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Comparison of vasodilatory properties between desflurane and sevoflurane using perfusion index: a randomised controlled trial

Kyoung-Ho Ryu, Sung-Ha Hwang, Jae-Geum Shim, Jin-Hee Ahn, Eun-Ah Cho, Sung-Hyun Lee* and Jae-Hoon Byun

Department of Anaesthesiology and Pain Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea

*Corresponding author. E-mail: hoho4321.lee@daum.net

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Abstract

Background: The perfusion index (PI), calculated from the photoplethysmographic waveform, reflects peripheral vasomotor tone. As such, the PI serves as a surrogate for quantitative measures of drug-induced vasoconstriction or vasodilation. This study aimed to compare the effect on the PI of desflurane and sevoflurane at equi-anaesthetic concentrations in patients undergoing single-agent inhalation anaesthesia, where equi-anaesthetic dose was based on the known minimum alveolar concentration of these agents.

Methods: We randomly allocated patients scheduled for arthroscopic knee surgery to receive either desflurane or sevoflurane general anaesthesia after target-controlled induction of anaesthesia with propofol. Anaesthesia was maintained at age-corrected minimum alveolar concentration 1.0, under neuromuscular block (rocuronium). The PI and haemodynamic data were recorded every minute for 35 min after induction of anaesthesia and after standardised nociceptive stimulation. The primary outcome was PI, compared between the groups over time (repeated-measures analysis of variance). Secondary outcomes included MAP and HR.

Results: Sixty-nine participants (mean [range] age: 42 yr [19–65 yr]; 49% females) were assigned to either desflurane (n=34) or sevoflurane (n=35). The PI remained higher under desflurane compared with sevoflurane, both before (mean difference [MD]: 3.3; 95% confidence intervals [CIs]: 2.0–4.7; P<0.001) and after tetanic stimulation (MD: 2.8; 95% CI: 2.0–3.7; P<0.001). Higher PI paralleled lower MAP in participants assigned to desflurane anaesthesia (P<0.001), both before (MD: 8 mm Hg; 95% CI: 4–12) and after nociceptive stimulation (MD: 14 mm Hg; 95% CI: 7–22). HR was similar throughout.

Conclusions: These findings suggest that at equipotent doses, desflurane exerts more potent vasodilatory properties and lowers blood pressure by a magnitude potentially associated with harm.

Clinical trial registration: NCT03570164.

Keywords: desflurane; haemodynamics; perfusion index; sevoflurane; vasodilation

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Editor's key points

- Objective clinical reasons for using desflurane are sparse, particularly in light of environmental concerns over its use.
- Comparative studies between commonly used inhalational anaesthetic agents are rare.
- The authors compared equi-anaesthetic doses of sevoflurane and desflurane (based on minimum alveolar concentration).
- Desflurane exhibited more potent vasodilatory properties, resulting in higher perfusion index and lower blood pressure.
- This carefully controlled study suggests that desflurane produces substantially more relative hypotension by a magnitude previously associated with developing organ dysfunction.

The ether derivatives desflurane and sevoflurane are commonly used as general anaesthetics, owing to their rapid pharmacokinetic profiles.[1,2] Most volatile agents cause concentration-related decreases in myocardial contractility and systemic vascular resistance (SVR), resulting in reductions in arterial pressure.[3] Older volatile anaesthetics, such as halothane and enflurane, reduce arterial pressure primarily by decreasing myocardial contractility, whereas modern volatile anaesthetics, such as desflurane and sevoflurane, reduce arterial pressure primarily by decreasing SVR.[4]

Obtaining quantitative *in vivo* measurements of vasodilation caused by anaesthetics has been challenging because of the need for invasive procedures[5–10] and because the calculated SVR is not attributed solely to peripheral vasomotor tone.[7,8] The recently developed perfusion index (PI) has been proposed as a useful tool for monitoring changes in peripheral vascular tone.[11] Accordingly, the PI might potentially be used as a surrogate for quantitative measurement of vasoconstriction and vasodilation produced by vasoactive drugs, including volatile anaesthetics.

Vasodilatory responses induced by volatile anaesthetics can increase microvascular perfusion.[12,13] Improved peripheral perfusion is associated with an increase of tissue oxygen tension, which may reduce tissue infection and improve wound repair.[14–16] Conversely, volatile anaesthetics with more potent vasodilatory properties may promote hypotension, which is associated with adverse perioperative outcomes.[1,17] Desflurane and sevoflurane appear to have different effects on vascular tone.[18] Here, we examined whether desflurane and sevoflurane had different vasodilatory properties, as measured using the PI, at equi-minimum alveolar concentration (MAC) in patients undergoing single-agent inhalation anaesthesia.

Methods

Study design and population

This prospective randomised trial was conducted at a single centre (Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea) and adhered to the tenets of the Declaration of Helsinki and the principles of Good Clinical Practice. After obtaining approval from the Institutional Review Board at Kangbuk Samsung Hospital (approval number: KBSMC 2018-05-019), we registered the study protocol at ClinicalTrials.gov international database with the identifier NCT03570164 (principal investigator: Kyoung-Ho Ryu; registration date: June 26, 2018).

Inclusion criteria

Participants scheduled for arthroscopic knee surgery under general anaesthesia were eligible provided they were 19–65 yr old with an American Society of Anesthesiologists (ASA) physical status 1 or 2.

Exclusion criteria

We excluded participants using the following criteria: receiving any medications that may affect vascular tone (e.g. vasoactive drugs, such as calcium channel blockers or angiotensin receptor blockers); cardiovascular or peripheral vascular disease (e.g. diabetic vasculopathy or Raynaud's disease); medications that may affect sympathetic or parasympathetic tone (e.g. beta blockers or anticholinergics); diabetes mellitus; and any neurological or psychiatric diseases, including history of, or treatment for, substance abuse, anxiety, or depression.

Treatment allocation

After obtaining written informed consent, subjects were randomly assigned to either desflurane or sevoflurane anaesthesia. The randomisation sequence was achieved *via* a computer-generated scheme, using a permuted block randomisation algorithm, in a 1:1 ratio. Opaque envelopes that were sealed were used to conceal the group assignments. Once the envelope was unsealed, the subject assignment was not altered.

Anaesthetic monitoring

None of the subjects received any premedication. After arrival at the operating theatre, a bispectral index sensor strip and standard monitors (S/5 Anesthesia Monitor; GE Healthcare, Helsinki, Finland), per ASA guidelines, including electrocardiography and noninvasive blood pressure measurement devices, were placed. A disposable pulse oximeter adhesive sensor (Masimo SET® Radical-7, model M-LNCS Adtx; Masimo Corporation, Irvine, CA, USA), from which photoelectric plethysmographic signals were obtained for the PI calculation, was positioned according to the manufacturer's instructions on the fourth finger of the hand contralateral to the arm on which the noninvasive blood pressure cuff was placed. The PI values were used as a surrogate measure for arteriolar vasomotor tone. Detailed descriptions and calculations of the algorithm for the PI can be found elsewhere.[19]

To remove motion artifacts caused by involuntary movement from the photoplethysmographic waveforms, a moderate neuromuscular block (train-of-four count of 1–2) was maintained throughout the study period using a piezoelectric neuromuscular monitoring device (M-NMT MechanoSensor™; GE Healthcare). The end-tidal anaesthetic gas concentration was continuously monitored with a multi-gas analyser (S/5 Anesthesia Gas Module; GE Healthcare). The end-tidal carbon dioxide partial pressure was also monitored to ensure normocarbia. The tidal volume and ventilatory frequency were adjusted in real time to maintain a target end-tidal carbon dioxide concentration of 4.7–4.9 kPa. The core body

temperature was monitored using a disposable nasopharyngeal temperature sensor (ETP1030; EWHA BIOMEDICS, Goyang, Republic of Korea) to ensure normothermia. The ambient operating theatre temperature was kept at 23–24°C throughout the study period to prevent hypothermia-provoked thermoregulatory arteriovenous shunt vasoconstriction.

Study protocol

An illustration of the study protocol is provided in Figure 1. Before induction of anaesthesia, baseline PI, MAP, and HR values (pre-induction data) were recorded in the conscious state. To minimise the induction dose and standardise the effect-site concentration between the groups, propofol was administered using a target-controlled infusion device (Orchestra® Base Primea; Fresenius Kabi, Brézins, France). Propofol was used only to induce anaesthesia, whereas the maintenance of anaesthesia was accomplished solely with the designated volatile anaesthetic (desflurane or sevoflurane).

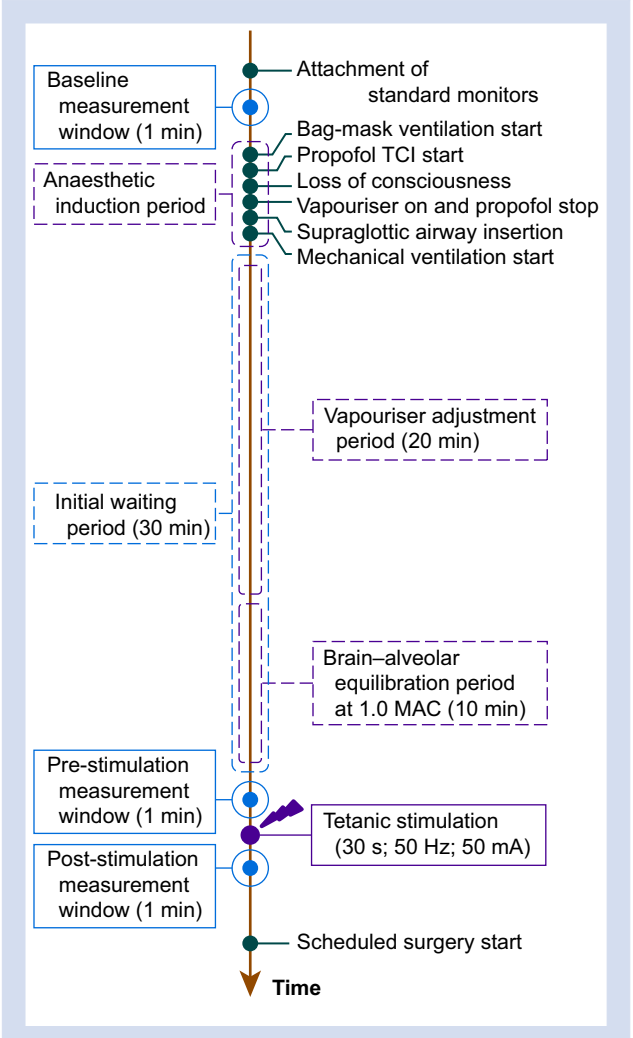

Fig 1. Study protocol. Haemodynamic parameters and perfusion indices were obtained at three predefined time points (blue target marks). To ensure brain–alveolar anaesthetic equilibration, an initial 30 min waiting period (outlined with blue dashed lines) was observed. Long-lasting tetanic stimulation was used as the standardised nociceptive stimulation (purple solid dot). MAC, minimum alveolar concentration; TCI, target-controlled infusion.

Propofol (Fresofol® MCT 1%; Fresenius Kabi Austria GmbH, Graz, Austria) infusion was initiated with a target effect-site concentration of 3.0 μg ml^{-1} using the Marsh pharmacokinetic model.[20] The target effect-site concentration was changed to 0.0 μg ml^{-1} directly after confirmation of loss of consciousness to minimise the propofol dose. After this, the propofol infusion line was disconnected and the dose used for induction was recorded. Simultaneously, to facilitate an end-tidal anaesthetic gas concentration increase, a supra-MAC dose of approximately 1.3 MAC was administered by bag-mask ventilation using a high fresh gas flow (8 L min^{-1}), with the goal of achieving 1.0 MAC. After administration of 0.6 mg kg^{-1} rocuronium, a supraglottic airway device (i-gel®; Intersurgical Ltd, Wokingham, UK) was inserted as per the manufacturer's recommendations. After induction of anaesthesia, controlled ventilation was commenced and maintained with a fresh gas flow of 4 L min^{-1} for 35 min where the study outcomes were measured.

The volatile anaesthetic vapouriser dial was continuously adjusted by an independent anaesthesiologist to maintain a constant target end-tidal anaesthetic concentration of 1.0 MAC during the study period. The independent anaesthesiologist was only involved in adjusting the vapouriser dial. Whether or not to perform vapouriser adjustment (up or down) was determined every 1 min based on the real-time end-tidal anaesthetic concentration, and the vapouriser dial was delicately adjusted in increments or decrements by step of 0.1 vol% to maintain the target end-tidal anaesthetic concentration. The MAC values were corrected for age based on age-related iso-MAC charts.[21] The randomly designated volatile anaesthetic, either desflurane (Suprane®; Baxter Healthcare, Guayama, Puerto Rico) or sevoflurane (Sevorane®; AbbVie Ltd, Maidenhead, UK), was used as the sole anaesthetic agent for maintenance of general anaesthesia; no other anaesthetic adjuvant, such as opioids or nitrous oxide, was administered during the study period. I.V. fluid administration was standardised to 5 ml kg^{-1} h^{-1} of Ringer's lactate solution in both groups.

Data collection

Data were continuously collected every minute for 35 min after induction of anaesthesia, and automatically stored on hard disks using high-frequency electronic recording programmes (Datex-Ohmeda™ S/5 Collect version 4.0, GE Healthcare; and Masimo Instrument Configuration Tool version 1.0.6.0; Masimo Corporation). The pre- and post-stimulation data were taken after establishing brain–alveolar anaesthetic equilibration state, wherein a constant target end-tidal anaesthetic concentration of 1.0 MAC was maintained without adjustment of the vapouriser for the final 10 min of the 30 min waiting period.

The pre-stimulation measurement window was set as the 1 min period before nociceptive stimulation. Under the brain–alveolar equilibration at 1.0 MAC, immediately before applying nociceptive stimulation, the mean pre-stimulation PI, MAP, and HR values obtained during the designated 1 min period were recorded. The nociceptive stimulation was standardised as a low-current electrical stimulation by a peripheral nerve stimulator (MiniStim®; Life-Tech, Stafford, TX,

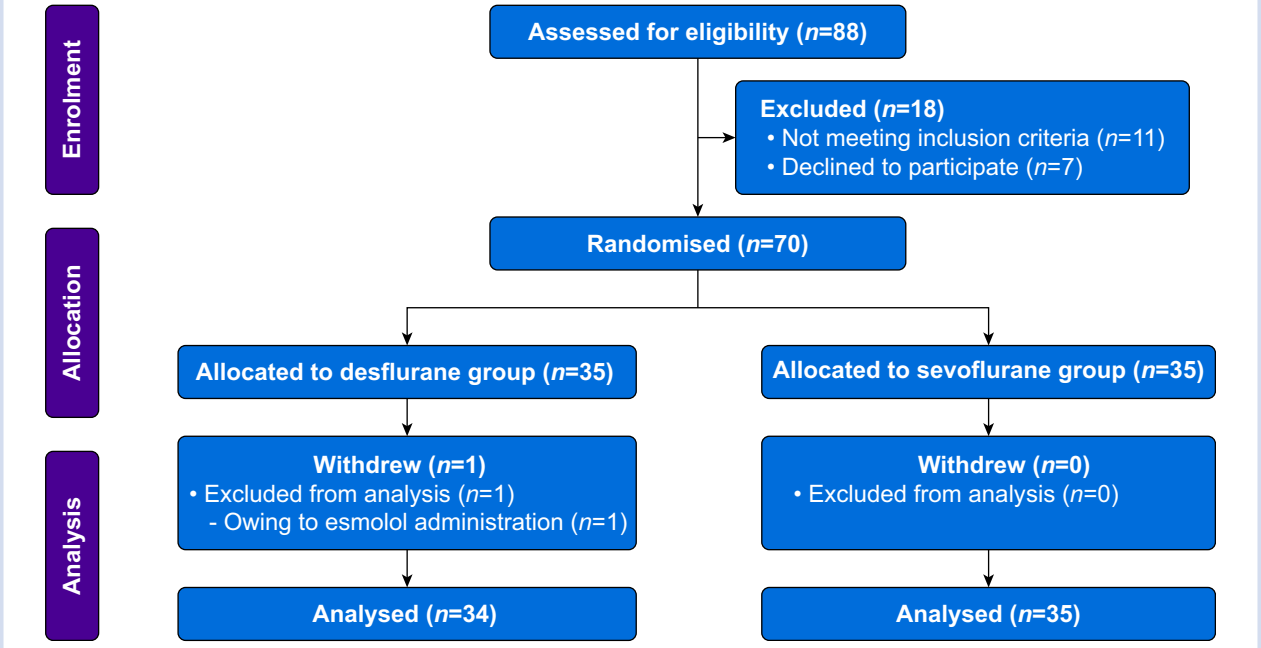

Fig 2. Consolidated Standards of Reporting Trials flow diagram.

USA). Long-lasting tetanic stimulation (square wave; 30 s duration; 50 Hz frequency; 50 mA amplitude) was applied through two Ag/AgCl hydrogel adhesive electrodes (Neuro Muscular Transmission electrodes, model 57268-HEL; GE Healthcare) that were attached over the ulnar nerve of the wrist contralateral to the pulse oximeter sensor.[22] The post-stimulation measurement window was set as the 1 min period after tetanic stimulation based on the earlier study, in which the maximum responses to tetanic stimulation were exhibited within 1 min.[22] Post-stimulation values were recorded when the maximum changes from the pre-stimulation values occurred within 1 min after the onset of tetanic stimulation.

To minimise the effects of propofol on haemodynamics, pre- and post-stimulation data were obtained after the calculated effect-site concentration of propofol had decreased to below 0.2 μg ml^{-1}. After all study data were obtained, the scheduled surgeries were initiated. Awareness with recall was assessed within 72 h postoperatively using the modified Brice questionnaire.[23] Several safety-related details for haemodynamic or anaesthetic depth changes were included in the study protocol. At any time during the study period, if the MAP was <60 or >130 mm Hg, the HR is <45 or >140 beats min^{-1}, or the bispectral index is >70, then appropriate medications were administered (vasoconstrictors, vasodilators, anticholinergics, beta blockers, and additional anaesthetics, respectively). Under any of these circumstances, the subject was considered a dropout, and none of the dropout-related data were included in the final analyses.

Primary outcome

Perfusion index was the primary outcome for the study.

Secondary outcomes

We assessed MAP and HR as secondary haemodynamic outcomes.

Statistical analysis

Statistical analyses were performed using SPSS Statistics software (release 24.0; IBM Corp., Armonk, NY, USA). The interim analysis was not planned or conducted. Data for categorical variables are presented as the frequency, whilst data for continuous variables are presented as the mean (standard deviation [SD]) or median (inter-quartile range), depending on their distribution. The distribution of continuous variables was tested for normality using the Shapiro–Wilk test.[24] The point difference and corresponding two-sided 95% confidence interval (CI) were presented for parametric data, whilst those for non-parametric data were quantified by the Hodges–Lehmann estimates and their distribution-free CIs.[25] Differences in the subject characteristics and study outcomes between the groups were evaluated using the χ^2 test or Fisher's exact test for categorical variables and using Student's *t*-test or the Mann–Whitney *U*-test for continuous variables, depending on their distribution. Differences in the consecutive measurements of the PI, MAP, and HR values between the groups were evaluated using repeated-measures analysis of variance (RM-ANOVA), followed by Bonferroni *post hoc* analysis for multiple comparisons. Differences were considered statistically significant at $P<0.05$.

Sample size estimation

The sample size was calculated using an online statistical calculator (https://www.quantitativeskills.com/sisa/

calculations/samsize.htm) based on a pilot study containing 30 patients (15 per group), wherein the pre-stimulation PI values (mean [SD]) were 5.5 (2.3) for the sevoflurane group and 7.3 (2.7) for the desflurane group.[18] We estimated a sample size of 31 patients per group using a two-sided *t*-test, a power of 80%, and a significance level of 5%. Given a potential dropout rate of 10%, we included 70 patients.

Results

Participant characteristics

From June to November 2018, 88 consecutive patients were assessed for eligibility for participation in this study; of these, seven patients declined participation and 11 patients were ineligible based on the exclusion criteria. Therefore, 70 subjects were included and randomly assigned to either the desflurane or sevoflurane group. One subject in the desflurane group received esmolol intraoperatively, resulting in 34 subjects in the desflurane group and 35 subjects in the sevoflurane group (Fig. 2). Participant characteristics (Table 1) and baseline haemodynamic parameters were similar before allocation (Table 2), including the induction dose of propofol and the total administered dose of rocuronium. The mean end-tidal anaesthetic concentrations of the age-corrected 1.0 MAC that were administered to the desflurane and sevoflurane groups (mean [SD]) were 6.5 (0.4) and 1.8 (0.1) vol%, respectively. No cases of explicit awareness with recall were reported.

Table 1 Subject characteristics. Data are presented as the mean (range), mean (standard deviation), or number of subjects, as appropriate.

	Desflurane group (*n*=34)	Sevoflurane group (*n*=35)
Age (yr)	42 (19–65)	42 (22–61)
Sex (M/F)	17/17	18/17
Height (cm)	167 (8)	165 (8)
Weight (kg)	70 (10)	66 (12)
BMI (kg m^{-2})	25.1 (2.7)	24.2 (3.5)
ASA physical status (1/2)	32/2	31/4

Table 2 Comparison of baseline and clinical data. Data are presented as the mean (standard deviation), median (interquartile range), or number of subjects. *Anaesthetic induction dose infused using target-controlled infusion. †Total dose administered to maintain moderate neuromuscular block. ‡Values measured at 30 min after the induction of anaesthesia. Et_{CO_2}, end-tidal carbon dioxide partial pressure.

	Desflurane group (*n*=34)	Sevoflurane group (*n*=35)	P-value
Pre-induction values			
Perfusion index	1.4 (0.9–2.0)	1.5 (1.0–2.2)	0.606
MAP (mm Hg)	99 (11)	101 (12)	0.584
HR (beats min^{-1})	66 (11)	69 (13)	0.346
Type of surgery			0.943
Meniscus repair or removal	25	26	
Ligament reconstruction	9	9	
Propofol dose (mg kg^{-1})*	1.11 (0.12)	1.16 (0.23)	0.257
Rocuronium dose (mg kg^{-1})†	0.79 (0.03)	0.79 (0.06)	0.608
Core body temperature (°C)‡	36.0 (0.4)	36.0 (0.5)	0.659
Et_{CO_2} (kPa)‡	4.7 (4.7–4.7)	4.7 (4.7–4.7)	0.770

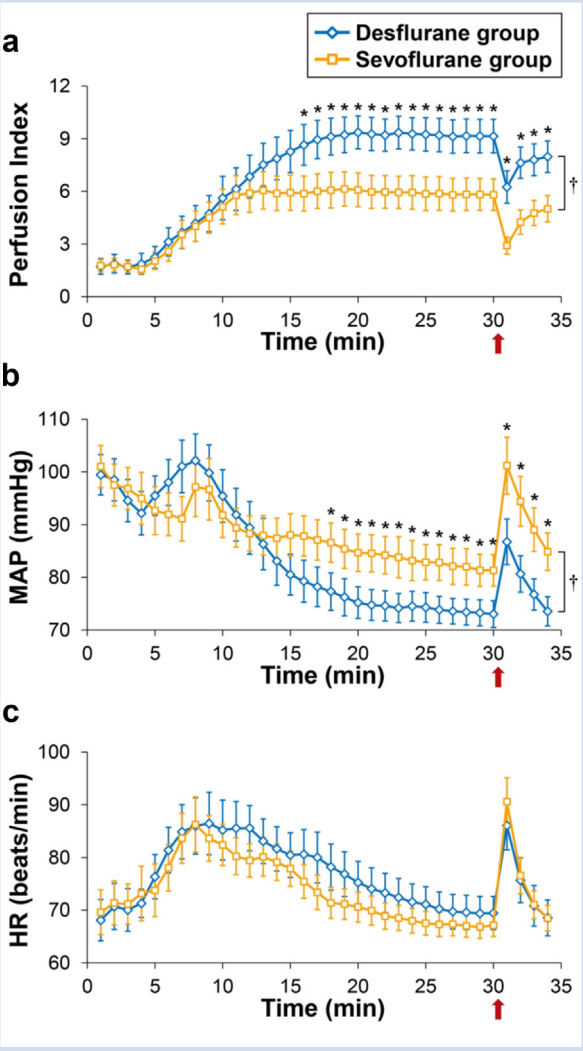

Fig 3. Change trends in the (a) perfusion index, (b) MAP, and (c) HR from the induction of anaesthesia to 5 min after tetanic stimulation. At 30 min after the induction of anaesthesia, standardised tetanic stimulation (red arrow) was applied under the brain–alveolar equilibration state of 1.0 minimum alveolar concentration. Values are the means and 95% confidence intervals. *Bonferroni-corrected $P<0.05$ by the *post hoc* test of repeated-measures analysis of variance at each measurement time point between groups; †$P<0.05$ by the between-subjects effects test of repeated-measures analysis of variance between groups.

Table 3 Comparison of the PI values and haemodynamic parameters produced by desflurane and sevoflurane of 1.0 MAC. Data are presented as the mean (standard deviation) or median (inter-quartile range). CI, confidence interval; MAC, minimum alveolar concentration; PI, perfusion index.

	Desflurane group (n=34)	Sevoflurane group (n=35)	Difference (95% CI)	P-value
Pre-stimulation values				
PI	9.1 (2.8)	5.8 (2.7)	3.3 (2.0–4.7)	<0.001
MAP (mm Hg)	73 (8)	81 (9)	−8 (−12 to −4)	<0.001
HR (beats min^{-1})	70 (9)	67 (7)	3 (−1 to 7)	0.191
Post-stimulation values				
PI	5.6 (4.6–6.8)	2.8 (1.9–3.9)	2.8 (2.0–3.7)	<0.001
MAP (mm Hg)	87 (13)	101 (16)	−14 (−22 to −7)	<0.001
HR (beats min^{-1})	87 (14)	90 (14)	−3 (−10 to 3)	0.304

Primary outcome: PI

From approximately 15 min after the induction of anaesthesia, the PI values in the desflurane group began to increase relative to those in the sevoflurane group (Fig. 3a). Pre-stimulation PI values were higher under desflurane than sevoflurane anaesthesia (mean difference: 3.3 [95% CI: 2.0–4.7]; P<0.001). After standardised nociceptive stimulation (Table 3), the PI values remained higher in participants randomised to desflurane compared with sevoflurane (mean difference: 2.8 [95% CI: 2.0–3.7]; P<0.001).

Secondary outcomes

The MAP values in participants assigned to desflurane were consistently lower compared with those in participants assigned to sevoflurane (Fig. 3b; P=0.026 by RM-ANOVA). Pre-stimulation, participants in the desflurane group had lower MAP values compared with the sevoflurane group (73 [8] *vs* 81 [9] mm Hg; mean difference: −8 mm Hg [95% CI: −12 to −4]; P<0.001). HR was similar between groups (Fig. 3c; P=0.269 by RM-ANOVA). After the standardised nociceptive (tetanic) stimulation, MAP and HR increased, but remained qualitatively similar to pre-stimulation values, with MAP in desflurane-assigned participants 14 mm Hg lower (95% CI: 7–22; P<0.001; Table 3).

Discussion

In this prospective randomised study in patients undergoing single-agent inhalation anaesthesia, we found that equi-anaesthetic doses of desflurane and sevoflurane at 1.0 MAC did not produce similar haemodynamic profiles. Desflurane produced higher PI values and lower arterial pressures compared with sevoflurane, both before and after a standardised nociceptive stimulation.

All volatile anaesthetics cause agent- and dose-dependent decreases in SVR and myocardial contractility to varying degrees, ultimately leading to decreases in arterial pressure.[3,4] Previous studies in chronically instrumented animals have shown that desflurane and sevoflurane produce similar dose-dependent decreases in myocardial contractility,[5,6] although this was not found in human volunteers, as measured by echocardiography.[9,10] In another study, lower SVR produced by desflurane was predominantly assigned to be caused by dilatation of arteriolar resistance vessels, whereas sevoflurane-induced decreases in left ventricular afterload may occur primarily *via* altering mechanical properties of the aorta.[8] Considered with these findings, our data suggest that desflurane might have vasodilatory properties that are more potent than are those of sevoflurane.[4] This interpretation is in accordance with the results of our study that desflurane produced higher PI values than sevoflurane did.

Because improved peripheral perfusion is associated with an increase of tissue oxygenation, which is known to improve wound healing and reduce tissue infection,[14–16] understanding the differences between the vasodilatory properties of anaesthetics may potentially be helpful for selecting the appropriate anaesthetic agent. The degree of vasodilation produced by volatile anaesthetics is difficult to measure directly *in vivo*.[4] It has been estimated using the SVR, as calculated from the MAP and mean arterial flow (i.e. cardiac output) indirectly.[7,8] Precise measurement of SVR requires invasive procedures and complicated techniques, such as thoracotomy[5–8] or pulmonary artery catheterisation.[9,10] If there was an alternative noninvasive approach for vasomotor tone measurements, then this could provide practical utility for evaluating the vasodilatory properties of drugs, including anaesthetics. The PI, which is derived from the photoelectric plethysmographic waveform, reflects the peripheral vasomotor tone in real time.[11,19,26] Several studies have reported that the PI may be used as an objective indicator of successful surgical[27,28] or pharmacological[29–33] sympathectomy-mediated vasodilation. Another previous study showed that the PI is a reliable indicator of the vasoconstriction that is caused by the intravascular injection of an epinephrine-containing epidural test dose.[34] Other recent studies have shown that baseline PI values (i.e. baseline vascular tone) may be useful for predicting the incidence of post-spinal hypotension during Caesarean delivery.[35,36] These findings suggest that the PI has the potential to be used as an alternative noninvasive approach for estimating vasoconstriction or vasodilation.

The strengths of this study include its use of only noninvasive *in vivo* haemodynamic measurements in humans, the application of age-adjusted MAC values, the use of standardised nociceptive stimulation, and the collection of data under pure inhalation anaesthesia without anaesthetic supplements (such as opioids). Nevertheless, the present study has several limitations of note. First, although the PI has the potential to be used as an alternative noninvasive approach for estimating vasoconstriction or vasodilation, it is still a surrogate measure for vascular tone. As physiological

conditions vary between patients, the PI may be considered a relative number that reflects the change trends rather than an absolute number. As such, whilst the PI may be a practical method of comparing vasoactive drugs, it cannot provide precise values or absolute numbers, such as quantitative indices of left ventricular afterload obtained based on the three-element Windkessel model.[7,8] Second, blood viscosity and intravascular volume status could affect the PI. The Radical-7 pulse oximeter device provides continuous monitoring for noninvasive haemoglobin concentration and pleth variability index. If noninvasive haemoglobin concentration and pleth variability index were recorded as study outcomes, then it may have provided more accurate information on whether the difference in the PI between groups is attributable to the difference in the effect of the two volatile anaesthetics on vascular tone.

In conclusion, at the equi-anaesthetic concentration of 1.0 MAC, desflurane produced higher PI values than did sevoflurane, but substantially lower MAP. These findings suggest that desflurane has greater vasodilating effects than sevoflurane at equipotent concentrations. However, further investigations are warranted to determine whether the vasodilatory properties of desflurane, which are more potent than sevoflurane, are associated with differences in clinical outcome.

Authors' contributions

Study conception/design: K-HR, S-HL
Study conduct: K-HR, S-HH, E-AC, J-HB
Data analysis: K-HR, S-HH, J-GS, J-HA, S-HL
Writing of paper: K-HR
Revising of paper: all authors

Declarations of interest

The authors declare that they have no conflicts of interest.

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