoactive drugs			
Continuous administration of phenylephrine, n	10 (66.7)	9 (60.0)	1.000
Continuous administration of phenylephrine, μg kg^{-1} min^{-1}	0.11 [0.00–0.19]	0.07 [0.00–0.14]	0.345
Bolus administration of phenylephrine, n[a]	5 (33.3)	5 (33.3)	1.000
Bolus administration of ephedrine, n[a]	3 (20.0)	1 (6.7)	0.598

Continuous variables are presented as mean ± 1 SD or median [interquartile range], and categorical variables are presented as number (percentage)

BIS bispectral index, *DAP* diastolic arterial pressure, $ETCO_2$ end-tidal carbon dioxide concentration, ET_{SEV} end-tidal sevoflurane concentration, *HR* heart rate, *MAP* mean arterial pressure, *SAP* systolic arterial pressure, SpO_2 percutaneous arterial oxygen saturation, *SVV* stroke volume variation

[a]Bolus administration of ephedrine or phenylephrine within 20 min before digital subtraction angiography

3.4 Analysis of DSA under sevoflurane- and propofol-based anesthesia

At all ROIs on the AP and lateral views except for OA in the lateral view, travel time was longer under propofol-based anesthesia than under sevoflurane-based anesthesia (Table 3). The mean difference in CCT (travel time at JB in the AP view) between sevoflurane- and propofol-based anesthesia was 1.984 s (95% confidence interval, 1.284–2.684; treatment effect, $P < 0.001$). The carry-over and period effects were not significant ($P = 0.878$ and $P = 0.803$, respectively). The risks of carry-over and period effects were also ruled out for other travel time values.

3.5 Analysis of DSA under sevoflurane- and propofol-based anesthesia, and the conscious state

In the AP view, travel time was prolonged at all ROIs under propofol-based anesthesia compared with the conscious state, whereas travel time was prolonged at M3–4, TS, and JB under sevoflurane-based anesthesia compared with the conscious state (Fig. 3a). In the lateral view, travel time was prolonged at all ROIs under propofol-based anesthesia compared with the conscious state, whereas travel time was prolonged at A2, MCA, VG, and PV under sevoflurane-based anesthesia compared with the conscious state (Fig. 3b).

Compared with conscious values, segmental circulation time under propofol-based anesthesia was longer in the ICA, MCA, and microvessel segments, whereas segmental circulation time under sevoflurane-based anesthesia was longer in the microvessel segment (Fig. 4). The ICA, MCA, and microvessel segmental circulation times differed significantly between sevoflurane- and propofol-based anesthesia (Fig. 4).

During $DSA_{conscious}$, HR, SAP, MAP, DAP, and SpO_2 were 76 ± 16 bpm, 136 ± 12 mmHg, 97 ± 7 mmHg, 78 ± 8 mmHg, and 98% (96–98%), respectively. Compared with corresponding parameters under sevoflurane- and propofol-based anesthesia (Table 2), hemodynamic parameters (HR, SAP, MAP, and DAP) were higher under the conscious state ($P < 0.001$ for all), and SpO_2 was lower under the conscious state ($P = 0.007$ versus sevoflurane-based anesthesia and $P = 0.003$ versus propofol-based anesthesia). Under

Table 3 Travel time (s) at each region of interest under sevoflurane- and propofol-based anesthesia

Region of interest	Sevoflurane-based anesthesia (n = 15)	Propofol-based anesthesia (n = 15)	*P*
AP view			
M1	0.53 (0.26–0.53)	0.54 (0.53–0.74)	0.006
M2–3	0.80 (0.80–1.26)	1.34 (1.33–1.60)	< 0.001
M3–4	1.07 (0.87–1.34)	1.60 (1.33–1.87)	0.002
TS	7.98 (7.45–8.71)	9.58 (9.05–10.38)	< 0.001
JB	8.78 (8.32–9.45)	10.91 (9.65–11.98)	< 0.001
Lateral view			
OA[a]	0.54 (0.53–0.80)	0.54 (0.53–0.54)	0.455
A2[b]	0.53 (0.27–0.80)	0.93 (0.80–1.07)	<0.001
MCA	1.06 (0.80–1.34)	1.34 (1.33–1.80)	0.002
VG	5.06 (4.60–5.32)	6.13 (5.85–6.66)	<0.001
PV	6.66 (6.19–7.19)	7.72 (7.45–8.45)	<0.001

Data are presented as median (interquartile range) (s)

A2 the genu of the anterior cerebral artery, *AP* anterior–posterior, *JB* jugular bulb, *M1* middle point of the first segment of the middle cerebral artery, *M2–3* transition region between the second and third segments of the middle cerebral artery, *M3–4* transition region between the third and the fourth segments of the middle cerebral artery, *MCA* transition region between the third and the fourth segments of the middle cerebral artery, *OA* edge of the first turn of the ophthalmic artery, *PV* parietal vein, *TS* middle of the transverse sinus, *VG* the junction of the vein of Galen and straight sinus

[a]One missing data point due to the unclear image of the ophthalmic artery on digital subtraction angiography (DSA) during propofol-based anesthesia in the PS sequence (propofol-based anesthesia, $n = 14$)

[b]One missing data point due to anterior cerebral artery unenhanced relative to ipsilateral internal carotid artery as determined by DSA during propofol-based anesthesia in the SP sequence (propofol-based anesthesia, $n = 14$)

both sevoflurane- and propofol-based anesthesia, changes in CCT did not correlate with changes in MAP and HR (Fig. 5).

4 Discussion

The primary finding of this study was that when the depth of anesthesia was adjusted to keep BIS values between 40 and 60 in patients undergoing endovascular treatment, propofol prolonged the travel time and the CCT derived from cerebral DSA compared with sevoflurane under the same hemodynamic and respiratory status. When CCT was divided into several segments, circulation times in the ICA, MCA, and microvessel segments were longer under propofol-based anesthesia than under sevoflurane-based anesthesia and the conscious state.

Travel time and CCT derived from DSA and conventional angiography have been shown to be reliable markers of the hemodynamics of the entire brain [9, 12–15], and CCT is prolonged in patients with an impaired cerebrovascular system [9, 12, 13]. In our current study, travel times and CCT were prolonged during propofol- and sevoflurane-anesthetized patients compared with values obtained when they were conscious. Although the effects of general anesthetic agents on travel time and CCT are unknown, previously reported reference values for normal intracranial travel time in the absence of general anesthesia [9] are similar to our travel times in conscious patients. Therefore, the prolonged travel time and CCT under sevoflurane- and propofol-based anesthesia most likely reflect the effects of sevoflurane and propofol on overall cerebral hemodynamics. Furthermore, in our study, segmental circulation time in the ICA, MCA, and microvessel segments was longer under propofol-based anesthesia than under sevoflurane-based anesthesia and the conscious state, whereas segmental circulation time in the sinus segment did not differ among the three conditions. Given that travel time and CCT reflect the time required for blood to flow between two cerebral regions, our results suggest that, compared with sevoflurane, propofol induced a greater reduction in CBFV at main arteries and microvessels.

CBF is regulated through multiple mechanisms to balance cerebral metabolic demand and supply. In addition, CBF regulation is influenced by neurovascular coupling, cardiac output, cerebral autoregulation, carbon dioxide, and body temperature [17–19]. In healthy subjects, surgical levels of propofol and sevoflurane reduce CBF due to indirect vasoconstriction in microvessel regions after a reduction in the cerebral metabolic rate of oxygen (flow–metabolism coupling) [4]. Similarly, in clinical settings, propofol and sevoflurane induce a reduction in CBFV at MCA and ICA, and the reduction in CBFV is thought to reflect a reduction of CBF due to flow–metabolic coupling [5, 7, 8]. Moreover, although cerebral autoregulation remains functional [5, 20–22], clinical doses of both propofol and sevoflurane reduce cardiac output [23, 24]. Therefore, during propofol- and sevoflurane-based anesthesia, the plateau of cerebral autoregulation is speculated to drop, reflecting the decrease in CBF [19]. Therefore, the reduction of CBFV during propofol- and sevoflurane-based anesthesia can be interpreted as a reduction in CBF that is induced through reductions in both cerebral metabolic demand and cardiac output. Furthermore, the greater increase in travel time and CCT during propofol- compared with sevoflurane-based anesthesia in the current study is consistent with previous studies, which demonstrated a greater reduction in CBF and CBFV at ICA and MCA under propofol compared with sevoflurane at comparable depths of anesthesia [4–8]. Thus, a greater reduction in CBFV during propofol-based anesthesia likely explains the greater increases in travel time and CCT during propofol- compared with sevoflurane-based anesthesia. In contrast, MAP and cardiac output did not differ between propofol- and sevoflurane-based anesthesia,

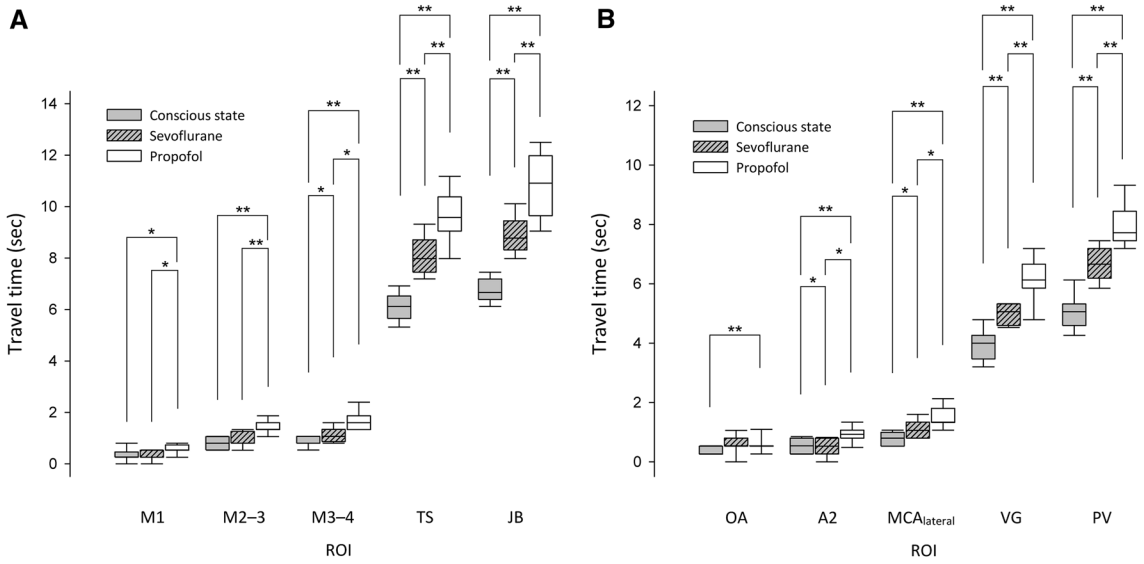

Fig. 3 Travel times at selected ROIs in the **a** anterior–posterior view and **b** lateral view of DSA under sevoflurane- and propofol-based anesthesia and the conscious state. *$P<0.05$, **$P<0.01$. Box plots show the median with 25th and 75th percentiles, and the whiskers represent the 5–95% range

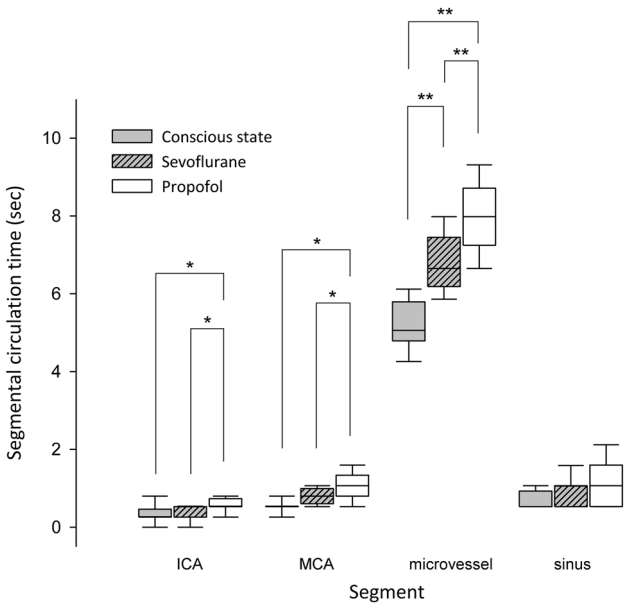

Fig. 4 Segmental circulation time in the anterior–posterior view of DSA under sevoflurane- and propofol-based anesthesia and the conscious state. *$P<0.05$, **$P<0.01$. Box plots show the median with 25th and 75th percentiles, and the whiskers represent the 5–95% range

and changes in HR and MAP relative to conscious values did not correlate with relative changes in CCT under either sevoflurane- or propofol-based anesthesia. Therefore, the reduction in hemodynamics is unlikely to be related to the difference in travel time and CCT during propofol- and sevoflurane-based anesthesia, and the longer travel time and CCT during propofol-based anesthesia may be interpreted as a greater reduction in CBF due to greater reduction in cerebral metabolic demand but not in cardiac output during propofol- compared with sevoflurane-based anesthesia. Thus, our results suggest that propofol-based anesthesia leads to decreased perfusion compared with sevoflurane-based anesthesia. In addition, normocapnia and normothermia were maintained during propofol- and sevoflurane-based anesthesia, and $ETCO_2$ and bladder temperature did not differ between the two conditions. Therefore, changes in carbon dioxide concentration and body temperature are unlikely to be related to the differences in travel time and CCT between propofol- and sevoflurane-based anesthesia.

Because travel time and CCT were defined as the DSA-determined times for contrast medium to move via blood flow between two ROIs, these values also depend on the distance between the two ROIs and the injection speed and amount of contrast medium. However, given the crossover design of this study, the TTP at each ROI during DSA_1 and DSA_2 was measured at the same anatomical site, and the amount and injection speed of the contrast medium were kept constant between DSA_1 and DSA_2 by using a power injector. Furthermore, DSA_2 occurred after endovascular treatment; consequently cerebral hemodynamic status might have differed between DSA_1 and DSA_2. However, our results showed no carry-over or period effects. Therefore, intervention-related factors likely have negligible effects on differences between experimental conditions in travel time at each ROI.

Our study has several limitations. First, our frame rate was relatively slow compared with that in a previous study

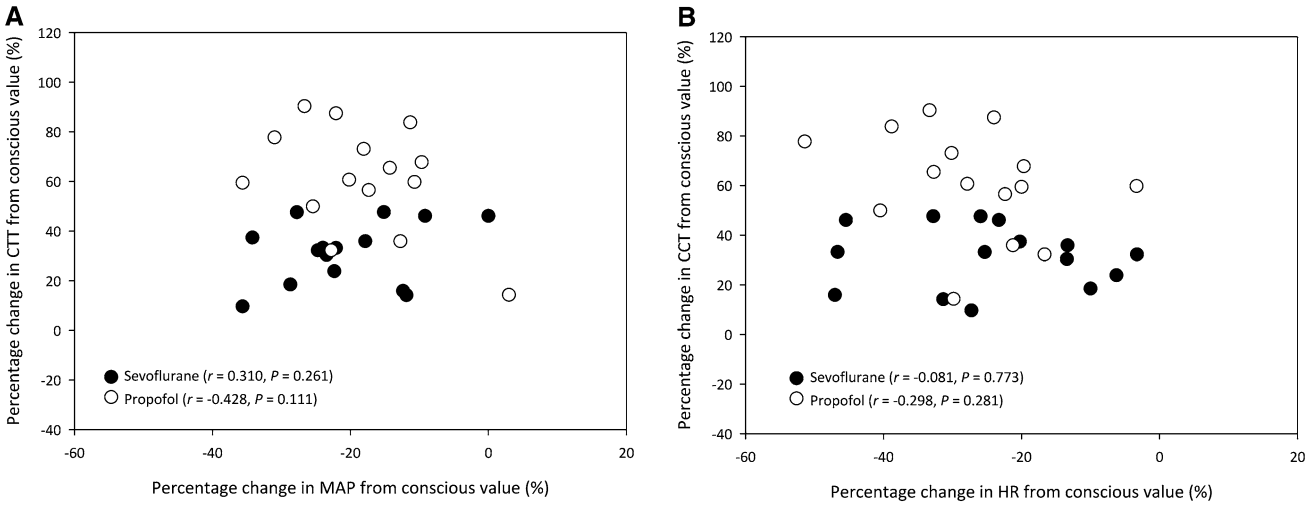

Fig. 5 Relationship between hemodynamic parameters and CCT under sevoflurane- and propofol-based anesthesia. MAP, HR, and CCT are expressed as percentage change from the corresponding conscious value

that reported reference values for normal intracranial travel times in conscious subjects [9]. Our study included patients with unruptured cerebral aneurysm as well as those with medically managed systemic diseases who have nearly normal cerebral circulation. The frame rate in our current study is the same as that which we routinely use clinically to minimize radiation dose. Nevertheless, travel times during the conscious state were similar between our study and previously reported findings. Therefore, the slow frame rate is unlikely to influence the present results. Second, we did not assess postoperative outcomes. In this regard, no aneurysms ruptured in the current study. However, the frequency of intraoperative aneurysmal rupture is 1.4–2.6%, and such ruptures lead to poor clinical outcome [25–27]. In addition, aneurysmal ruptures are not only interventional-related but also anesthesia-related [27]. A decrease in CBFV may decrease intra-arterial and intra-aneurysmal pressure, whereas congestion due to vasoconstriction after a reduction in the cerebral metabolic rate of oxygen might increase intra-arterial and intra-aneurysmal pressures. Thus, judicious selection of anesthetic agents is crucial to optimize outcomes for patients undergoing endovascular treatment. Moreover, although near-infrared spectroscopy is a clinically useful for monitor cerebral ischemia during neurovascular and cardiovascular surgeries [28–33], this modality is not always available during DSA and cannot assess the perfusion of deep brain structures. In contrast, CCT is derived directly from DSA and reflects the status of the entire brain. Therefore, if CCT varies due to switching between anesthetic agents or if it predicts potentially devastating perioperative complications, such as cerebral hyperperfusion syndrome after carotid artery stenting and abnormal pressure perfusion in coiling for intracranial arteriovenous malformation, CCT could facilitate the selection of an appropriate anesthetic agent for patients undergoing endovascular treatment. Further studies that include assessment of postoperative outcomes are warranted.

5 Conclusions

This study demonstrated that, at comparable anesthetic depths, CCT was significantly longer during propofol- than sevoflurane-based anesthesia. Furthermore, circulation times in the ICA, MCA, and microvessel segments were longer under propofol- than under sevoflurane-based anesthesia. Therefore, our results suggest that cerebral perfusion is decreased during propofol-based compared with sevoflurane-based anesthesia.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the insti-

tutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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