

Anesthesiology  
80:1035-1045, 1994  
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## ***Rapid Increase in Desflurane Concentration Is Associated with Greater Transient Cardiovascular Stimulation Than with Rapid Increase in Isoflurane Concentration in Humans***

Richard B. Weiskopf, M.D.,\* Mark A. Moore, B.A.,† Edmond I. Eger II, M.D.,‡ Mimi Noorani, B.A.,§  
Lawrence McKay, M.B., Ch.B.,|| Ben Chortkoff, M.D.,# Paul S. Hart, M.B., Ch.B.,\*\* Michael Damask, M.D.††

**Background:** Increases in desflurane and isoflurane concentrations can transiently increase arterial blood pressure or heart rate or both during induction of anesthesia. The current study tested the hypothesis that a rapid increase of desflurane concentration in humans increases sympathetic activity and hormonal variables and heart rate and arterial blood pressure more than does an equivalent increase in isoflurane concentration.

**Methods:** Twelve healthy male volunteers were assigned randomly to receive desflurane and on a separate occasion isoflurane. After induction of anesthesia with propofol 2 mg/kg, anesthesia was maintained at 0.55 MAC (desflurane, 4.0%; isoflurane 0.71% end-tidal) for 32 min. Mechanical ventilation maintained normocapnia throughout anesthesia. Mean arterial blood pressure and heart rate were recorded continuously, and arterial blood was sampled for

plasma catecholamine and vasopressin (AVP) concentrations, and plasma renin activity. Anesthetic concentration was increased rapidly to 1.66 MAC (desflurane, 12.0%; isoflurane 2.12% end-tidal), and maintained at this concentration for 32 min, and then rapidly decreased to and maintained at 0.55 MAC for an additional 32 min.

**Results:** Neither anesthetic produced sympathetic or cardiovascular stimulation during their initial rapid wash-in to 0.55 MAC. The rapid increase to 1.66 MAC increased mean arterial blood pressure, heart rate, and plasma epinephrine and norepinephrine concentrations, and plasma renin activity with both desflurane and isoflurane, the former usually producing a response of greater magnitude than the latter. Plasma AVP concentration increased with desflurane only. Increased mean arterial blood pressure returned to control in 4 min. Heart rate decreased 50% of the difference between its peak and the value at 32 min at 1.66 MAC in 2 min with desflurane and in 4 min with isoflurane but did not return to the value at 0.55 MAC with either anesthetic. With desflurane, plasma epinephrine and AVP concentrations decreased quickly from their peak values, remaining elevated for 8 min. Decrease of concentrations of desflurane and isoflurane from 1.66 MAC to 0.55 MAC rapidly decreased heart rate and increased mean arterial blood pressure with both anesthetics. Thirty-two minutes after return to 0.55 MAC, with both anesthetics, only heart rate remained increased relative to the values at 32 min of the initial period of 0.55 MAC anesthesia.

**Conclusions:** In healthy male volunteers, rapid increases of desflurane or isoflurane from 0.55 to 1.66 MAC increase sympathetic and renin-angiotensin system activity, and cause transient increases in arterial blood pressure and heart rate. Desflurane causes significantly greater increases than isoflurane, and also causes a transient increase in plasma AVP concentration. The temporal relationships suggest that the increased sympathetic activity increases mean arterial blood pressure and heart rate, with mean arterial blood pressure also increased by increased plasma AVP concentration, whereas the delayed, increased plasma renin activity is likely a response to the ensuing hypotension, or earlier inhibition by AVP, or both. (Key words: Anesthetics, volatile: desflurane; isoflurane. Hormones: renin-angiotensin system; vasopressin. Sympathetic nervous system: epinephrine; norepinephrine.)

\* Professor, Department of Anesthesia and Department of Physiology; Staff, Cardiovascular Research Institute; Consultant to Ohmeda, Inc., Liberty Corner, New Jersey.

† Medical Student.

‡ Professor and Vice Chair for Research, Department of Anesthesia; Consultant to Ohmeda, Inc., Liberty Corner, New Jersey.

§ Staff Research Associate, University of California, San Francisco.

|| Vice President for Drug Development, Pharmaceutical Products Division, Ohmeda, Inc., Liberty Corner, New Jersey.

# Assistant Professor, Department of Anesthesia.

\*\* Visiting Assistant Professor, Department of Anesthesia.

†† Director of Clinical Research and Development, Pharmaceutical Products Division, Ohmeda, Inc., Liberty Corner, New Jersey.

Received from the Department of Anesthesia and the Department of Physiology, and the Cardiovascular Research Institute, University of California, San Francisco, California. Accepted for publication January 18, 1994. Supported by Anaquest, Inc. and the Anesthesia Research Foundation. Presented in part at the annual meeting of the American Society of Anesthesiologists, Washington, DC, October 1, 1993.

Address reprint requests to Dr. Weiskopf: Department of Anesthesia, University of California, San Francisco, California 94143-0648.

THE initial clinical evaluation of desflurane provided reports of increases in heart rate and blood pressure during induction of anesthesia.<sup>1-4</sup>## In patients undergoing coronary artery bypass grafting, Helman *et al.* found that rapid increase of desflurane concentration increased heart rate and blood pressure.<sup>5</sup> These cardiovascular changes were not seen during steady-state anesthesia with desflurane in young healthy men.<sup>6</sup>

These studies did not have as their focus the prospective quantitative definition of the relationship between the increase in the concentration of desflurane and the resulting circulatory changes, nor did they quantitatively compare the effects of desflurane with those of isoflurane. Recently Ebert and Muzi, in a non-randomized study, reported that an increase in the vaporizer setting for desflurane, but not for isoflurane, from 1 to 1.5 MAC, increased mean arterial blood pressure and muscle sympathetic nerve activity.<sup>7</sup> However, the comparative aspects of this report were compromised by the failure to use comparable alveolar anesthetic concentrations and to apply equally rapid changes in those concentrations.<sup>8</sup> The current study tested the hypothesis that a rapid increase of desflurane concentration in humans increases sympathetic activity, heart rate and arterial blood pressure more than does an equivalent rapid equivalent increase in the concentration of isoflurane.

## Materials and Methods

We studied 12 healthy male volunteers after obtaining their informed consent and with approval of the protocol by the University of California, San Francisco Committee on Human Research. No volunteer had general anesthesia within 6 months of this study, medications within 7 days, alcohol for at least 2 days, or food or drink within 9 h of the study. Each was studied on two occasions, separated by 7-10 days. Each was assigned randomly to receive isoflurane on one occasion, and desflurane on the other. After skin infiltration with less than 1 ml 1% lidocaine, peripheral venous and radial arterial cannulae were inserted, before administration of any other drugs. Mean systemic arterial blood pressure (23XL transducer, Gould Statham),

calibrated with a mercury manometer before and after each study, and heart rate were recorded continuously by a digital polygraph (ES 2000, Gould). Awake values for mean arterial blood pressure and heart rate were accepted after at least 10 min of stability, at which time arterial blood was sampled for measurement of pH, oxygen tension, carbon dioxide tension (by standard electrodes), plasma catecholamines (collected in heparin, immediately placed in wet ice, separated and frozen at  $-70^{\circ}\text{C}$  until measured by high performance liquid chromatography), and vasopressin (AVP) concentrations (collected in ethylenediamine tetraacetate and measured by radioimmunoassay<sup>9</sup>), and plasma renin activity (PRA; collected in ethylenediamine tetraacetate and measured by radioimmunoassay<sup>10</sup>). Anesthesia was induced with intravenous propofol 2 mg/kg. One minute after induction of anesthesia, desflurane or isoflurane in oxygen was administered at delivered and inspired concentrations that rapidly produced and sustained an end-tidal concentration of 0.55 MAC (desflurane 4.0% and isoflurane 0.71%). Neuromuscular blockade provided by intravenous vecuronium 0.1 mg/kg, facilitated tracheal intubation. Mechanical ventilation of the volunteers' lungs maintained normocapnia, and surface warming with heated air maintained normothermia throughout the study. Anesthesia was maintained at 0.55 MAC for 32 min, at which time all measurements were repeated.

The alveolar anesthetic concentration was then increased rapidly (desflurane  $66 \pm 7$  s and isoflurane  $99 \pm 12$  s; mean  $\pm$  SE) to 1.66 MAC (desflurane, 12%; isoflurane, 2.12%), by temporarily increasing the background oxygen flow rate to approximately 10 L/min and the delivered anesthetic concentration to 18% desflurane or 5% isoflurane. This increased, stable end-tidal concentration was maintained for 32 min. Anesthetic concentration was measured continuously at the proximal orifice of the endotracheal tube by an infra-red spectrometer (Datex Ultima, Helsinki), which was calibrated before and after each study by secondary (tank) standards, which in turn were calibrated against primary (volumetric) standards using gas chromatography. The end-tidal sample was protected by the addition of a 20-ml deadspace. To determine the timing of events after the abrupt increase in anesthetic concentration, we defined "time zero" ( $t_0$ ) as the time of inspiration of the first breath that contained an anesthetic concentration greater than that during 0.55 MAC steady-state

## Rampil IJ Zwass M, Lockhart S, Eger EI II, Johnson BH, Yasuda N, Weiskopf RB: Hemodynamics of 1653 in patients. *ANESTHESIOLOGY* 71:A25, 1989.

anesthesia. We defined the beginning of increased heart rate or mean arterial blood pressure ( $t_1$ ) as the time the value of the variable increased to at least 1.10 times its value at  $t_0$ . The duration of increase of mean arterial blood pressure was defined as the interval between  $t_1$  and the time when the value decreased to its value at  $t_0$ . Because heart rate did not return to its value at  $t_0$ , to obtain a measure of its rate of decrease, we determined the interval from the peak value to the time heart rate decreased by 50% from its peak value toward the value at 32 min at 1.66 MAC.

Arterial blood was sampled 1, 2, 4, 8, 16, 24, and 32 min after reaching the desired end-tidal anesthetic concentration. If cardiovascular stimulation was observed, an additional blood sample was obtained at or close to the time of the occurrence of peak arterial blood pressure.

After 32 min at 1.66 MAC, end-tidal anesthetic concentration was rapidly reduced to 0.55 MAC. All cardiovascular measurements were repeated at 1, 2, 4, 8, 16, and 32 min, and blood was sampled for hormonal analyses at 2, 8, and 32 min after again reaching 0.55 MAC.

#### *Analysis of Hormones*

Plasma for analyses of epinephrine, norepinephrine, and AVP concentrations and PRA were stored at  $-70^\circ\text{C}$  until thawed for analysis. Plasma catecholamine concentrations were determined by high performance liquid chromatography, with limits of detection of 14 pg/ml for epinephrine and 25 pg/ml for norepinephrine. Coefficients of variation were epinephrine 2% and norepinephrine 1% within runs and epinephrine 7% and norepinephrine 3% between runs. AVP<sup>9</sup> and PRA<sup>10</sup> were measured by radioimmunoassays, with limits of detection of 0.7 pg/ml and 0.5 ng AI  $\cdot$  ml<sup>-1</sup>  $\cdot$  2 h<sup>-1</sup>, respectively. Sample values less than the limit of detection were considered as having a concentration just below the limit of detection.

#### *Statistical Analysis*

Data within and between anesthetic groups were compared by Fisher's exact probability test, by analysis of variance with repeated measures and the Newman-Keuls method of multiple comparisons, or by paired  $t$  test with Bonferroni's correction. Statistical significance was accepted at  $P < 0.05$ .

## Results

The volunteers were  $23.8 \pm 1.1$  (mean  $\pm$  SE) yr old; weighed  $75.9 \pm 3.8$  kg; were  $178.5 \pm 2.5$  cm tall; and had a body surface area of  $1.89 \pm 0.07$  m<sup>2</sup>. Variables measured before anesthesia on the 2 days did not differ (table 1). Arterial pH and carbon dioxide tension did not change during anesthesia with either anesthetic, and did not differ between the two anesthetics at any time. During anesthesia, arterial oxygen tension reflected the increased fraction of inspired oxygen and always exceeded 480 mmHg.

Induction of anesthesia with propofol increased heart rate (awake  $67 \pm 2$  to  $90 \pm 3$  beats/min after propofol, before desflurane administration,  $P < 0.001$ ; awake  $66 \pm 2$  to  $95 \pm 3$  after propofol, before isoflurane administration,  $P < 0.001$ ) (fig. 1). The end-tidal concentration reached at least 90% of the target value of 0.55 MAC (end-tidal) within 1.5 min after initiating administration of desflurane or isoflurane. Thirty seconds after the initiation of inhalation of desflurane and isoflurane heart rate decreased, to  $69 \pm 2$  and  $72 \pm 2$  beats/min, respectively, from the increased heart rate which had resulted from administration of propofol. Propofol also increased mean arterial blood pressure transiently ( $84 \pm 2$  to  $96 \pm 2$  mmHg before desflurane,  $P < 0.001$ ;  $87 \pm 2$  to  $99 \pm 3$  mmHg before isoflurane,  $P < 0.001$ ). The inhaled anesthetics were added 1 min after administration of propofol, after mean arterial blood pressure (but not heart rate) had returned to its value before propofol administration. Neither inhaled anesthetic altered mean arterial blood pressure during the 2.5 min of its administration, before laryngoscopy (fig. 1). Neither heart rate nor mean arterial blood pressure differed between volunteers given desflurane and those given isoflurane during the initial 2.5-min wash-in period before laryngoscopy and tracheal intubation. Laryngoscopy and tracheal intubation produced significant increases in heart rate (desflurane  $76 \pm 2$  to  $105 \pm 2$  beats/min,  $P < 0.001$ ; isoflurane  $76 \pm 2$  to  $102 \pm 2$  beats/min;  $P < 0.001$ ) and mean arterial blood pressure (desflurane  $74 \pm 3$  to  $118 \pm 6$  mmHg,  $P < 0.001$ ; isoflurane  $73 \pm 5$  to  $122 \pm 6$  mmHg,  $P < 0.001$ ) that did not differ between anesthetics.

Although 32 min of 0.55 MAC desflurane or isoflurane anesthesia did not alter heart rate or plasma norepinephrine concentration from awake values with either anesthetic (table 1), mean arterial blood pressure and plasma epinephrine concentration decreased with both

Table 1. Values at 0, 0.55, 1.66, and Return to 0.55 MAC

	Awake		32 Min at 0.55 MAC		Peak MAP at 1.66 MAC		32 Min at 1.66 MAC		32 Min at 0.55 MAC	
	Desflurane	Isoflurane	Desflurane	Isoflurane	Desflurane	Isoflurane	Desflurane	Isoflurane	Desflurane	Isoflurane
HR (beats/min)	67 ± 2	66 ± 2	62 ± 2	66 ± 2*	118 ± 4†	102 ± 5*†	82 ± 4§†	74 ± 3*†	70 ± 2**	72 ± 2**
MAP (mmHg)	81 ± 2	81 ± 2	64 ± 2†	64 ± 1†	117 ± 6†	84 ± 6*†	60 ± 4†	52 ± 2*§†	71 ± 3	68 ± 3
Epi (pg/ml)	42 ± 7	44 ± 12	17 ± 2†	13 ± 1†	268 ± 43†	14 ± 1*	30 ± 5†	16 ± 2*	18 ± 4	15 ± 5
Norepi (pg/ml)	160 ± 20	175 ± 30	194 ± 14	160 ± 17*	335 ± 42†	283 ± 51*†	520 ± 56§†	295 ± 21*§	195 ± 16	206 ± 28
PRA (ng A/ml/2 h)	1.8 ± 0.5	0.9 ± 0.2	8.3 ± 1.0†	7.4 ± 2.0†	9.7 ± 1.5	6.6 ± 1.6	16.9 ± 1.3§†	17.8 ± 2.8§†	12 ± 2	11 ± 2
AVP (pg/ml)	1.7 ± 0.2	1.7 ± 0.3	1.0 ± 0.2†	1.6 ± 0.3†	10.8 ± 2.9†	1.4 ± 0.2‡	2.4 ± 0.4‡†	1.5 ± 0.3	1.6 ± 0.2	2.3 ± 0.5

HR: heart rate; MAP: mean arterial blood pressure; Epi: plasma epinephrine concentration; Norepi: plasma norepinephrine concentration; PRA: plasma renin activity.

The "values at peak MAP at 1.66 MAC" differ from the "peak" values in the abstract in that the latter are the greatest values noted at any time at 1.66 MAC.

Data are mean ± SE; n = 12, except for plasma catecholamines, where n = 11.

\*  $P < 0.05$  between anesthetics at equivalent concentration.

†  $P < 0.05$  between awake and 0.55 MAC with same anesthetic.

‡  $P < 0.05$  between peak at 1.66 MAC and 0.55 MAC with same anesthetic.

§  $P < 0.05$  between 32 min at initial 0.55 MAC and 32 min at 1.66 MAC.

¶  $P < 0.05$  between peak at 1.66 MAC and 32 min at 1.66 MAC.

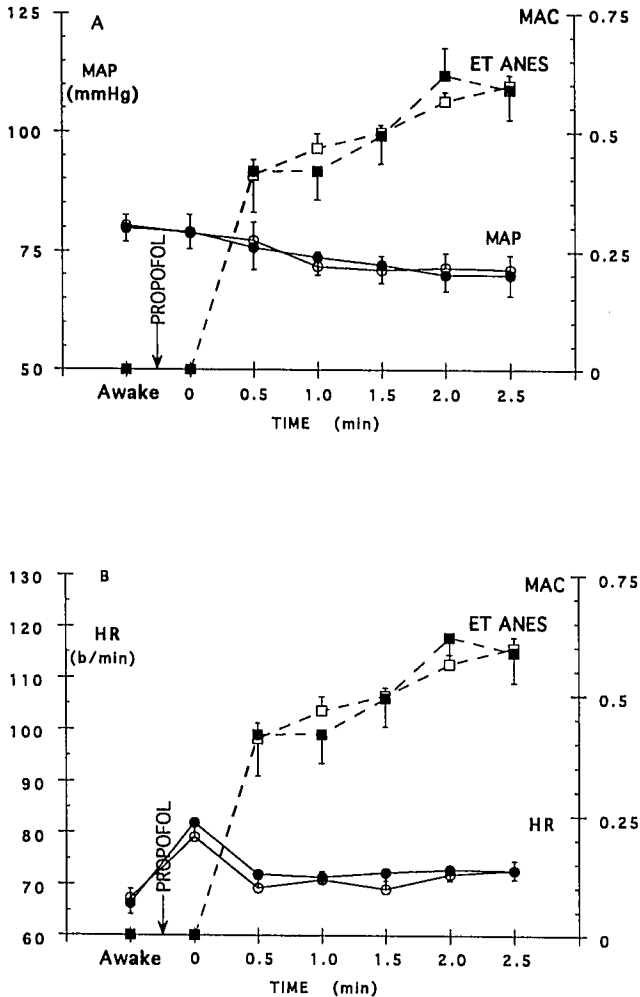
\*\*  $P < 0.05$  between 32 min at initial 0.55 MAC and 32 min at return to 0.55 MAC.

anesthetics, AVP decreased with desflurane only, and PRA increased with both anesthetics ( $P < 0.05$ ). At 0.55 MAC, heart rate (desflurane  $62 \pm 2$  and isoflurane  $66 \pm 2$  beats/min; mean ± SE,  $P < 0.05$ ) and plasma norepinephrine concentration (desflurane  $194 \pm 14$  and isoflurane  $160 \pm 14$ ;  $P < 0.05$ ) differed between the two anesthetics (table 1), but other measured variables did not (table 1).

Rapid increase of end-tidal anesthetic concentration from 0.55 MAC to 1.66 MAC (achieved with desflurane in  $66 \pm 7$  s and with isoflurane in  $99 \pm 12$  s;  $P < 0.005$ ) abruptly increased (time of onset: desflurane  $30 \pm 8$  s and isoflurane  $53 \pm 5$  s;  $P < 0.05$ ) mean arterial blood pressure (fig. 2) and heart rate (fig. 3) with both anesthetics. In response to the rapid increase in desflurane concentration, all volunteers had an increased mean arterial blood pressure and heart rate; all given a similarly rapid (albeit 33 s slower than with desflurane) increase of isoflurane concentration, had an increase in heart rate, but mean arterial blood pressure increased in only 8 of 12 volunteers (as defined by our prospective criterion of at least 1.1 times the value at  $t_0$ ; some of the others had lesser increases; incidence not different between anesthetics by Fisher's exact probability test,  $P > 0.1$ ). Although volunteers anesthetized with desflurane had an increased mean arterial blood pressure 1 and 2 min after reaching 1.66 MAC, the duration of increased mean arterial blood pressure was brief, returning to the mean arterial blood pressure at 0.55 MAC in  $256 \pm 63$  s and not differing from the 0.55 MAC value for the ensuing time at 1.66 MAC (fig. 2).

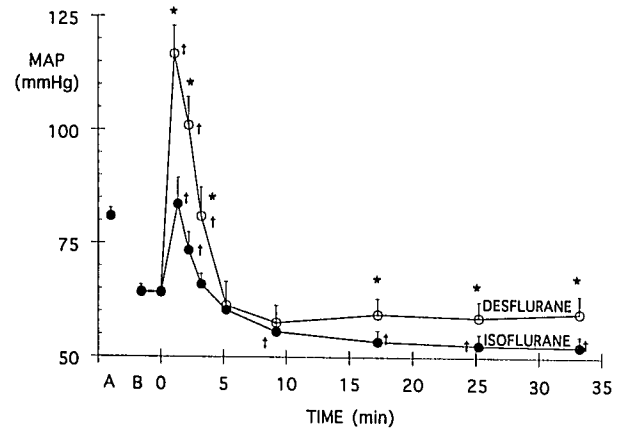
The rapid increase in end-tidal isoflurane concentration to 1.66 MAC also increased mean arterial blood pressure, but the increase in mean arterial blood pressure began later than after that occurring with the rapid increase in desflurane concentration. With isoflurane, mean arterial blood pressure reached its maximum value later than with desflurane (desflurane  $62 \pm 9$  s and isoflurane  $98 \pm 13$  s;  $P < 0.025$ ) but had a similar duration (desflurane  $256 \pm 63$  and isoflurane  $238 \pm 25$  s;  $P > 0.8$ ) (fig. 2). This approximately 30-s delay in cardiovascular response to isoflurane was similar to its approximately 30-s lag to reach 1.66 MAC, in comparison with desflurane. Mean arterial blood pressure was higher at 1 min of 1.66 MAC isoflurane, not different at 2 and 4 min, and lower at 8 through 32 min of 1.66 MAC isoflurane when compared to the mean arterial blood pressure at 0.55 MAC isoflurane. Peak mean arterial blood pressure and values at 1 and 2 min after reaching end-tidal 1.66 MAC were higher during

## CARDIOVASCULAR STIMULATION WITH DESFLURANE AND ISOFLURANE

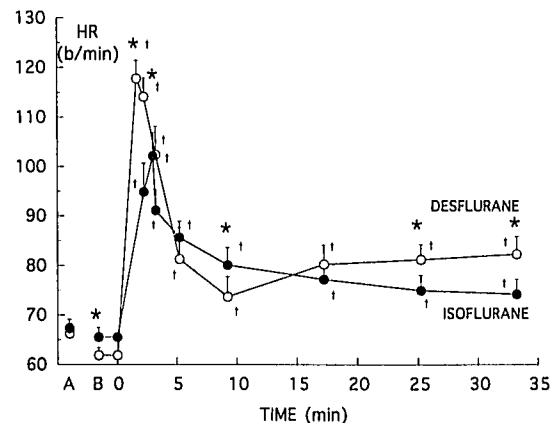


**Fig. 1.** In response to initial rapid, equivalent, wash-in of anesthetic concentration to 0.55 MAC after induction of anesthesia with 2 mg/kg propofol, 12 volunteers did not exhibit stimulation when given desflurane (open squares and open circles) or isoflurane (filled squares and filled circles). The two anesthetics similarly decreased mean arterial blood pressure (MAP) (A) and similarly decreased heart rate (HR) (B) from the increase caused by propofol. There were no differences between desflurane and isoflurane. Data are mean  $\pm$  SE. A = awake value; 0 = time of the initiation of wash-in of the inhaled anesthetics, 1 min after intravenous propofol 2 mg/kg. The times for "awake" and "propofol" are not drawn to scale. † $P < 0.05$  compared with value at 0.55 MAC of the same anesthetic.

desflurane anesthesia than during isoflurane anesthesia (fig. 2). Mean arterial blood pressure did not differ between the anesthetics 4 and 8 min after reaching 1.66 MAC, but after 16, 24, and 32 min mean arterial blood



**Fig. 2.** In response to a rapid increase in anesthetic concentration, 12 volunteers given desflurane (open circles) showed a greater increase in mean arterial blood pressure (MAP) than when given isoflurane (filled circles). Data are mean  $\pm$  SE. A = awake value; B = value at 32 min of 0.55 MAC; time "0" = time of first breath of increased anesthetic concentration ( $t_0$  in text). Timing of measurements was based on time after reaching the target end-tidal anesthetic concentration, which occurred approximately 1 min after time 0. † $P < 0.05$  compared with value at 0.55 MAC of the same anesthetic; \* $P < 0.05$  compared with isoflurane at the same time point.



**Fig. 3.** In response to a rapid increase in anesthetic concentration, 12 volunteers given desflurane (open circles) showed a greater increase in heart rate (HR) than when given isoflurane (filled circles). Data are mean  $\pm$  SE. A = awake value; B = value at 32 min of 0.55 MAC; time "0" = time of first breath of increased anesthetic concentration ( $t_0$  in text). Timing of measurements was based on time after reaching the target end-tidal anesthetic concentration, which occurred approximately 1 min after time 0. † $P < 0.05$  compared with value at 0.55 MAC of the same anesthetic; \* $P < 0.05$  compared with isoflurane at the same time point.

pressure was lower with isoflurane than with desflurane.

The rapid increase of anesthetic concentration from 0.55 MAC to 1.66 MAC also increased heart rate with both anesthetics (fig. 3), but did so later than it increased mean arterial blood pressure. Peak heart rate (at  $99 \pm 7$  s with desflurane and  $189 \pm 36$  s with isoflurane;  $P < 0.05$ ) and heart rate at all times at 1.66 MAC desflurane or isoflurane was higher than at 0.55 MAC ( $P < 0.05$ ). At the peak value, and 1, 24, and 32 min after reaching 1.66 MAC, heart rate was higher with desflurane than with the equivalent concentration of isoflurane. Values at 2, 4 and 16 min did not differ between the two anesthetics; at 8 min, heart rate was higher during isoflurane than during desflurane anesthesia. Heart rate decreased quickly from peak value, faster with desflurane than with isoflurane, decreasing 50% toward the 32 min value at 1.66 MAC in  $122 \pm 16$  s with desflurane and in  $225 \pm 43$  s with isoflurane ( $P < 0.05$  between anesthetics) and by 90% within 4 min with desflurane and within 8 min with isoflurane.

With both anesthetics, plasma catecholamine concentrations rapidly increased with the increase from 0.55 to 1.66 MAC (figs. 4 and 5). With desflurane, plasma epinephrine concentration reached its peak

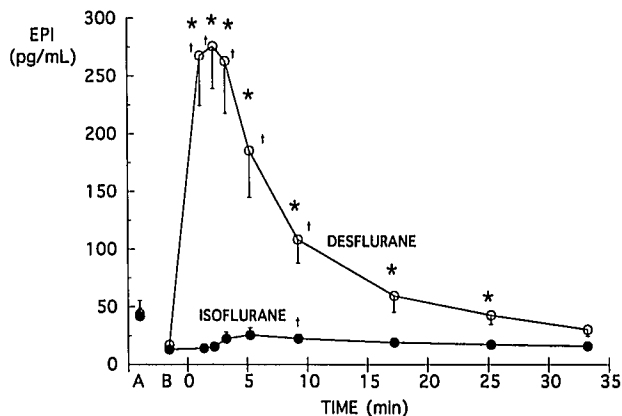


Fig. 4. In response to a rapid increase in anesthetic concentration, 12 volunteers given desflurane (open circles) showed a larger increase in plasma epinephrine concentration (Epi) than when given isoflurane (filled circles). Data are mean  $\pm$  SE. A = awake value; B = value at 32 min of 0.55 MAC; time 0 = time of first breath of increased anesthetic concentration ( $t_0$  in text). Timing of measurements was based on time after reaching the target end-tidal anesthetic concentration, which occurred approximately 1 min after time "0". † $P < 0.05$  compared with value at 0.55 MAC of the same anesthetic; \* $P < 0.05$  compared with isoflurane at the same time point.

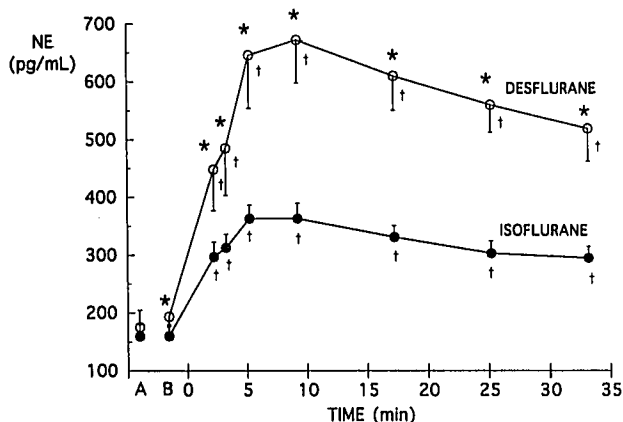


Fig. 5. In response to a rapid increase in anesthetic concentration, 12 volunteers given desflurane (open circles) showed a greater increase in plasma norepinephrine concentration (NE) than when given isoflurane (filled circles). The rate of increase of NE is less than the rate of increase of blood pressure, heart rate, or plasma epinephrine concentration (compare with figs. 1–3). Data are mean  $\pm$  SE. A = awake value; B = value at 32 min of 0.55 MAC; time "0" = time of first breath of increased anesthetic concentration, which occurred approximately 1 min after time 0. † $P < 0.05$  compared with value at 0.55 MAC of the same anesthetic; \* $P < 0.05$  compared with isoflurane at the same time point.

value 1 min after reaching 1.66 MAC, declining with a plasma half-life of 4–5 min, remaining increased for 8 min. With isoflurane, the small increase in plasma epinephrine concentration was significant only at 8 min (fig. 4). At 1.66 MAC, plasma epinephrine concentration was always greater with desflurane than with isoflurane ( $P < 0.05$ ), except at 32 min.

Plasma norepinephrine concentration increased quickly after rapid increase to 1.66 MAC with both anesthetics (fig. 5). The time-course of the increase was similar with the two anesthetics: plasma norepinephrine concentration did not decrease after increasing with either anesthetic ( $P > 0.05$ ) and was always greater with desflurane than with isoflurane ( $P < 0.05$ ).

Plasma AVP concentration increased rapidly with rapid increase of desflurane, but not isoflurane concentration (fig. 6). The time course was similar to that of epinephrine, with plasma AVP concentration remaining significantly greater than the value before increase of desflurane concentration and significantly different from the AVP concentration during isoflurane for 4 and 16 min, respectively, after the increase of desflurane concentration (fig. 6).

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PRA increased several minutes after the increases in arterial blood pressure and plasma catecholamine and AVP concentrations. At the time of initial increase of PRA, mean arterial blood pressure had decreased to or below the value at  $t_0$ . The increase of PRA was similar with both anesthetics, except at 8 min, when PRA was greater with isoflurane than desflurane ( $P < 0.05$ ; fig. 7). Although mean arterial blood pressure was lower with isoflurane than with desflurane at 16, 24 and 32 min of 1.66 MAC, PRA did not differ between the two anesthetics at these times (fig. 7).

Decrease of anesthetic concentration from 1.66 MAC to 0.55 MAC resulted in rapid return of all variables toward the values measured at 32 min of the initial period at 0.55 MAC. At 1 min of 0.55 MAC, mean arterial blood pressure increased, and plasma epinephrine and norepinephrine concentrations decreased to values not different from the values measured at 32 min of the initial period at 0.55 MAC. These values did not change during the succeeding 31 min. Mean arterial blood pressure and plasma epinephrine and AVP concentrations did not differ between anesthetics at any time at 0.55 MAC. With the decrease of anesthetic concentration, heart rate decreased with desflurane but not isoflurane. With desflurane, heart rate was higher at 2, 3, 4, and 8 min, but not 16, 24, or 32 min, and norepinephrine was higher with desflurane at 2 and 8 min, but not 32 min than with isoflurane. Heart rate with both anesthetics remained significantly higher than the value at 32 min of the first period of 0.55 MAC (table 1).

## Discussion

Desflurane, isoflurane, and other inhaled anesthetics can produce transient or sustained sympathetic and cardiovascular changes—effects related to anesthetic dose, to the rate of increase of anesthetic concentration, to a threshold concentration, or to a combination of these. After induction of anesthesia with propofol, desflurane and isoflurane do not produce stimulation during their initial wash-in to 0.55 MAC or during 32 min of steady-state 0.55 MAC, but both produce transient effects when their concentrations are increased rapidly to 1.66 MAC. Both produce similarly brief (approximately 4 min) increases in mean arterial blood pressure, greater with desflurane than with isoflurane. The increase in heart rate is substantial, but brief, and is sustained at a far smaller increase than the peak values.

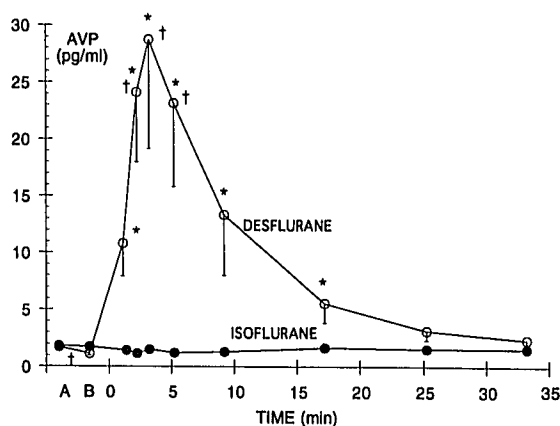


Fig. 6. In response to a rapid increase in anesthetic concentration, 12 volunteers showed an increase in plasma vasopressin (AVP) concentration when given desflurane (open circles) but not when given isoflurane (filled circles). Data are mean  $\pm$  SE. A = awake value; B = value at 32 min of 0.55 MAC; time "0" = time of first breath of increased anesthetic concentration ( $t_0$  in text). Timing of measurements was based on time after reaching the target end-tidal anesthetic concentration, which occurred approximately 1 min after time 0. † $P < 0.05$  compared with value at 0.55 MAC of the same anesthetic; \* $P < 0.05$  compared with isoflurane at the same time point.

The greater increases in heart rate and mean arterial blood pressure with desflurane than with isoflurane, were associated with an increased plasma AVP concentration, and with larger increases in plasma epinephrine and norepinephrine.

In addition to anecdotal reports of increased heart rate or arterial blood pressure during induction of anesthesia in adults, Zwass *et al.*<sup>2</sup> noted that mean arterial blood pressure and heart rate increased by more than 20% above baseline in 59% and 43%, respectively, of children during the first 4 min of induction of anesthesia with desflurane. Helman *et al.* found that rapid induction of anesthesia with desflurane after a dose of thiopental increased heart rate and mean arterial blood pressure in 99 adults having coronary artery bypass graft surgery.<sup>5</sup> The sympathetic stimulation we observed in our volunteers may be the cause of the increase in heart rate and mean arterial blood pressure they observed and may explain the myocardial ischemia in their patients, who were not given any opioid, capable of decreasing heart rate and mean arterial blood pressure during inhalation anesthesia.<sup>11</sup>

As do we in the current study, Ebert and Muzi<sup>7</sup> recently reported that a rapid increase in the concentration of desflurane increases heart rate and mean arterial

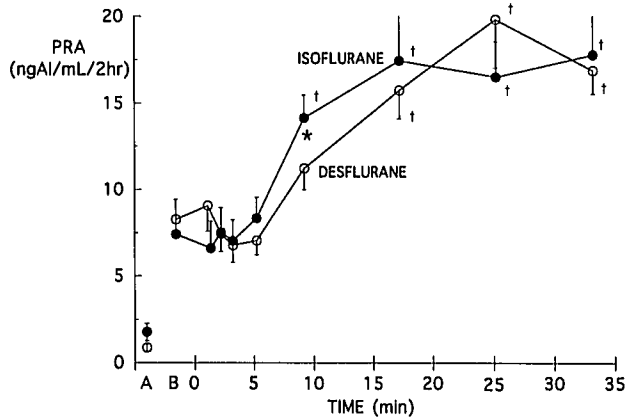


Fig. 7. In response to a rapid increase in anesthetic concentration, 12 volunteers showed similar increases in plasma renin activity (PRA) when given desflurane (open circles) or isoflurane (filled circles). The increase in PRA is delayed when compared to the increases in blood pressure, heart rate, and plasma catecholamine concentrations (compare with figs. 2–5). Data are mean  $\pm$  SE. A = awake value; B = value at 32 min of 0.55 MAC; time "0" = time of first breath of increased anesthetic concentration ( $t_0$  in text). Timing of measurements was based on time after reaching the target end-tidal anesthetic concentration, which occurred approximately 1 min after time 0. † $P < 0.05$  compared with value at 0.55 MAC of the same anesthetic; \* $P < 0.05$  compared with isoflurane at the same time point.

blood pressure. In contrast with our results, they found no increase in mean arterial blood pressure and a delayed (7.5 min) increase in heart rate after a rapid increase of isoflurane concentration. Again, in contrast to our findings, they also reported a sustained muscle sympathetic nerve stimulation with increasing desflurane concentration and no sympathetic stimulation with isoflurane. They reported a smaller increase of heart rate and mean arterial blood pressure with desflurane than we found. We believe that these differences result from differences in experimental design.<sup>8</sup> We used a randomized, cross-over study design in 12 volunteers receiving both anesthetics, rather than Ebert and Muzi's sequential, nonrandomized design of two different groups of 7 volunteers each. Ebert and Muzi controlled vaporizer setting, ( $F_D$ ), while we controlled end-tidal anesthetic concentration, thereby producing critical differences between the two studies. We increased end-tidal concentrations of the two anesthetics in a similar period of time (desflurane 67 s, isoflurane 99 s), but, in the study of Ebert and Muzi, given the more than 3-fold difference in the blood/gas solubilities of desflurane and isoflurane, the end-tidal concentration of iso-

flurane must have increased more gradually and to a lesser extent (in terms of MAC-multiple changes) than did the end-tidal concentration of desflurane. Ebert and Muzi did not report the end-tidal concentrations they obtained and, thus, we can but speculate on the magnitude and importance of this difference. The longer period of sympathetic stimulation provided by a progressive increase in anesthetic concentration may account for the difference in quantity and duration of cardiovascular changes between the two studies.<sup>12</sup> The intensity and duration of sympathetic stimulation caused by desflurane and isoflurane is likely related to either the rapidity of change of anesthetic concentration, or the ultimate concentration reached, or both. Both of these probably differed between desflurane and isoflurane in the study of Ebert and Muzi.

Our study differs from that of Ebert and Muzi<sup>7</sup> in another regard. Unlike Ebert and Muzi's volunteers, our volunteers did not experience any upper airway difficulty: the volunteers' lungs were easily ventilated, there was no evidence of laryngospasm, or perception of abnormal airway pressures. Despite our having administered a smaller dose of vecuronium, satisfactory conditions for tracheal intubation were obtained in all volunteers in 3–5 min, rather than the 13–15 min required by Ebert and Muzi. This difference may have resulted from the use by Ebert and Muzi of a different induction agent (thiopental) and the application of higher inspired concentrations of desflurane, or other undefined factors. Our highest inspired desflurane concentrations during induction of anesthesia equaled  $7.7 \pm 0.3\%$ , whereas they set the vaporizer to deliver 11%.

Desflurane is not unique in its ability to increase sympathetic activity. The greater myocardial contractility exhibited during desflurane than other inhaled anesthetics likely results from increased autonomic activity.<sup>13,14</sup> Yli-Hankala *et al.*,<sup>15</sup> Ishikawa *et al.*,<sup>16</sup> and we (in the current study) demonstrated that isoflurane has a similar property. Nitrous oxide also has mild sympathomimetic properties.<sup>17–19</sup> In healthy young volunteers, similar to those in this study, systemic vascular resistance was higher when desflurane was combined with 60%  $N_2O$  than it was when desflurane at equivalent MAC was given in oxygen.<sup>20</sup> Fluroxene, a halogenated ether which is no longer manufactured, produces sympathetic stimulation and increases cardiac output at deep levels of anesthesia.<sup>21,22</sup> Older anesthetics, such as cyclopropane<sup>23,24</sup> and diethyl ether<sup>25,26</sup> have similar effects.



Despite the use of isoflurane for more than a decade, only recently did Yli-Hankala *et al.* report that rapid increases in its concentration can cause cardiovascular stimulation and increased plasma catecholamine concentrations.<sup>15</sup> Although our findings of increased heart rate and systemic arterial blood pressure confirm those of Yli-Hankala *et al.*, our subjects appear to have had smaller increases in heart rate, and plasma epinephrine and norepinephrine concentrations than did theirs. Because the lungs take up circulating norepinephrine,<sup>27</sup> the lesser increase in plasma norepinephrine concentration in our volunteers than in theirs could be a result of our having sampled arterial blood, whereas Yli-Hankala *et al.*<sup>15</sup> sampled central venous blood. However, because the lungs do not take up appreciable quantities of circulating epinephrine, sampling site differences cannot account for our finding a slight increase in plasma epinephrine (maximum < 30 pg/ml) while they found concentrations exceeding 100 pg/ml.

The parallel increase and decrease of blood pressure and plasma epinephrine and AVP concentrations in our volunteers anesthetized with desflurane suggests that these circulating vasoactive substances contribute to the cardiovascular stimulation. The decrease in plasma epinephrine concentration from the peak value was rapid, with a plasma half-life of 4 to 5 min, close to that reported for conscious normal humans of similar age by Rosen *et al.*,<sup>28</sup> although longer than that reported for men by Persson *et al.*<sup>29</sup> This suggests that the rapid increase of desflurane concentration caused a brief release of epinephrine from the adrenals and that desflurane does not appear to inhibit epinephrine clearance.

Our volunteers in this study did not receive drugs, such as opioids, which might have blunted the sympathetic response.<sup>11</sup> We do not think that the propofol we administered interfered substantially with our assessment of stimulation by the inhaled anesthetics. Although propofol produces sympathetic inhibition in dogs<sup>30</sup> and decreases muscle sympathetic nerve activity in humans,<sup>31-33</sup> the decreased sympathetic activity is insufficient to block the effect of the stimulation of laryngoscopy and tracheal intubation,<sup>32</sup> and as seen in our volunteers. Our volunteers responded to laryngoscopy and tracheal intubation with increased heart rate and mean arterial blood pressure approximately 3-5 min after administration of propofol, with a magnitude similar to that which occurred after increasing anes-

thetic concentration, indicating that while sympathetic response could have been attenuated, it was not blocked. Furthermore, the redistribution and elimination that must have occurred in the 35 min before the increase of anesthetic concentration to 1.66 MAC must have dissipated most or all of the effect of propofol.

Whatever the mechanism of the sympathetic response, the rapidity of response is noteworthy, beginning within 30 s after the first breath of increased desflurane concentration and within 60 s after increased isoflurane concentration. Any proposed mechanism must account for this temporal relationship. The early initial and maximal cardiovascular and epinephrine responses followed the wash-in characteristics of the two anesthetics, suggesting that the afferent limb of the response is located either in the airways, lungs (note that both desflurane and isoflurane are airway irritants), or a very rapidly perfused tissue.

Circulating norepinephrine reflects excess norepinephrine taken up by the circulation rather than by nerve endings.<sup>29</sup> Thus, the increase in plasma norepinephrine concentration produced by desflurane and isoflurane (and the differences in the effects of the two anesthetics) may reflect altered norepinephrine reuptake at the synaptic cleft, decreased norepinephrine clearance, or increased sympathetic activity, although the site of activity cannot be delineated. Anesthetics can alter clearance of plasma norepinephrine,<sup>30</sup> and could have contributed to the continued increase of plasma norepinephrine concentration. The continuing increase in plasma norepinephrine concentration at a time when heart rate and mean arterial blood pressure were decreasing toward and below the value at 0.55 MAC, suggests that a generalized sympathetic response was not responsible alone for the observed cardiovascular changes.

Our findings may represent a combination of sympathetic stimulation and simultaneous blunting of sympathetic response. In similar volunteers, Yasuda *et al.* found that 1.66 MAC, but not 0.83 MAC or 1.24 MAC blunted or blocked the cardiovascular response to supra-maximal electrical stimulation of the ulnar nerve.<sup>34</sup> Thus, it is possible that the rapid increase of anesthetic concentration evoked a rapid sympathetic response, which was blunted or blocked when anesthetic concentration in the volunteers exceeded 1.24 MAC. Alternatively, our results could be explained by a stimulation of rapidly-adapting receptors in the air-

ways, resulting in only a brief period of afferent neural traffic and sympathetic response.<sup>35</sup>

The rapid increase in plasma AVP concentration in response to increased anesthetic concentration likely resulted from the same mechanism causing the increased plasma epinephrine concentration. Circulating catecholamines inhibit AVP secretion,<sup>36,37</sup> and thus, they were not a likely cause of the increased AVP. The delayed response of PRA, increasing only after mean arterial blood pressure had decreased to or below control values, suggests that it was a response to, rather than responsible for the initial increase in blood pressure. The delayed response could also have been a result of the increased AVP concentrations, which inhibit renin release.<sup>38-40</sup> When increased, PRA likely helped support mean arterial blood pressure. Sympathetic stimulation increases renin release,<sup>38-40</sup> and this could, in part explain the greater PRA associated with increased desflurane concentration than with isoflurane.

We intended to produce rather than avoid cardiovascular stimulation. Thus, we achieved high anesthetic concentrations by imposing a greater, more rapid step change in concentration than would be usual in clinical practice. A slower approach to an increase in concentration, or a lesser increase in concentration, or addition of drugs that attenuate sympathetic responses, each might attenuate or abolish the cardiovascular and endocrine response.

In summary, we speculate that the responses found in this study may be explained as follows. The rapid increase of concentration of desflurane, and to a lesser extent isoflurane, stimulates medullary centers, either directly, or indirectly via irritant receptors in the airway. The resulting heightened medullary activity transiently increases sympathetic outflow and stimulates the pituitary. Both of these outcomes are reflected in transient increases in plasma concentrations of epinephrine and AVP which, combined with the increased sympathetic outflow, increase heart rate and mean arterial blood pressure. The transient nature of these responses and the return toward, to, or below control values may result from an adaptation to the stimulus (at the level of airway receptors, at the medulla, or at both) combined with a direct depressant effect of the higher concentrations of the anesthetic. The delayed increases in PRA and plasma norepinephrine may be a response to the later reduction of mean arterial

blood pressure, itself a consequence of circulatory depression and peripheral vasodilation, or decreased inhibition of renin and norepinephrine release by AVP, or both.

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