Comparison of age-differentiated incidence of sympathetic stimulation effect from rapid increases in desflurane concentration during induction of anesthesia with propofol and remifentanil; prospective randomized single-blind clinical investigation

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ABSTRACT

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Desflurane, since its introduction in clinical anesthetic practice in the 1990's, had been known to have sympathetic stimulation effects, including tachycardia and/or hypertension, when administered rapidly in > 1 minimal alveolar concentration (MAC) during induction of anesthesia. The present study is to compare hemodynamic responses to inhalation anesthetics of 1 MAC desflurane with those to 1 MAC sevoflurane, which were calculated with age-based formula in adult patients undergoing elective spine surgery.

A total of 400 patients were enrolled in this prospective, randomized, single-blinded investigation. They were divided into two groups: the Desflurane (D) group and the Sevoflurane (S) group. Each group was subdivided by age: 20-29, 30-39, 40-49 and 50-59 years (D20, D30, D40, D50, and S20, S30, S40, S50, respectively).

1 MAC of desflurane or sevoflurane was calculated with an age-based formula, suggested by Mapleson WW. Measured parameters were compared between the D and S groups, and between age subgroups in each group.

When a patient arrived in the operating room, electrocardiogram lead Ⅱ, pulse oximetry, non-invasive blood pressure, oxygen saturation (S_PO_2) and Bispectral index (BIS) were applied. Intravenous (IV) remifentanil infusion of 0.1㎍/㎏/min was initiated, and for 5-10 minutes, the heart rate, systolic, diastolic and mean arterial pressure, and peripheral oxygen saturation were measured, and used as baseline values. Anesthesia was

induced with IV propofol of 1-1.5㎎/㎏, and 10㎎ was additionally given until the patient was unconscious. 1 MAC of desflurane of sevoflurane in oxygen (O_2)/air > 5L/min was given via the face mask with manual ventilation. IV rocuronium of 0.4㎎/㎏ was given to induce muscle relaxation. Heart rate(HR), systolic, diastolic and mean arterial pressure (SAP, DAP and MAP) were measured and recorded every minute for five minutes. After endotracheal intubation, hemodynamic parameters were measured and recorded every minute for five minutes with mechanical ventilation.

Inter-group comparison: After induction of anesthesia, the HR was elevated in the D group, in contrast to reductions in the S group ($p<0.01$ every minute, except for 2 min.). After endotracheal intubation, the HR was elevated in both groups, but significantly more elevated in the D group ($p<0.01$, except for 1 min.). In both groups, the arterial blood pressures were generally reduced after induction and after intubation, but the decreases were significantly greater in the S group after induction ($p<0.05$, except for 2min.).

Intra-group comparison: In the D group, the HR in patients older than 30 years was reduced from the baseline values, in contrast to continuous elevations in D20. After endotracheal intubation, the elevated HR was maintained in all groups, but significantly less elevated in D40 and D50 at 3,4, and 5 min. compared to that in D20 ($p<0.05$, except for D40 at 2 min.). In the S group, the changes in HR after induction of anesthesia were diverse in direction without significant differences among age subgroups.

Compared to sevoflurane, 1 MAC of desflurane given for induction of anesthesia caused more elevations in HR, especially in younger patients. And, this might be related to baroreceptor reflex to desflurane-induced vasodilation because inhalation of 1 MAC desflurane did not induce hypertensive responses in all age subgroups. Further investigations are necessary to find methods to mitigate adverse hemodynamic effects of inhalation anesthetics.

Key words : Sympathetic stimulation effect, desflurane, age-difference, sevoflurane, remifentanil

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I. INTRODUCTION

Desflurane, since its introduction in clinical anesthetic practice in the 1990's, had been known to have sympathetic stimulation effect, inducing tachycardia and/or hypertension, when rapidly administered in > 1 minimal alveolar concentration (MAC) during induction of anesthesia [1-4]. Due to those detrimental hemodynamic responses, desflurane has generally been avoided in induction of anesthesia, especially in patients with risks of myocardial infarction, including those with hypertension or ischemic heart disease [5]. Inhalation anesthetics are still used for induction of anesthesia, but not necessarily used in high concentration of > 1 MAC because a potent but short-acting synthetic opioid, remifentanil, is widely used in combination. There were not many reports on hemodynamic responses to 1 MAC desflurane inhalation during induction of anesthesia, especially used in combination with remifentanil. In our daily practice, tachycardia is more often observed when desflurane is used in patients in their twenties or thirties, than patients of other ages. Moreover, sympathetic stimulation effect of desflurane was demonstrated in the investigations performed in young and healthy volunteers. Such an age-dependent difference in hemodynamic responses to 1 MAC desflurane was also

rarely reported.

The aim of this investigation is to compare hemodynamic responses to inhalation of 1 MAC desflurane with those to 1 MAC sevoflurane, which were calculated with age-based formula in adult patients undergoing elective spine surgery.

II. METHODS

After obtaining approval of the local ethics committee and written informed consent, patients undergoing elective spine surgery were enrolled in this prospective, randomized, single-blinded investigation. This study was registered in the Clinical Research Information Service (CRIS) of the Republic of Korea (KCT 0001819). Patients who were older than 60 years or younger than 18 years of age, who had uncontrolled or untreated hypertension or diabetes, active upper respiratory infection or asthma, and cancer metastasis in spine, and who had a history of cerebrovascular accident, renal insufficiency, valvular or ischemic heart disease or any metabolic disorders were excluded. In addition, patients who had a history of difficult airway during previous surgery or anesthesia or who had morphologic characteristics predicting difficult airway (i.e. hypoplastic mandible, Mallampati class Ⅲ or higher, thyromental distance of < 2 finger-breadth) were also excluded.

When a patient who had no premedication in the general ward arrived in the OR, routine hemodynamic monitoring devices, including ECG lead Ⅱ, pulse oximetry, non-invasive blood pressure (NIBP) and BIS, were applied. After confirmation of patency of the peripheral intravenous (IV) route, remifentanil infusion of 0.1 ㎍/㎏/min was initiated as soon as possible. For 5-10 minutes, no further manipulation was done to calm down the patient along with rapid infusion of IV fluid 100-200 ㎖. Then, hemodynamic parameters, such as heart rate (HR), systolic, diastolic and mean arterial pressure (SAP, DAP and MAP), oxygen saturation (S_PO_2) and Bispectral index (BIS) were measured twice with the interval of 3 minutes. The average value of those two measurements of

hemodynamic parameters was used as the baseline value.

Before induction of anesthesia began, IV glycopyrrolate 0.1 ㎎ was given. Anesthesia was induced with IV propofol of 1-1.5 ㎎/㎏ for over 30 seconds. When unconsciousness was not confirmed with the loss of the verbal response, IV propofol of 10 ㎎ was additionally given every 10 seconds. When the loss of consciousness was confirmed, 1 MAC of desflurane or sevoflurane in O_2/air with the flow rate of > 5 L/min was given via the face mask while an end-tidal CO_2 level of 35-40 mmHg and peak airway pressure of < 25 cmH_2O were maintained with manual ventilation. With opening sealed envelope, patients were randomly allocated into two groups; D group (desflurane) or S group (sevoflurane) based on inhalation anesthetics used during induction of anesthesia. The vol% of 1 MAC of inhalation anesthetics was calculated with an age-based formula, suggested by Mapleson WW [6]. Muscle relaxation was induced with IV rocuronium of 0.4 ㎎/㎏ along with IV lidocaine of 30-40 ㎎ to prevent injection pain. An end-tidal fraction (F_{ET}) of designated inhalation anesthetics was monitored to maintain within 70-80 % of inspiratory fraction (Fi) of designated inhalation anesthetics. From initiation of inhalation anesthetic administration, hemodynamic parameters, including HR, SAP, DAP and MAP, were measured and recorded at every minute for five minutes. Then, the patient was intubated with direct laryngoscopy or light wand, based on surgical requirements for lumbar/thoracic or cervical spine surgery, respectively. Appropriate placement of endotracheal tube was confirmed with bilateral chest auscultation and waveform observation of end-tidal CO_2. Then, hemodynamic parameters were measured and recorded at every minute for 5 minutes with mechanical ventilation to maintain end-tidal CO_2 of 35-40 mmHg. If airway maintenance or endotracheal intubation was difficult, requiring oral or nasal airway insertion or > 3 attempts for intubation, the patient was not included into the final analysis and further investigational procedures were just aborted.

During induction of anesthesia, reductions in arterial blood pressure are commonly encountered. For such an instance of hemodynamic derangement, defined as decrease in SAP by > 30 % of baseline value, reduction in anesthetic

dose was done as follows; initially, reduce remifentanil infusion dose by half. If hypotension persisted for > 1 minutes, decrease the inhalation anesthetic concentration by half. In case of persistent hemodynamic derangement even with reductions in inhalation anesthetic dose, endotracheal intubation was immediately done. Conversely, hypertension or tachycardia is commonly seen after endotracheal intubation, probably due to massive stimulation of direct laryngoscopy or tube insertion. If SAP or HR was elevated by > 30% of baseline value, bolus dose of remifentanil 0.5 ㎍/㎏ was initially given, and if hypertension or tachycardia was continued for > 1 minutes, IV esmolol of 5-10 ㎎ was given as secondary rescue therapy. When the SAP was continuously reduced by > 30% of baseline value for > 1 minute even with reductions in anesthetic dose, rescue therapy of IV ephedrine 2 ㎎ was given every minute until the SAP was maintained within 70% of baseline value. Rapid infusion of phenylephrine was secondary rescue therapy for persistent hypotension. If bradycardia, defined as HR reduction by > 30 % of baseline value, was shown, IV atropine 0.5 ㎎ was given as a rescue therapy. Timing and frequency of rescue therapy given during induction of anesthesia and endotracheal intubation were recorded.

The primary endpoint of this investigation was to compare the hemodynamic responses to 1 MAC desflurane inhalation during induction of anesthesia and endotracheal intubation between D group and S group (inter-group comparison). Then, the secondary endpoint was to evaluate the age-dependent differences in hemodynamic responses. To evaluate the age-dependent difference, each group of desflurane and sevoflurane was subdivided into 4 subgroups based on patient's age; 20-29 years, 30-39 years, 40-49 years and 50-59 years of age (D20, D30, D40 and D50 for D group, and S20, S30, S40 and S50 for S group, respectively). Comparison of hemodynamic responses among the four age subgroups within each group of desflurane and sevoflurane (intra-group comparison) was done first, and then comparison between the same age subgroups of each group of desflurane and sevoflurane (inter-subgroup comparison) was done.

To obtain sample power of 0.8, it was calculated to have at least 45 patients for each age subgroup on the assumption of medium effect size of 0.25 and α of 0.05, using G*Power software (Ver. 3.1.9.2, Universität Kiel, Germany, http://www.gpower.hhu.de/). Considering drop-out, it was decided to recruit 50 patients for each age subgroup, resulting in a total of 400 patients for D group and S group.

Discrete data were shown as number (percent) of patients and compared with χ^2 test or Fisher's exact test. To compare the magnitude and direction of hemodynamic variations after induction of anesthesia and after endotracheal intubation, percent changes of each hemodynamic parameter from baseline value were calculated. According to normality test, baseline values and percent changes of hemodynamic parameters were represented as mean ± SD or median [interquartile range(IQR)]. Statistical analyses of hemodynamic parameters were done as follows; 1) inter-group comparison between the two groups (i.e. D group vs. S group) at every minute after induction of anesthesia and after endotracheal intubation, 2) intra-group comparison among the four age subgroups within each group of desflurane and sevoflurane with post-hoc test (i.e. D20 vs. D30 vs. D40 vs. D50), and 3) inter-subgroup comparison between the same age subgroups of each group of desflurane and sevoflurane (i.e. D20 vs. S20). Continuous variables were statistically evaluated with T test or Kruskal-Wallis test, as appropriate with normality test, and post hoc test was done with Tuckey's method. Statistical analyses were done with performed with R studio (Ver. 0.99.902, RStudio Team (2015). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA URL. http://www.rstudio.com/) and R version 3.3.1 (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

III. RESULTS

A total of 400 patients undergoing elective spine surgery were enrolled, but 45

patients (18 in D group, and 27 in S group) were excluded from analysis because of unexpected difficulty in maintaining airway or in endotracheal intubation requiring oral or nasal airway or > 3 attempts, respectively. Finally, 355 patients (182 in D group, and 175 in S group) were included in the statistical analyses. Patient characteristics including co-morbidity and data on induction of anesthesia and endotracheal intubation were represented in Table 1 with no significant difference between the two groups.

1. *Inter-group comparison*

Baseline values of hemodynamic parameters were similar between the two groups (Table 1). The hemodynamic variations after induction of anesthesia and after endotracheal intubation in the two groups were shown in Table 2. After induction of anesthesia, the HR was shown to be elevated in D group, in contrast to reductions in S group ($p<0.01$ at every minute, except for significantly less reduced at 2 min). The SAP, DAP and MAP were shown to be reduced in both groups, but the magnitude of decreases was significantly greater in S group after induction of anesthesia ($p<0.05$, except for DAP and MAP at 2 minute). After endotracheal intubation, the HR was shown to be elevated in both groups, but significantly more elevated in D group ($p<0.01$, except for 1 minute). The arterial blood pressures were generally shown to be reduced in both groups. The magnitude of reductions in SAP was similar in both groups, except for 1 minute after intubation where greater decrease was found in D group ($p<0.01$). DAP and MAP were significantly more reduced in D group ($p<0.05$, except for MAP at 3 minute). Data on rescue therapy and reductions in dose of remifentanil infusion and/or inhalation agents to mitigate hemodynamic derangements during induction of anesthesia and endotracheal intubation were represented in Table 3. As an initial regimen of rescue therapy, bolus dose of remifentanil was more frequently given in D group ($p<0.01$), and so was esmolol bolus dose as secondary regimen in D group ($p<0.001$). Those rescue medications were given more frequently to mitigate tachycardia ($p<0.001$) and after induction of anesthesia ($p<0.001$) in D group. The

frequency of reductions in anesthetic dose was not significantly different between the two groups. In S group, however, anesthetic dose reduction was significantly more frequently done after induction of anesthesia ($p<0.05$).

Table 1. Patient characteristics, co-morbidity, data on induction of anesthesia and endotracheal intubation and baseline hemodynamic profile.

Group		D (N=182)	S (N=173)	p
Sex	F	73 (40.1 %)	70 (40.5 %)	1
	M	109 (59.9 %)	103 (59.5 %)	
Age		43.0 [30.0;51.0]	41.0 [32.0;54.0]	0.324
Height		168.1 ± 8.6	166.8 ± 9.8	0.194
Weight		65.2 [60.0;75.0]	65.0 [56.0;74.0]	0.303
Co-morbidity				
	Hypertension	19 (10.4%)	14 (8.1%)	0.563
	Diabetes	3 (1.6%)	6 (3.5%)	0.452
	Thyroid Disease	1 (0.5%)	3 (1.7%)	0.58
Induction and intubation				
Propofol Dose		110.0 [100.0;120.0]	100.0 [100.0;120.0]	0.517
Endotracheal intubation				
Method	Laryngoscopy	98 (53.8%)	105 (60.7%)	0.232
	Light wand	84 (46.2%)	68 (39.3%)	0.232
Number of trial	1	159 (87.4%)	148 (85.5%)	0.731
	> 2	23 (12.6%)	25 (14.5%)	0.731
Baseline hemodynamic profile				
	HR	72.8 [64.5;84.5]	74.0 [66.5;84.5]	0.378
	SAP	135.8 [124.5;149.0]	135.5 [125.0;150.0]	0.672
	DAP	79.5 [73.5;87.0]	79.5 [74.0;85.5]	0.721
	MAP	95.5 [87.5;105.0]	93.5 [87.0;102.5]	0.083
	SpO_2	98.5 [97.5;99.5]	98.5 [97.5;100.0]	0.562
	BIS	96.0 [92.5;97.0]	95.5 [92.0;97.0]	0.497

Data are represented as mean ± SD, median [interquartile range] or number (%), as appropriate. D: desflurane, S: Sevoflurane, HR: heart rate, SAP: systolic arterial blood pressure, DAP: diastolic arterial blood pressure, MAP: mean arterial blood pressure, SpO_2: oxygen saturation, BIS: bispectral index.

Table 2. Hemodynamic variations from baseline values after induction of anesthesia and after endotracheal intubation.

		After induction of anesthesia			After endotracheal intubation		
	Group Time	D (N=182)	S (N=173)	p	D (N=182)	S (N=173)	P
HR	1 min	2.4 [-5.1;10.4]	0.0 [-9.5; 7.8]	0.005	19.5 [5.6;36.9]	18.0 [4.3;31.9]	0.182
	2 min	-2.0 [-10.1; 7.7]	-5.1 [-13.6; 3.9]	0.006	19.8 [6.0;36.8]	13.2 [-1.3;24.5]	0.001
	3 min	2.0 [-7.9;14.5]	-4.8 [-13.6; 6.0]	0	15.1 [3.1;31.7]	6.2 [-5.6;19.3]	0
	4 min	4.0 [-6.5;20.9]	-5.9 [-13.4; 7.0]	0	13.5 [2.3;30.0]	3.7 [-6.1;15.5]	0
	5 min	9.1 [-3.2;23.3]	-2.7 [-12.9; 8.2]	0	12.2 [0.6;27.4]	1.6 [-9.0;12.6]	0
SAP	1 min	-11.6 [-17.3; -5.5]	-14.0 [-19.0; -8.4]	0.046	-17.7 ± 14.4	-13.2 ± 15.8	0.006
	2 min	-18.7 ± 9.3	-21.4 ± 9.5	0.008	-17.6 [-25.9; -8.8]	-15.0 [-22.3; -8.5]	0.198
	3 min	-22.6 ± 10.8	-27.4 ± 10.4	0	-21.8 [-29.3; -13.8]	-20.5 [-27.8; -14.7]	0.803
	4 min	-25.8 [-33.3; -19.3]	-30.3 [-38.7; -23.6]	0	-26.0 ± 11.2	-24.2 ± 9.9	0.122
	5 min	-27.0 [-32.5; -20.1]	-28.1 [-35.4; -23.1]	0.015	-27.5 [-36.0; -21.9]	-25.5 [-34.8; -19.5]	0.081
DAP	1 min	-14.6 [-22.3; -6.1]	-17.2 [-23.1; -11.7]	0.013	-12.4 [-24.2; -0.8]	-2.8 [-18.3; 9.3]	0
	2 min	-19.7 [-26.6; -9.0]	-20.6 [-26.3; -12.8]	0.18	-15.3 [-25.3; -4.6]	-11.4 [-20.6; 0.3]	0.005
	3 min	-25.1 [-31.8; -14.1]	-27.6 [-33.3; -21.5]	0.001	-22.5 [-30.4; -12.8]	-19.2 [-25.6; -11.0]	0.01
	4 min	-27.0 [-36.5; -18.1]	-31.8 [-38.1; -26.2]	0	-26.7 [-35.0; -19.4]	-22.8 [-29.1; -14.9]	0
	5 min	-26.7 [-33.7; -17.8]	-31.0 [-36.2; -25.5]	0	-29.7 ± 12.0	-23.1 ± 11.3	0
MAP	1 min	-13.5 [-20.5; -6.2]	-16.7 [-21.7; -11.7]	0.009	-14.5 [-25.4; - 3.2]	-6.6 [-19.8; 4.2]	0
	2 min	-18.7 [-26.4; -11.6]	-21.7 [-26.2; -14.7]	0.055	-15.6 [-24.5; -6.3]	-13.0 [-21.1; -3.3]	0.022
	3 min	-24.5 [-30.5; -15.3]	-27.9 [-32.8; -22.6]	0	-22.2 [-28.2; -13.8]	-20.4 [-25.8; -12.7]	0.122

	4 min	-26.8 [-33.9; -19.2]	-31.3 [-37.4; -26.5]	0	-27.1 [-34.0; -19.3]	-23.7 [-29.2; -16.8]	0.001
	5 min	-26.5 [-33.3; -18.3]	-30.9 [-36.2; -25.9]	0	-29.5 [-36.3; -22.1]	-24.9 [-30.5; -17.9]	0

Data are percent changes from baseline values, represented as mean ± SD or median [interquartile range], as appropriate. D: Desflurane, S: Sevoflurane. HR: heart rate, SAP: systolic arterial blood pressure, DAP: diastolic arterial blood pressure, MAP: mean arterial blood pressure.

Table 3. Data on rescue therapy and reductions in dose of remifentanil infusion and/or inhalation agents to mitigate hemodynamic derangements during induction of anesthesia and endotracheal intubation.

Group			D (N=182)	S (N=173)	p
Hypertension or tachycardia					
Rescue therapy		Remifentanil bolus	101 (55.5%)	53 (30.6%)	0
		Esmolol	16 (8.8%)	0 (0.0%)	0
Hypotension					
Anesthetic dose reduction		Remifentanil	73 (40.1%)	68 (39.3%)	0.963
		Inhalation agent	9 (4.9%)	12 (6.9%)	0.569
Rescue therapy		Ephedrine	1 (0.5%)	0 (0.0%)	1
		Phenylephrine	4 (2.2%)	2 (1.2%)	0.727
Reason for Rescue Therapy					
		Tachycardia	90 (49.5%)	46 (26.6%)	0
		Hypertension	10 (5.5%)	7 (4.0%)	0.696
		Hypotension	4 (2.2%)	2 (1.2%)	0.727
Timing					
Anesthetic dose reduction		After induction of anesthesia	1 (0.6%)	9 (5.4%)	0.02
		After endotracheal intubation	71 (39.2%)	53 (31.7%)	0.099
Rescue therapy		After induction of anesthesia	53 (29.1%)	14 (8.1%)	0
		After endotracheal intubation	36 (19.8%)	33 (19.1%)	0.973
		Both	15 (8.2%)	8 (4.6%)	0.243

Data are represented as number (%) of patients. D: Desflurane, S: Sevoflurane.

2. *Intra-group comparison with post-hoc test*

Baseline values of hemodynamic parameters in D group and S were classified by age subgroup in Table 4. Both groups were shown to have similar pattern with subgroup classification; the HR was not significantly different among age subgroups in both groups, the SAP was significantly higher in patients of D50 and S50, compared to all other age subgroups ($p<0.05$), and the DAP and MAP were significantly higher in patients older than 40 years, compared to patients in D20 and S20 ($p<0.05$). Furthermore, the MAP of D50 and S50 was shown to be significantly higher than that of D30 and S30, respectively ($p<0.05$).

Changes in hemodynamic parameters from baseline values after induction of anesthesia and after endotracheal intubation in D group and S group, classified by age subgroup, are shown in Table 5 and 6, respectively. In D group, the HR was elevated in all subgroups immediately after induction of anesthesia without significant difference among subgroups. Then, the HR in patients older than 30 years was shown to be reduced from baseline value, in contrast to continuous elevations in D20. In D40 and D50, the HR was significantly reduced from baseline value, compared to that in D20 at 2-4 minute after induction of anesthesia ($p<0.05$, except for D40 at 2 minute). In D50, the HR was shown to be significantly reduced from baseline value, compared to that in D30 at 3 and 4 minute ($p<0.05$). The HR was finally elevated in all subgroups just before the endotracheal intubation without significant difference among subgroups. The SAP, DAP and MAP were shown to be reduced in all subgroups of D group after induction of anesthesia. The magnitude of reductions in the SAP was significantly greater in subgroups of D40 and D50, compared to D20 ($p<0.05$). In D50, the SAP was significantly reduced from baseline value, compared not only to D20 and D30 ($p<0.05$, except for 1 minute), but also to D40 at 3, 4 and 5 minute ($p<0.05$). In D40, reductions in SAP was significantly greater than those in D30 at 2 and 4 minute ($p<0.05$). Reductions in DAP were not significantly different in all subgroups of D group, and those in MAP were

significantly greater in D50, compared to D20 at 1, 3 and 4 minute, and to D30 at 3 and 4 minute ($p<0.05$). After endotracheal intubation, the HR was generally shown to be elevated in all subgroups. Such an elevated HR was shown to be maintained in all subgroups, but significantly less elevated in D40 and D50 at 3, 4 and 5 minute compared to that in D20 ($p<0.05$, except for D40 at 3 minute). The SAP was generally shown to be reduced in all subgroups after endotracheal intubation, but significantly more reduced in D40 and D50, compared to that in D20 ($p<0.05$, except for D40 at 2 and 3 minute). In D50, SAP was significantly more reduced than that in D30 at 4 and 5 minute ($p<0.05$), and even that in D40 at 5 minute ($p<0.05$). The changes in DAP and MAP were not significantly different among subgroups after endotracheal intubation.

Table 4. Baseline hemodynamic parameters in the Desflurane and Sevoflurane group, classified by Age subgroups

Subgroup	D20	D30	D40	D50	p	S20	S30	S40	S50	p
	(N=43)	(N=35)	(N=49)	(N=55)		(N=30)	(N=46)	(N=39)	(N=58)	
HR	74.0 [64.8;85.0]	76.0 [64.5;82.0]	72.5 [65.5;86.0]	71.0 [64.5;82.5]	0.93	73.5 [64.0;92.0]	77.8 [68.0;87.5]	76.5 [66.8;85.2]	70.0 [64.0;83.0]	0.126
SAP	129.4 ± 13.3	134.4 ± 15.1	137.5 ± 16.6	146.3 ± 16.6*,†,‡	0	129.7 ± 13.1	130.8 ± 14.5	135.6 ± 15.7	146.0 ± 18.6*,†,‡	0
DAP	74.5 ± 9.9	79.6 ± 11.0	81.6 ± 12.5*	84.2 ± 11.1*	0	74.2 ± 7.7	79.1 ± 9.4	82.3 ± 8.3*	81.3 ± 10.9*	0.003
MAP	88.5 [82.0;95.2]	94.5 [85.8;101.8]	97.0 [91.0;103.5]*	103.0 [92.5;112.8]*,†	0	87.1 ± 7.6	91.8 ± 10.0	97.1 ± 10.0*	99.2 ± 12.1*,†	0

Data are baseline values, represented as mean ± SD or median [IQR], as appropriate. D20: desflurane-given patients, aged 20-29 years, D30: desflurane-given patients, aged 30-39 years, D40: desflurane-given patients, aged 40-49 years, D50: desflurane-given patients, aged 50-59 years, S20: sevoflurane-given patients, aged 20-29 years, S30: sevoflurane-given patients, aged 30-39 years, S40: sevoflurane-given patients, aged 40-49 years, S50: sevoflurane-given patients, aged 50-59 years, *: $p<0.05$, compared to D20 (S20), †: $p<0.05$, compared to D30 (S30), ‡: $p<0.05$, compared to D40 (S40).

Table 5. Hemodynamic changes from baseline values after induction of anesthesia and after endotracheal intubation in the Desflurane group, classified by age subgroup.

		After induction of anesthesia					After endotracheal intubation				
	Subgroup	D20	D30	D40	D50	p	D20	D30	D40	D50	p
	Time	(N=43)	(N=35)	(N=49)	(N=55)		(N=43)	(N=35)	(N=49)	(N=55)	
HR	1 min	8.2 [-4.5;14.9]	4.7 [-5.1;12.2]	2.2 [-4.1;10.2]	0.6 [-5.7; 5.1]	0.086	27.7 [11.6;42.3]	15.2 [8.7;43.7]	13.5 [0.8;35.8]	18.6 [4.9;34.4]	0.213
	2 min	3.2 [-4.8;10.2]	-1.1 [-7.6;10.6]	-3.0 [-10.7; 4.4]	-3.7 [-11.9; 4.5]*	0.027	28.7 [12.0;40.2]	22.3 [10.4;38.2]	16.3 [4.3;29.8]	15.6 [2.8;31.3]	0.091
	3 min	11.4 [2.4;20.8]	6.6 [-5.3;17.4]	-2.3 [-8.2; 9.8]*	-3.1 [-12.3; 7.3]*,†	0.00031	28.7 [11.4;36.8]	11.2 [4.2;32.8]	11.4 [1.1;28.2]	15.0 [-1.2;28.3]*	0.035
	4 min	15.9 [0.7;29.3]	10.5 [-2.2;23.2]	0.0 [-6.2;15.2]*	-3.0 [-12.8;10.5]*,†	0.00051	24.6 [10.6;35.9]	9.6 [3.1;31.3]	12.0 [1.9;23.7]*	10.4 [-4.5;21.0]*	0.00462
	5 min	15.2 [3.1;27.5]	13.1 [1.8;24.4]	0.8 [-6.9;18.2]	4.4 [-7.3;25.1]	0.082	20.7 [9.0;37.2]	10.2 [3.9;32.5]	8.1 [-1.7;21.6]*	8.0 [-7.8;17.7]*	0.004
SAP	1 min	-9.0 [-12.2;-2.6]	-11.3 [-14.8;-6.1]	-13.7 [-18.8;-7.0]*	-16.5 [-22.1;-5.8]*	0.00192	-11.4 [-19.6;-0.9]	-18.3 [-25.7;-8.5]	-22.6 [-27.8;-13.6]*	-25.0 [-33.3;-14.0]*	0
	2 min	-13.2 ± 7.7	-14.8 ± 7.6	-20.2 ± 9.2*,†	-24.1 ± 8.3*,†	0	-11.4 ± 12.8	-15.0 ± 11.4	-18.5 ± 12.7	-20.6 ± 15.8*	0.0066
	3 min	-19.7 [-23.0;-9.1]	-19.3 [-20.9;-15.1]	-23.2 [-27.7;-19.8]*	-29.4 [-35.5;-25.7]*,†,‡	0	-16.6 [-23.4;-8.2]	-21.2 [-27.9;-13.5]	-21.8 [-27.2;-16.0]	-26.4 [-33.1;-18.1]*	0.0006
	4 min	-19.8 [-24.8;-13.2]	-20.0 [-26.4;-16.7]	-27.1 [-32.0;-22.7]*,†	-33.8 [-39.2;-29.4]*,†,‡	0	-18.6 [-27.5;-15.1]	-22.9 [-30.9;-19.6]	-26.4 [-33.6;-20.3]*	-32.5 [-38.4;-24.4]*,†	0
	5 min	-22.7 [-26.8;-12.8]	-23.6 [-30.4;-17.3]	-28.7 [-31.2;-22.7]*	-33.1 [-38.8;-27.8]*,†,‡	0	-22.3 [-29.0;-15.7]	-25.9 [-30.9;-20.5]	-27.9 [-36.4;-23.0]*	-35.6 [-41.8;-27.2]*,†,‡	0
DAP	1 min	-13.1 [-22.2;-3.6]	-15.9 [-21.3;-8.6]	-14.3 [-24.0;-5.6]	-16.2 [-21.6;-8.4]	0.71	-10.3 [-26.8; 2.8]	-11.8 [-21.1;-1.1]	-14.1 [-25.0;-1.2]	-12.3 [-22.8;-1.9]	0.839

	2 min	-22.6 [-30.6;-10.5]	-19.7 [-24.4;-9.8]	-17.5 [-25.5;-10.3]	-19.0 [-27.6;-8.9]	0.457	-17.3 ± 16.9	-14.4 ± 15.4	-15.3 ± 17.2	-12.9 ± 17.6	0.646
	3 min	-26.9 [-32.6;-10.3]	-24.0 [-28.8;-15.5]	-23.4 [-31.7;-14.1]	-26.6 [-32.8;-16.7]	0.627	-22.7 ± 15.9	-23.2 ± 11.2	-21.1 ± 14.7	-20.1 ± 12.4	0.688
	4 min	-30.3 [-40.1;-12.8]	-23.9 [-30.1;-18.1]	-25.8 [-34.2;-19.0]	-28.9 [-37.0;-19.9]	0.378	-28.3 [-39.3;-17.2]	-28.5 [-31.7;-18.5]	-27.3 [-33.7;-19.3]	-25.3 [-33.9;-21.9]	0.885
	5 min	-27.8 [-41.4;-17.2]	-28.3 [-31.6;-18.6]	-25.6 [-30.3;-19.0]	-26.6 [-33.0;-16.7]	0.848	-31.6 ± 12.6	-29.7 ± 11.4	-27.8 ± 12.0	-29.9 ± 11.8	0.493
MAP	1 min	-9.8 [-14.9;-2.3]	-14.6 [-19.6;-8.2]	-14.3 [-22.7;-6.2]	-14.6 [-21.7;-10.4]*	0.028	-7.7 [-24.8; 0.3]	-13.2 [-22.2;-4.3]	-16.1 [-27.3;-5.3]	-17.3 [-25.4;-7.5]	0.156
	2 min	-18.7 [-26.1;-10.8]	-15.3 [-22.9;-8.4]	-17.5 [-26.5;-11.1]	-20.8 [-28.8;-14.8]	0.157	-15.3 [-25.1;-4.5]	-18.1 [-22.9;-5.9]	-14.9 [-23.9;-6.4]	-17.7 [-25.3;-7.4]	0.916
	3 min	-21.2 [-28.5;-10.4]	-21.0 [-26.1;-16.0]	-23.8 [-30.6;-15.0]	-28.1 [-32.8;-20.1]*,†	0.01	-19.8 [-28.3;-7.0]	-22.5 [-27.7;-15.5]	-21.8 [-27.4;-14.1]	-23.4 [-28.4;-15.4]	0.618
	4 min	-24.4 [-32.6;-8.8]	-22.0 [-28.4;-16.8]	-27.4 [-33.0;-19.2]	-30.9 [-37.7;-25.2]*,†	0.00177	-24.3 [-33.3;-15.0]	-26.8 [-33.3;-17.2]	-27.9 [-32.7;-21.2]	-29.6 [-35.2;-23.7]	0.145
	5 min	-24.1 [-34.4;-14.6]	-26.2 [-30.8;-18.2]	-26.3 [-31.5;-18.3]	-28.1 [-36.3;-20.5]	0.272	-28.5 [-33.0;-19.6]	-29.0 [-33.0;-20.2]	-28.8 [-35.6;-21.2]	-31.7 [-39.6;-26.3]	0.051

Data are percent changes from baseline values, represented as mean ± SD or median [IQR], as appropriate. D20: desflurane-given patients, aged 20-29 years, D30: desflurane-given patients, aged 30-39 years, D40: desflurane-given patients, aged 40-49 years, D50: desflurane-given patients, aged 50-59 years, *: $p<0.05$, compared to D20, †: $p<0.05$, compared to D30, ‡: $p<0.05$, compared to D40.

Table 6. Hemodynamic changes from baseline values after induction of anesthesia and after endotracheal intubation in the Sevoflurane group, classified by Age subgroup.

		After induction of anesthesia					After endotracheal intubation				
	Subgroup	S20	S30	S40	S50	p	S20	S30	S40	S50	p
	Time	(N=30)	(N=46)	(N=39)	(N=58)		(N=30)	(N=46)	(N=39)	(N=58)	
HR	1 min	1.8 [-7.2; 8.8]	-2.0 [-12.5; 8.4]	4.8 [-4.2;10.8]	-2.8 [-10.5; 5.2]	0.107	17.6 [3.0;40.0]	20.5 [2.2;26.7]	24.4 [8.0;36.4]	12.9 [1.5;30.5]	0.214
	2 min	-4.1 [-11.9; 7.1]	-5.7 [-14.3; 1.1]	-4.8 [-12.3; 4.6]	-6.8 [-14.5; 2.4]	0.696	16.4 [1.8;26.2]	14.5 [-2.0;24.3]	21.1 [-2.5;28.9]	7.1 [-1.0;18.5]	0.474
	3 min	0.8 [-12.3;10.3]	-3.0 [-15.1; 2.9]	-1.2. [-10.2; 7.0]	-9.7 [-13.8; 0.5]	0.093	11.6 ± 19.4	6.9 ± 17.6	10.8 ± 20.9	5.9 ± 15.6	0.385
	4 min	2.1 [-11.0;11.4]	-4.9 [-13.0; 7.2]	0.0 [-9.6; 7.1]	-10.9 [-14.9;-2.8]*	0.011	8.9 ± 19.8	3.9 ± 17.2	6.1 ± 19.8	2.1 ± 14.2	0.33
	5 min	4.5 ± 16.4	-2.4 ± 15.4	-2.9 ± 15.1	-7.6 ± 10.6	0.056	7.2 [-8.4;15.0]	2.4 [-6.9;14.5]	2.8 [-7.1;14.3]	-1.2 [-9.6; 7.6]	0.452
SAP	1 min	-12.9 [-18.1;-8.4]	-14.3 [-18.1;-9.3]	-13.1 [-18.6;-9.1]	-15.5 [-23.2;-6.1]	0.78	-9.8 [-14.6;-3.7]	-14.0 [-19.8;-6.4]	-10.3 [-18.0;-0.4]	-16.3 [-34.2;-5.2]	0.039
	2 min	-14.7 ± 8.1	-18.1 ± 5.5	-22.7 ± 7.4*	-26.5 ±10.8*,†	0	-13.1 [-17.5;-8.9]	-14.3 [-20.2;-8.6]	-14.0 [-21.3;-8.1]	-18.9 [-28.9;-9.5]	0.101
	3 min	-20.6 ± 7.6	-22.8 ± 7.4	-26.2 ± 9.1*	-35.3 ± 9.5*,†,‡	0	-18.0 [-22.1;-13.9]	-19.7 [-24.6;-13.2]	-20.0 [-25.3;-15.7]	-26.6 [-34.7;-15.9]*,†	0.006
	4 min	-24.4 ± 6.7	-26.4 ± 7.9	-29.5 ± 8.1	-40.0 ± 9.4*,†,‡	0	-20.7 [-24.3;-15.8]	-21.7 [-27.8;-18.0]	-23.4 [-28.9;-18.8]	-31.6 [-38.6;-20.3]*,†	0
	5 min	-24.0 ± 6.2	-26.2 ± 6.6	-29.8 ± 7.0*	-38.2 ± 6.6*,†,‡	0	-21.8 ± 6.2	-23.1 ± 7.7	-26.5 ± 9.5	-32.0 ± 10.6*,†,‡	0
DAP	1 min	-20.1 [-27.0;-9.9]	-19.8 [-24.0;-12.9]	-16.4 [-20.1;-11.7]	-15.4 [-21.2;-11.0]	0.178	-7.0 ± 17.4	-4.8 ± 18.1	1.1 ± 21.3	-2.7 ± 21.7	0.378
	2 min	-16.0 ± 9.7	-20.9 ± 9.7	-21.3 ± 8.8	-20.4 ±10.8	0.112	-12.4 [-25.0;-5.7]	-13.9 [-21.9;-5.6]	-11.0 [-18.0; 1.1]	-5.9 [-19.8; 5.0]	0.06

	3 min	-27.0 [-31.6;-21.5]	-29.7 [-33.7;-20.5]	-27.8 [-32.7;-21.4]	-27.0 [-35.0;-22.2]	0.861	-21.5 [-25.2;-14.3]	-20.5 [-27.9;-13.2]	-19.7 [-23.3;-12.5]	-15.3 [-25.6;-3.3]	0.122
	4 min	-32.1 [-37.5;-25.2]	-31.6 [-36.5;-25.7]	-29.9 [-35.8;-26.2]	-35.1 [-39.3;-27.0]	0.352	-24.5 [-32.9;-16.2]	-23.6 [-29.4;-15.7]	-23.3 [-27.5;-16.7]	-21.6 [-28.4;-10.6]	0.363
	5 min	-30.4 [-37.2;-24.4]	-30.4 [-34.3;-24.2]	-32.0 [-35.5;-25.9]	-33.8 [-39.2;-28.4]	0.581	-25.2 ± 9.2	-24.4 ± 10.6	-23.3 ± 9.6	-21.0 ± 13.4	0.307
MAP	1 min	-16.2 [-21.7;-11.7]	-18.0 [-21.9;-13.1]	-15.5 [-20.3;-12.7]	-16.6 [-22.3;-10.3]	0.752	-6.3 ± 15.3	-8.2 ± 16.5	-2.2 ± 19.2	-9.1 ± 19.9	0.306
	2 min	-16.0 [-21.7;-9.1]	-20.0 [-24.1;-14.5]	-22.9 [-27.5;-17.3]*	-24.3 [-30.7;-16.3]*	0.0003	-13.5 [-21.3;-5.9]	-13.2 [-20.7;-4.0]	-13.1 [-19.0;-2.6]	-10.5 [-23.8; 0.0]	0.748
	3 min	-23.9 [-28.9;-20.6]	-27.4 [-32.2;-20.0]	-27.1 [-32.5;-22.4]	-30.4 [-36.6;-26.7]*,†	0.001	-18.8 [-25.1;-12.7]	-19.3 [-25.6;-12.8]	-21.2 [-24.6;-14.0]	-21.0 [-28.1;-9.2]	0.99
	4 min	-27.9 ± 7.5	-29.3 ± 9.0	-30.4 ± 8.9	-36.8 ± 9.0*,†,‡	0	-22.9 [-30.7;-17.1]	-23.3 [-27.4;-15.5]	-23.5 [-27.1;-18.5]	-25.9 [-31.4;-18.1]	0.573
	5 min	-28.7 [-30.1;-23.3]	-28.9 [-33.3;-24.4]	-32.0 [-33.3;-29.8]	-37.9 [-40.5;-32.0]*,†	0.001	-23.3 ± 8.0	-23.7 ± 9.2	-24.6 ± 8.9	-25.6 ± 11.4	0.709

Data are percent changes from baseline values, represented as mean ± SD or median [IQR], as appropriate. S20: sevoflurane-given patients, aged 20-29 years, S30: sevoflurane-given patients, aged 30-39 years, S40: sevoflurane-given patients, aged 40-49 years, S50: sevoflurane-given patients, aged 50-59 years, *: $p<0.05$, compared to S20, †: $p<0.05$, compared to S30, ‡: $p<0.05$, compared to S40.

The changes in HR after induction of anesthesia with sevoflurane were diverse in direction without significant difference among age subgroups, except for significantly greater reduction in S50 compared to S20 at 4 minute ($p<0.05$).

The SAP was shown to be continuously reduced in all subgroups during induction of anesthesia with sevoflurane. The magnitude of reductions in SAP was significantly greater in S40 and S50, compared to those in S20 at 2-5 minute ($p<0.05$, except for 4 minute in S40). In S50, decreases in SAP were significantly greater, compared to S30 at 2-5 minute, and even to S40 at 4-5 minute ($p<0.05$). The DAP was also shown to be continuously reduced in all subgroups, but no significant difference was found among subgroups. Decreases in MAP after induction of anesthesia with sevoflurane were significantly greater in S50, compared to S20 at 2-5 minute, to S30 at 3-5 minute, and even to S40 at 4 minute ($p<0.05$). And, so was in S40, compared to S20 at 2 minute ($p<0.05$). After endotracheal intubation, the HR was shown to be elevated, but soon decreased to baseline values without significant difference among age subgroups. The SAP was shown to be continuously reduced after endotracheal intubation, but magnitude of decreases in SAP was significantly greater in S50, compared to S20 and S30 at 3-5 minute ($p<0.05$), and even to D40 at 5 minute ($p<0.05$). The DAP and MAP were also shown to be reduced after endotracheal intubation in all age subgroups in S group, but no significant difference was found among subgroups.

3. Inter-subgroup comparison

Baseline values of hemodynamic parameters were not significantly different between the same age subgroups in each group of desflurane and sevoflurane. Comparison of hemodynamic variations between the corresponding age subgroups in each group of desflurane and sevoflurane revealed that significantly greater elevations in the HR in younger patients in D group (D20 and D30) after induction of anesthesia and after endotracheal intubation, compared to S20 and S30, respectively ($p<0.05$, except for 1-2 minute after induction of anesthesia in D20 and 1 minute after endotracheal intubation in

D20 and D30). In contrast, no significant difference in HR changes was found between older subgroups in both groups after induction of anesthesia and after endotracheal intubation, except for significantly less reductions in HR in D50, compared to S50 at 4-5 minute after induction of anesthesia ($p<0.05$) and significantly more elevated HR in D50 at 3-5 minute after endotracheal intubation than those in S50 ($p<0.05$). For changes in arterial blood pressure, similar pattern shown in the inter-group comparison was also found; significantly more reduced arterial blood pressure was shown in S group after induction of anesthesia, but so was in D group after endotracheal intubation. After induction of anesthesia, the SAP was shown to be more reduced in S20 at 1 and 4 minute, in S30 at 2-4 minute, and in S50 at 3-5 minute, compared to corresponding subgroups in D group ($p<0.05$). The DAP was shown to be more reduced in S20 at 1 minute, in S30 at 1, 3 and 4 minute, in S40 at 3 and 5 minute, and in S50 at 4-5 minute, compared to corresponding subgroups in D group ($p<0.05$) after induction of anesthesia. And so was the MAP in S20 at 1 minute, in S30 at 3-4 minute, in S40 at 5 minute and in S50 at 3-5 minute, compared to corresponding subgroups in D group ($p<0.05$) after induction of anesthesia. After endotracheal intubation, no significant difference in changes in arterial blood pressure was found in younger patients, except for more reduced DAP in D20 and D30 at 5 minute after intubation ($p<0.05$), compared to those in S20 and S30, respectively. In older patients, however, significantly more reduced arterial blood pressure was found sporadically in D group; in D40, SAP at 1 minute, DAP at 1-2 minute, and MAP at 1 minute after endotracheal intubation and in D50, DAP at 1 and 3-5 minute, and MAP at 4-5 minute ($p<0.05$).

IV. DISCUSSION

The HR was shown to be continuously elevated during induction of anesthesia and endotracheal intubation in patients given with 1 MAC desflurane, in contrast to continuous reductions in HR after induction of anesthesia and then

less elevations in HR after endotracheal intubation in patients given with 1 MAC sevoflurane. Usage of the rescue therapy reflected those hemodynamic characteristics in D group; bolus doses of remifentanil and then esmolol were more frequently given in D group than in S group to mitigate tachycardia, especially after induction of anesthesia. Within D group, such a HR-accelerating effect of desflurane was demonstrated to be more prominent in patients in their twenties or thirties compared to patients in their forties and fifties. In contrast, no significant difference in changes in HR was found among age subgroups within S group. Furthermore, compared to the patients in the same age subgroup of S group, increases in HR during induction of anesthesia and endotracheal intubation were shown to be significantly greater in younger patients of D group. Even older desflurane-given patients were shown to have more elevated HR after induction of anesthesia and after endotracheal intubation, compared to the sevoflurane-given patients of the same age subgroup. However, vasopressor effect of desflurane was not demonstrated in this investigation.

Ebert et al. designed observational investigation in healthy and young volunteers, and demonstrated that rapid increase in desflurane concentration during induction of anesthesia and transition period from 1.0 MAC to 1.5 MAC induced sympathetic stimulation, resulting in tachycardia and hypertension [1]. Later, Weiskopf et al. suggested that desflurane might affect rapid-adapting irritant receptors on tracheobronchial tree, and thus exert sympathetic stimulation effect [7-8]. In this investigation, arterial blood pressure was not shown to be elevated with rapid increases in concentration of desflurane during induction of anesthesia, which had been demonstrated in many of previous investigations [1-4]. The sole difference in study protocol between the previous investigations and the current investigation was the target concentration of desflurane; > 1 MAC vs. 1 MAC, respectively. In the previous investigations, the HR was shown to be elevated from baseline value without significance when the inspiratory concentration of desflurane did not reach 1 MAC, whereas the MAP and SVR were shown to be significantly reduced from baseline value

even at < 1 MAC of desflurane. The HR was then eventually shown to be significantly elevated with deeper plane of anesthesia with > 1 MAC of desflurane [9]. Rapid increases in inspiratory concentration of desflurane, but not exceeding 1 MAC in this investigation would not be enough to saturate rapid-adapting irritant receptors in tracheobronchial tree, which are considered to be an origin of sympathetic stimulation effect of desflurane [7-8, 10]. Direct depression effect of desflurane on the vascular system, however, was shown to be intact with such a relatively lower concentration, resulting in elevations in HR from baroreceptor reflex. In this investigation, arterial blood pressure was reduced as soon as desflurane was administered. The magnitude of increases in HR was just less than 10 % of baseline value even though it was significantly greater than that of decreases in HR in S group. Moreover, the increases in HR appeared with a brief latency to decreases in arterial blood pressure in all age subgroups in S group, probably compensating decreases in SAP from reduced vascular resistance. Then, the direction of HR changes was diverse among age subgroups; the younger the patients were, the greater, the earlier and the longer the HR was elevated. Furthermore, the older the patients were, the greater the SAP was reduced primarily. In S group, those HR-accelerating responses to increasing concentration of inhalation anesthetics were shown in similar fashion; elevated HR in younger patients, in contrast to less elevations or even decreases in HR in older patients, but the speed and magnitude of responses were much more attenuated than those in D group. Those changes in HR were accompanied by reductions in arterial blood pressure, suggesting hemodynamic changes related to baroreceptor reflex. The ratio of F_{ET}/F_i of inhalation anesthetics was not significantly different between D and S group during induction of anesthesia (Data are not shown). Although inhalation anesthetics were commonly shown to depress sympathetic nervous system activity, especially baroreceptor reflex activity [11], sevoflurane was demonstrated to attenuate sympathetic nervous system activity to a greater degree than desflurane with equipotent dose [12]. Thus, the HR was significantly more elevated with desflurane than with sevoflurane in response to reductions in arterial blood pressure. Because advancing age

reportedly blunted baroreceptor reflex in previous investigations [13], the magnitude of elevations in HR was shown to be age-related. Moreover, reductions in arterial blood pressure were shown to have a time-related fashion; immediate reductions in arterial blood pressure with sevoflurane, in contrast to delayed reductions with desflurane. Those manifestations in reductions in arterial blood pressure in this investigation had been similarly demonstrated in previous investigation with inhalation anesthetics given via CPB circuit [14].

Previous investigations regarding sympathetic stimulation effect of desflurane did employ relatively higher concentration of desflurane, which is not commonly used in daily practice; at least, 1.5 MAC or even as high as 12 vol%. Additionally, they did not give any medication to ease potential sympathetic stimulation effect, like remifentanil in this investigation. To mitigate sympathetic stimulation effect of rapid increases in desflurane concentration, various medications were evaluated, including opioids, α- and/or β-adrenergic blocking agents [15-19]. Recently, use of remifentanil was widespread, being considered as a replacement of nitrous oxide for general anesthesia [20]. Consequently, a lot of investigations, using target concentration infusion (TCI) method, were done to find an optimal effect-site concentration of remifentanil to mitigate adverse hemodynamic responses during induction of anesthesia with desflurane, most of which demonstrated that at least > 3 ng/ml of effect-site concentration of remifentanil was required for stable hemodynamic profile [21-23]. Continuous infusion scheme of remifentanil in this investigation was simulated using RUGLOOP software (Ghent University) to calculate effect-site concentrations of remifentanil at 20 minutes of investigational procedures, corresponding to the time point between the induction of anesthesia and the endotracheal intubation. The effect-site concentration of remifentanil was simulated to be 2.0 - 3.0 ng/ml at 20 minutes of procedures. The effect-site concentration of 2.0 ng/ml was previously demonstrated to be inadequate for prevention of sympathetic stimulation effect of rapid increase in desflurane concentration from 1.0 to 1.5 MAC during induction of anesthesia [22]. Therefore,

remifentanil continuous infusion scheme used in this investigation would be insufficient to effectively prevent sympathetic stimulation effect of desflurane. Hemodynamic variations, demonstrated in previous investigations with higher inspiratory concentration of desflurane and higher target concentration of remifentanil using TCI, were shown to be similar to that demonstrated in this investigation; initial increases and subsequent decreases in HR, and gradual decreases in arterial blood pressure. In fact, with relatively lower concentration of remifentanil concentration, hemodynamic variations to increases in desflurane concentration and tracheal intubation were well controlled in this investigation, maintaining hemodynamic changes within 20 % of baseline value. However, patients in D20 were demonstrated to have hemodynamic variations beyond 20 % of baseline value, especially in HR. As the purpose of this investigation was to compare age-dependent difference in hemodynamic responses to increases in desflurane concentration among age subgroups, the portion of younger patients might be relatively higher than those in previous investigations. Resultantly, the changes in HR might be shown to be exaggerated in this investigation.

Limitations of this investigation were as follows; first, remifentanil was given with manual continuous infusion scheme, not with TCI using pharmacokinetic model to ensure age- and weight-based effect-site concentration, enabling precise and fast adjustment. However, we designed the protocol for this investigation with the emphasis to monitor hemodynamic responses to induction of anesthesia and endotracheal intubation using desflurane, which was done in an ordinary setting of general operating theater. So, use of sophisticated device other than standardized monitoring equipment was intentionally excluded. Second, this investigation was only observational to find difference in hemodynamic responses to inhalation anesthetics. So, further investigation to evaluate a certain method of intervention to mitigate adverse hemodynamic effect of inhalational anesthetics would be necessarily required in the future. Last, in spite of thorough preoperative evaluation, more patients than expected

were excluded from final analysis due to unpredicted airway abnormalities, which resulted in weakened statistical power of this investigation.

V. CONCLUSION

Compared to sevoflurane, 1 MAC of desflurane given for induction of anesthesia caused more elevations in HR, especially in younger patients. And, this might be related to baroreceptor reflex to desflurane-induced vasodilation because inhalation of 1 MAC desflurane did not induce hypertensive responses in all age subgroups. Manual infusion scheme of remifentanil 0.1 ㎍/㎏/min was not shown to be effective in mitigating tachycardia in younger patients, which reserved further investigations to find methods to mitigate adverse hemodynamic effects of inhalation anesthetics.

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ABSTRACT(IN KOREAN)

Propofol과 remifentanil을 이용한 마취 유도 시 Desflurane의 흡입농도 증가에 따라 나타날 수 있는 교감신경계 자극효과의 연령대별 발생빈도 비교 연구: 전향적 무작위배정 단일맹검 임상연구

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강 효 정

Desflurane 은 1990년대 임상 마취에 도입 된 이래로 마취 유도 시 MAC 1 이상으로 빠르게 투여할 때 빈맥 및 고혈압을 유발하는 교감 신경 자극 효과가 있는 것으로 알려졌다. 본 연구는 척추수술을 받는 성인환자를 대상으로 마취유도시 흡입마취제로 1 MAC(Minimal alveolar concentration) 농도의 desflurane 를 사용하여 이에 대한 혈역학적 반응을 1 MAC sevoflurane 이용시와 비교하였으며, 1 MAC의 desflurane 및 sevoflurane의 농도는 Mapleson이 제안한 연령에 따른 공식을 사용하여 계산하였다.

총 400명의 환자를 대상으로 전향적, 무작위배정, 단일맹검 임상연구로 Desflurane (D) 그룹 및 Sevoflurane (S) 그룹, 두 그룹 중 하나로 나누었으며, 두 그룹 모두 각각 연령대별로 20대, 30대, 40대, 50대의 하위군으로 나뉘었다. (각각 D20, D30, D40, D50 및 S20, S30, S40, S50). 측정된 값들에 대한 통계분석은 우선

desflurane과 sevoflurane 두 군 사이의 비교를 시행하였고, 이어서 각 군 내에서 연령에 따른 하위군 사이의 비교를 시행하였다.

마취유도를 시작하기 전에 remifentanil 0.1 ㎍/㎏/min 투여를 시작하고, 혈역학적 지수들(심박수, 수축기, 이완기 및 평균 동맥압)과 말초산소포화도 및 BIS(Bispectral index)를 측정하여 기준값으로 사용한다. Propofol 1.0 ㎎/㎏를 약 30초에 걸쳐 천천히 정주하고, 의식 소실시까지 10초 마다 propofol 10 ㎎을 정주하여 마취유도를 시행한다. 이후 안면 마스크를 통해 흡입마취제인 desflurane 과 sevoflurane 를 미리 Mapleson WW이 제안한 연령에 따른 공식을 이용하여 산출된 1 MAC에 해당하는 농도로 각각 산소 및 공기 (최소유량 5L/min)와 투여하며, 5분 동안 1분 마다 혈역학적 지수들과 말초산소포화도 및 BIS를 측정, 기록한다. 근이완 유도를 위해 rocuronium 0.6 ㎎/㎏을 투여하고 약 4분 뒤에 기관내삽관을 시행하며, 기계환기를 시행하면서 혈역학적 지수들과 말초산소포화도 및 BIS 를 5분 동안 1분 간격으로 측정한다.

Desflurane (D) 군과 Sevoflurane (S) 군, 두 군 간의 비교에서, 마취 유도 후, 심박수은 D 군에서 증가하는 것으로 나타났으며, S 군에서는 감소하였다.($p<0.01$, 2분 제외). 기관 내 삽관 후 심박수는 두 군 모두에서 상승한 것으로 나타났으나 D 군에서 유의하게 더 많이 상승 하였다 ($p<0.01$, 1분 제외). 혈압은 일반적으로 두 군 모두에서 마취유도 후와 삽관 후에 감소하는 것으로 나타났으나, 마취유도 후에는 S 군에서 유의하게 더 감소했다. ($p<0.05$, 2분 제외). 각 군 내의 비교에서 D 군에서

심박수는 30세 이상의 환자에서 지속적으로 상승했으나, 20대의 환자에서는 기준치에서 감소한 것으로 나타났다. 기관내 삽관 후, 상승 된 심박수은 모든 군에서 유지되는 것으로 나타났으나, 삽관 3,4,5분 후 심박수는 D40과 D50에서 D20에 비해 유의하게 적게 상승하였다.($p<0.05$, D40에서 2분 제외). S 군에서 마취 유도 후 심박수의 변화는 연령 하위군 간 유의한 차이가 없었다.

Sevoflurane과 비교하여, 1 MAC 농도의 desflurane를 이용한 마취유도에서 특히 젊은 환자에서 심박수 상승을 유발하였다. 또한, 이는 모든 연령대에서 나타나지 않았으므로 압력수용체 반응으로 인해 발생하는 desflurane 유도 혈관확장과 관련이 있을 것으로 생각한다. 이러한 흡입마취제의 혈역학적 역효과를 상쇄시키는 방법을 찾기 위한 추가적인 연구가 필요하다.

핵심되는 말 : 교감신경계 자극 효과, desflurane, 연령대별, sevoflurane, remifentanil