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Effects of Rapid Increases of Desflurane and Sevoflurane to Concentrations of 1.5 MAC on Systemic Vascular Resistance and Catecholamine Response during Cardiopulmonary Bypass

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Background: **Airway irritation was hypothesized to trigger the transient cardiovascular stimulation associated with desflurane. The authors administered desflurane during cardiopulmonary bypass (CPB), thus avoiding airway contact, and compared the effects of rapid increases of desflurane to 1.5 MAC on systemic vascular resistance index (SVRI) and catecholamine response to those of 1.5 MAC sevoflurane.**

Methods: **Forty-eight patients, undergoing elective coronary bypass surgery, were randomly allocated to receive either desflurane or sevoflurane during hypothermic (32–33°C) nonpulsatile CPB at exhaust gas concentrations of 1.5 MAC for 15 min. SVRI was calculated at baseline, 1, 2, 3, 4, 5, 7, 9, 12, and 15 min after starting volatile anesthetics' delivery. Plasma catecholamine concentrations were determined in 12 desflurane-treated patients and 12 sevoflurane-treated patients at baseline, 5, and 15 min.**

Results: **The time-course of ΔSVRI, (changes in SVRI from baseline), from baseline to 5 min was significantly different between desflurane- and sevoflurane-treated patients, whereas there was no difference from 7 to 15 min. In the desflurane group, SVRI from 1 to 7 min remained unchanged to baseline level, thereafter declining to significantly lower values at 9, 12, and 15 min compared with values from 0 to 5 min, whereas sevoflurane produced an immediate and significant reduction in SVRI. With desflurane, catecholamine concentrations remained unchanged to baseline level at 5 and 15 min; with sevoflurane, they decreased with time.**

Conclusions: **The authors' results indicate that desflurane is associated with a different hemodynamic and catecholamine response compared with sevoflurane when administered into the oxygenator's gas supply line during CPB. (Key words: Anesthetics, volatile: desflurane; sevoflurane. Blood pressure: systemic vascular resistance. Catecholamines. Surgery, cardiovascular; cardiopulmonary bypass.)**

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DESFLURANE has been associated with transient cardiovascular stimulation when its concentration is increased rapidly to end-tidal concentrations exceeding approximately 1 MAC.[1-6] The mechanisms mediating the increases in sympathetic outflow are not yet fully understood. Because desflurane is a pungent agent, it has been suggested that airway irritation is involved in the marked activation of the neuroendocrine axis.[1,2,7] In contrast, sevoflurane, the least pungent of the volatile anesthetics, has not been found to cause neurocirculatory activation.[8] Strategies used to define the sites at which desflurane initiates its neurocirculatory activation revealed that activation of airway and systemic receptors may be involved.[9-12]

Application of volatile anesthetics into the oxygenator's gas supply line during cardiopulmonary bypass (CPB) avoids direct airway irritation by pungent agents.

Thus, we rapidly increased the exhaust gas concentration of desflurane and sevoflurane to 1.5 MAC during CPB and compared the effects on systemic vascular resistance (SVR), during the first 5 min, to assess early transient effects, and for another 10 min of steady state delivery of volatile anesthetics, and the catecholamine response, to further delineate the impact of airway irritation by desflurane.

Methods and Materials

After obtaining approval of the local Ethics Committee and written informed consent, 48 patients (37 men) scheduled for elective coronary artery bypass graft surgery were studied. All patients were aged 65 yr or older

(median, 68 yr; range, 65–74 yr). Patients were excluded if they had significant renal or hepatic impairment, peripheral vascular disease, or an ejection fraction of < 50%.

Patients were premedicated with oral clorazepate, 20–30 mg, on the evening before surgery and with clorazepate, 20 mg, approximately 1 h before surgery. All patients received their routine antianginal and antihypertensive medication up to and, except ACE inhibitors, including the morning of surgery.

Anesthesia was induced with intravenous sufentanil, 0.5 μg/kg, followed by etomidate until loss of consciousness. Neuromuscular block was obtained with pancuronium, 100 μg/kg. Before institution of CPB anesthesia was maintained with an infusion of propofol of 5 $mg \cdot kg^{-1} \cdot h^{-1}$, supplemented with sufentanil bolus doses up to 2 μg/kg, and pancuronium, 50 μg/kg. The last sufentanil bolus was administered approximately 10 min before CPB.

A standard CPB technique was used in all patients. Before aortic cannulation, patients were anticoagulated with heparin (375 U/kg). A two-stage cannula was used for drainage of venous blood from the right atrium. The bypass circuit consisted of a capillary membrane oxygenator (Quadrox, Jostra Medizintechnik, Hirlingen, Germany) and a nonpulsatile pump (Stöckert Instruments, Munich, Germany). The circuit was primed with a balanced crystalloid solution (1500 ml). A hardshell venous reservoir, open to air, was used. Nonpulsatile pump flow rates of 2.6 $l \cdot min^{-1} \cdot m^2 \pm 10\%$ were used and kept constant throughout the test sequence. Alpha-stat acid–base management was used during the entire bypass period. After application of the aortic cross-clamp and administration of cold crystalloid-based cardioplegic solution (Kardioplegische Perfusionslösung Fresenius, Bad Homburg, Germany), time was allowed for a stable level of perfusion pressure and mild hypothermia to develop (arterial and rectal temperature 32–33°C). These variables remained constant for approximately 10 min before initiating the test sequence. Baseline values were recorded at the end of the stabilization period. Thereafter, the delivery of volatile anesthetics was started *via* a vaporizer, inserted into the oxygenator's gas supply line, during a constant gas flow of 3 l/min. Propofol was stopped in all patients at the beginning of CPB, and no opioids were given throughout the study period while surgery continued with the surgeons performing the coronary anastomoses.

The 48 patients were randomized according to the information on 48 closed envelopes to receive either desflurane, (24 patients, 12 patients including catecholamine measurements), or sevoflurane, at inspired concentrations that produced an exhaust gas concentration of 1.5 MAC (desflurane, 7.8 vol%; sevoflurane, 2.3 vol%[13]) within 2 min. These exhaust gas concentrations were sustained for another 13 min during stable hypothermia. Anesthetic gas concentrations were measured with a Datex multiple gas analysis monitor (Capnomac Ultima, Hoyer, Bremen, Germany) next to the gas inlet port and at the gas outlet port of the oxygenator. The sampling flow rate was 200 ml/min.

Systemic arterial pressures, measured *via* a femoral artery cannula, were continuously measured throughout the procedure. Recordings were made of mean arterial pressure (MAP) 1, 2, 3, 4, 5, 7, 9, 12, and 15 min after starting volatile anesthetic delivery. Systemic vascular resistance (SVR) was calculated from MAP (mmHg) and pump flow rate Q (l/min) as: SVR = (MAP / Q) 80 [$dyn \cdot s \cdot cm^{-5}$]. Systemic vascular resistance index (SVRI) was equal to the SVR multiplied by the body surface area.

Hypotension during CPB requiring intervention was defined as MAP < 35 mmHg. When intervention was necessary in any patient, *e.g.*, administration of exogenous catecholamines, all data from these patients were withdrawn from the study.

Arterial blood was sampled at baseline, 5, and 15 min after initiating administration of volatile anesthetics to measure catecholamine concentrations in 12 desflurane-treated patients and in 12 sevoflurane-treated patients. Blood samples were immediately placed in wet ice and separated and frozen at −70°C until thawed for analysis. Plasma norepinephrine and epinephrine concentrations were determined by high performance liquid chromatography (HPLC) and electrochemical detection using a commercially available kit (Recipe, Munich, Germany). The intra- to interassay variation at physiologic levels (300 pg/ml norepinephrine, 30 pg/ml epinephrine) was 4.2/9.2% for norepinephrine and 19/11% for epinephrine. The limit of quantification was 10 pg/ml for both catecholamines when 1 ml plasma was taken for analysis.

Hematocrit was determined at the beginning and at the end of the 15-min experimental period, during a period when no cardioplegic solution or any additional fluid was added to the bypass circuit.

Statistical Analysis

All data are presented as median (range) unless otherwise stated.

Nonparametric tests were used for statistical analysis because the Kolmogorov-Smirnov test showed that the data were not normally distributed. The Friedmann two-way analysis of variance, followed by the Wilcoxon and Wilcox test for repeated measurements, was used for within-group comparisons of SVRI and catecholamine measurements. To compare the time course of ΔSVRI from baseline to 5 min and from 7 to 15 min values between groups, we calculated the slopes of a line, fitted to the corresponding ΔSVRI data of each patient, by linear regression analysis.[14] The slopes were compared by the Mann-Whitney U-test. Changes of catecholamine concentrations were analyzed by the Mann-Whitney U-test for intergroup comparisons, and the level of significance was corrected according to Bonferroni to compensate for the effect of multiple comparisons. The chi-square test was applied to categorical data. $P < 0.05$ was considered significant.

Results

The groups were not significantly different for demographic data (sex, age, weight, body surface area), preoperative medication, and intraoperative medication before the study. Total doses of anesthetics before starting the test sequence did not differ between the groups (sufentanil, 2.5 μg/kg; propofol, 5 $mg \cdot kg^{-1} \cdot h^{-1}$; pancuronium, 150 μg/kg). The target value of 1.5 MAC (exhaust gas) was achieved in all patients within 2 min after initiating administration of desflurane or sevoflurane.

There were no significant differences between the groups in baseline SVRI measurements. SVRI at baseline was 1,783 $dyn \cdot s \cdot cm^{-5} \cdot m^2$ (1,273–2,016) in the desflurane group and 1,804 $dyn \cdot s \cdot cm^{-5} \cdot m^2$ (1,254–2,275) in the sevoflurane group. Intragroup comparisons (table 1) revealed that SVRI in the desflurane group initially remained unchanged to baseline level, thereafter declining to significantly lower values at 9, 12, and 15 min compared with values from 0 to 5 min. However, the addition of equi-MAC concentrations of sevoflurane to the fresh gas resulted in an immediate and significant reduction in SVRI (table 1). A perfusion pressure of 35 mmHg, defined as the lowest acceptable level, was reached in one patient receiving sevoflurane at 9 min and in one patient at 12 min. Two patients receiving desflurane, one of them from the group including catecholamine measurements, reached the limit of 35 mmHg at 12 min. All data from these four patients who did not complete the protocol were withdrawn from the study. Figure 1 presents the changes in SVRI from baseline values (ΔSVRI) in the 22 patients receiving desflurane and in the 22 patients receiving sevoflurane, during a constant pump-flow rate. The time-course of ΔSVRI from baseline to 5 min was found to differ significantly between desflurane- and sevoflurane-treated patients, whereas there was no statistically significant difference between the curves from 7 to 15 min.

Plasma norepinephrine concentrations, 383 pg/ml (113–841) in 11 desflurane-treated patients and 580 pg/ml (215–927) in 12 sevoflurane-treated patients, and epinephrine concentrations, 67 pg/ml (10–293) in the desflurane-treated patients, respectively, 55 pg/ml (24–279) in the sevoflurane-treated patients, did not differ between groups at baseline, although there were substantial differences in individual baseline values of norepinephrine and epinephrine. Individual changes in catecholamine concentrations are presented in figure 2 to delineate the relation between the initial catecholamine concentration and subsequent changes in the catecholamine concentration initiated by desflurane or sevoflurane. Changes in plasma norepinephrine concentrations from baseline values were significantly different in the desflurane-treated patients at 5 and 15 min (table 2) compared with the sevoflurane-treated patients, whereby concentrations in the desflurane group were higher compared with those of the sevoflurane group. Differences in changes in plasma epinephrine concentrations reached statistical significance between groups at 15 min. In patients receiving 1.5 MAC desflurane, there were no differences in norepinephrine and epinephrine concentrations with time. In sevoflurane-treated patients, norepinephrine concentrations at 15 min were significantly lower compared with baseline and 5 min values, and epinephrine concentrations at 15 min were lower compared with baseline. Exogenous catecholamines were not administered to any patient before CPB or during the test sequence.

Hematocrit did not change significantly in any patient during the 15-min study.

Discussion

It has been suggested that the pungent properties of desflurane may cause airway irritation, thus stimulating

Table 1. SVRI and MAP after Increases in Desflurane and Sevoflurane Concentrations to 1.5 MAC

	Desflurane		Sevoflurane	
Time (min)	SVRI (dyn·s·cm^{-5}·m^2)	MAP (mmHg)	SVRI (dyn·s·cm^{-5}·m^2)	MAP (mmHg)
0	1,738 (2,016, 1,273)	56 (72, 42)	1,804 (2,275, 1,254)	57 (72, 44)
1	1,603 (1,961, 1,245)	52 (73, 41)	1,606 (2,153, 1,226)	52 (70, 43)
2	1,564 (2,347, 1,273)	52 (78, 42)	1,542 (2,000, 1,197)	50 (65, 41)
3	1,591 (2,526, 1,330)	54 (90, 42)	1,465 (1,931, 1,189)†	48 (62, 39)
4	1,563 (2,666, 1,330)	51 (95, 41)	1,454 (1,931, 1,162)‡	47 (60, 38)
5	1,490 (2,722, 1,232)	50 (97, 42)	1,398 (1,862, 1,207)§	46 (57, 36)
7	1,460 (2,400, 1,184)	48 (84, 40)	1,362 (1,862, 1,030)§	45 (56, 36)
9	1,408 (1,730, 1,096)*	46 (61, 36)	1,332 (1,848, 1,076)¶	44 (56, 36)
12	1,366 (1,730, 1,105)*	45 (58, 36)	1,300 (1,848, 1,008)¶	43 (56, 36)
15	1,335 (1,641, 1,096)*	42 (55, 36)	1,274 (1,793, 990)**	41 (53, 35)

Values are median (range).

0 min = baseline value prior to initiating volatile anesthetics' delivery.

* $P < 0.05$ *versus* 0 to 5 min within the desflurane group.

Comparisons within the sevoflurane group: † $P < 0.05$ *versus* 0 min; ‡ $P < 0.05$ *versus* 0 and 1 min; § $P < 0.05$ *versus* 0 to 2 min; ¶ $P < 0.05$ *versus* 0 to 3 min; ** $P < 0.05$ *versus* 0 to 5 min within the sevoflurane group.

a sympathetic response.[1,2,7,15] Application of volatile anesthetics into the oxygenator's gas supply line during CPB avoids direct airway irritation as a possible trigger of sympathetic stimulation. The bronchial and pleural circulation originating from systemic arteries constituting 1–3% of cardiac output may only bring negligible amounts of volatile anesthetics into contact with the trachea or lungs.[16]

Exhaust gas concentrations measured at the gas outlet port of the oxygenator correlate reasonably well with simultaneously obtained arterial blood partial pressures of volatile anesthetics using bubble oxygenators.[17] *In*

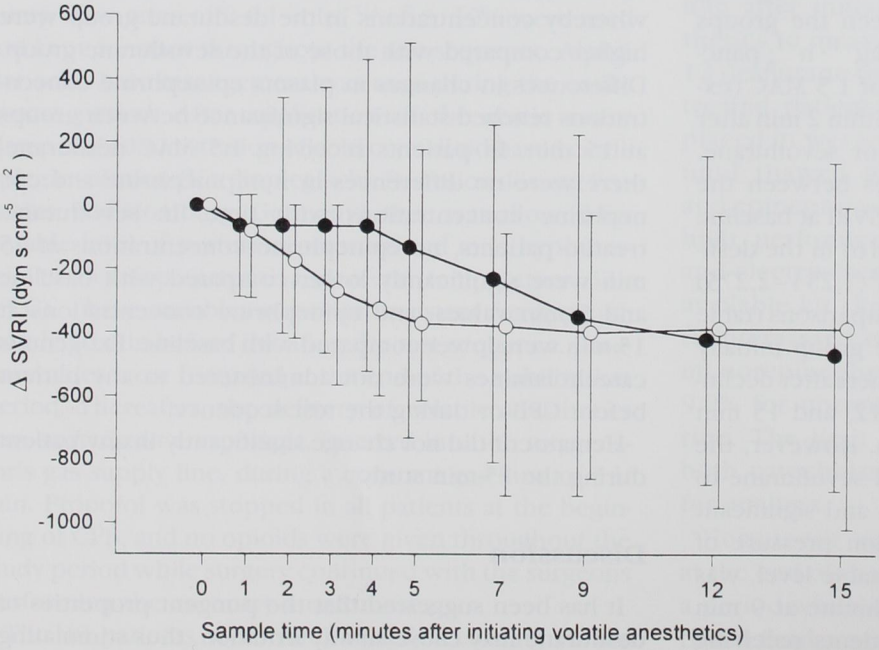

Fig. 1. Time-course of changes of SVRI (median, range) from baseline (0 min) in 22 desflurane-treated (●) and 22 sevoflurane-treated (○) patients. A significant difference in the time-course (slope analysis of curves) from 0 to 5 min was found. No difference between groups from 7 to 15 min was noted.

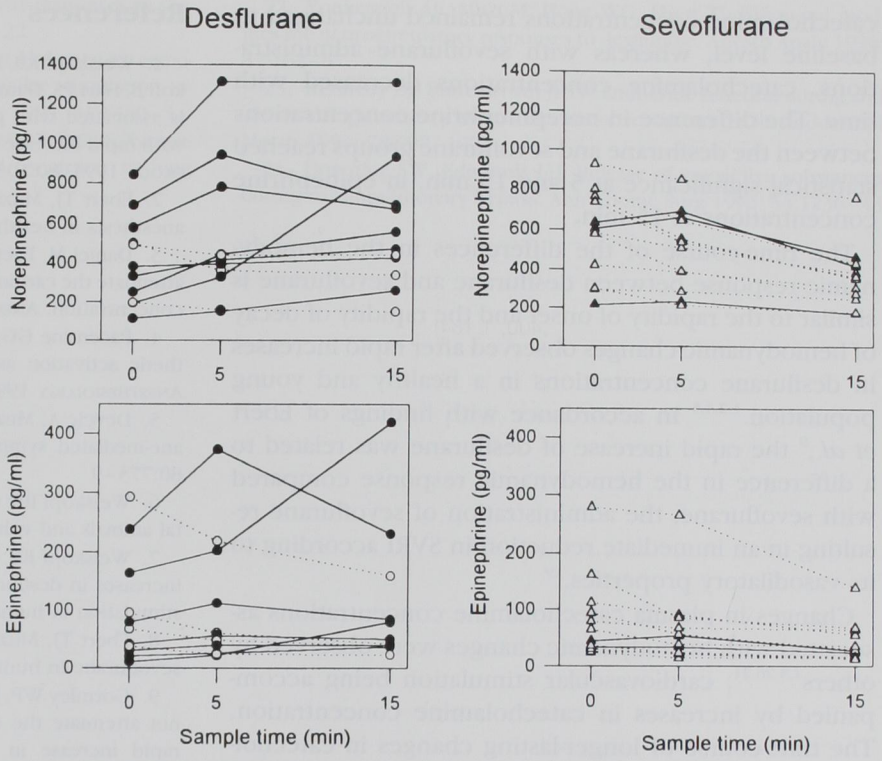

Fig. 2. Individual changes in plasma norepinephrine and epinephrine concentrations from baseline (0 min) in 11 desflurane-treated (*left*) and in 12 sevoflurane-treated patients (*right*), *solid lines* and *filled symbols* denote patients with an initial (from 0 to 5 min) increase in concentrations, whereas *dotted lines* and *white symbols* indicate no change or decrease in catecholamine concentrations.

vitro studies of volatile anesthetics' pharmacokinetics using membrane oxygenators revealed differences as a result of membrane oxygenators' design and composition. Even though exact data of the QUADROX we used (polypropylene in hollow-fiber form) are not available, an acceptable correlation between exhaust gas concentrations and arterial blood partial pressures is assumed.[18]

For the first 5 min after initiating the delivery of desflurane and sevoflurane into the oxygenator' gas supply line during CPB, the time-course of ΔSVRI was significantly different in the desflurane group compared with the sevoflurane group, whereas there was no difference from 7 to 15 min. In the desflurane group, SVRI initially remained unchanged to baseline level, thereafter declining to lower levels at 9, 12, and 15 min, whereas sevoflurane produced an immediate and significant reduction in SVRI.

This different hemodynamic response between desflurane and sevoflurane was associated with a difference in plasma norepinephrine and epinephrine concentrations in the desflurane group compared with the sevoflurane group. With desflurane administration, plasma

Table 2. Changes in Catecholamine Concentrations from Baseline

	Desflurane		Sevoflurane	
Time (min)	ΔNE (pg/ml)	ΔE (pg/ml)	ΔNE (pg/ml)	ΔE (pg/ml)
5	+83 (−138, +473)	+9 (−73, +134)	−74 (−210, +59)*	−12 (−77, +9)
15	+97 (−160, +742)	+6 (−132, +255)	−181 (−409, −44)*†	−20 (−140, −9)*‡

Values are median (range).

ΔNE (pg/ml) = changes in norepinephrine concentrations from baseline; ΔE (pg/ml) = changes in epinephrine concentrations from baseline.

* $P < 0.05$, desflurane *versus* sevoflurane.

Comparison within the sevoflurane group: † $P < 0.05$ *versus* baseline and 5 min; ‡ $P < 0.05$ *versus* baseline within the sevoflurane group.

catecholamine concentrations remained unchanged to baseline level, whereas with sevoflurane administrations, catecholamine concentrations decreased with time. The difference in norepinephrine concentrations between the desflurane and sevoflurane groups reached statistical significance at 5 and 15 min, in epinephrine concentrations at 15 min.

The time-course of the differences in the hemodynamic response between desflurane and sevoflurane is similar to the rapidity of onset and the rapidity of decay of hemodynamic changes observed after rapid increases in desflurane concentrations in a healthy and young population.[1,2,4,5] In accordance with findings of Ebert *et al.*,[8] the rapid increase of desflurane was related to a difference in the hemodynamic response compared with sevoflurane, the administration of sevoflurane resulting in an immediate reduction in SVRI according to its vasodilatory properties.[19]

Changes in plasma catecholamine concentrations associated with hemodynamic changes were observed by others[1,3,20,21]; cardiovascular stimulation being accompanied by increases in catecholamine concentration. The time-course of longer-lasting changes in catecholamine concentrations compared with peak cardiovascular changes is comparable with findings of Weiskopf[1] and Gormely.[9] The hormonal activation may be counteracted by direct, relaxing effects of desflurane.[6]

However, we neither observed cardiovascular stimulation, as would be indicated by significant increases in SVRI, nor significant increases in catecholamine concentrations in our patients aged more than 65 yr and who, in addition, had received opioids known to blunt the hemodynamic stimulation to desflurane,[20,22] during the conditions of desflurane application during hypothermic CPB.

CPB alone may affect SVRI and catecholamine concentrations depending on the degree of hypothermia, the composition of pump circuit priming fluids, the pulsatility of the perfusion, or the degree of hemodilution.[23,24] However, because all our patients were treated identically other than anesthetic agent selected, the observed differences between groups should be agent-related.

Because our data show significant differences in the hemodynamic and catecholamine response between desflurane and sevoflurane, when rapidly increased to concentrations of 1.5 MAC during mild hypothermic CPB and thus avoiding airway contact, these results strongly suggest a trigger besides airway irritation.

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