Repulsive Rapid Increases in Desflurane Concentration Blunt Transient Cardiovascular Stimulation in Humans


Background: Rapid increases in desflurane concentrations above minimum alveolar concentration (MAC) can cause transient (2–4 min) circulatory changes, possibly from stimulation of rapidly-adapting airway receptors. We hypothesized that the initial increase in concentration would produce greater changes than subsequent increases.

Methods: Anesthesia was induced with propofol in nine volunteers (25 ± 1 yr old, mean ± SE) and maintained with 4% end-tidal desflurane for 32 min. We increased the desflurane to 8% (1.1 MAC) in 1 min, maintained this concentration for 10 min, and then decreased it to 4% for 32 min. We repeated this process twice. After 1 week, 5 subjects were treated similarly except that the second increase in concentration occurred in 5 min and (on a separate occasion) 75 min after the first. Four subjects received the initial increase after 75 rather than 32 min of anesthesia. In four we applied the repeated sequences in a background of 60% nitrous oxide. When a minimal cardiovascular response followed an increase of anesthetic concentration, a 60-s supramaximal 100-Hz tetanic stimulus was applied to an ulnar nerve percutaneously to test for sympathetic responsiveness.

Results: The initial increase in concentration increased heart rate (HR) from 57 ± 2 to a peak of 119 ± 7 beats/min (P < 0.05); mean arterial blood pressure (MAP) from 66 ± 3 to 119 ± 5 mmHg (P < 0.05); and plasma epinephrine by >10-fold (P < 0.05). The second and third increases in desflurane concentration increased HR and MAP by less than 20% of the initial increases, regardless of the timing of the later concentration increases. Responses to initial concentration increases after 75 min of anesthesia did not differ from those after 32 min. Increases in plasma epinephrine with the second and third increases in desflurane concentration were attenuated. Subjects who did not respond to the second or third increase in desflurane always responded to tetanic electrical stimulation with substantial increases in HR and MAP (P < 0.05). Addition of nitrous oxide did not change results except for a smaller increase in MAP (P < 0.05). Ulnar nerve stimulation increased HR and MAP but not epinephrine or norepinephrine concentrations.

Conclusions: An initial rapid increase in desflurane to 1.1 MAC produces much more stimulation than do subsequent increases, regardless of the presence of nitrous oxide. The decreased response is consistent with the hypothesis that stimulation of rapidly-adapting airway receptors produce the initial response. (Key words: Anesthetics, volatile; desflurane, Blood pressure; Heart; heart rate. Stimulation; repetitive. Sympathetic nervous system, catecholamines; epinephrine; norepinephrine.)

A rapid increase in the concentration of desflurane or isoflurane greater than 1 MAC can cause a transient increase in sympathetic activity,1–3 plasma epinephrine concentration,2,3 vasopressin secretion,2 and heart rate (HR) and arterial blood pressure.1–4 The mechanism(s) of these increases is (are) not known. The transient nature of the stimulation suggests the possibility of a rapidly adapting mechanism. We hypothesized that the afferent limb of the response may arise from inhaled anesthetic stimulation of rapidly-adapting receptors in the airway. This hypothesis suggests that repetitive increases of end-tidal desflurane to concentrations exceeding 1 MAC, should evoke a smaller sympathetic and cardiovascular response than those evoked by the initial increase of desflurane concentration. We tested this prediction in the current study.

Materials and Methods

We studied nine healthy male volunteers (age 25 ± 1 yr, weight 73 ± 4 kg, height 177 ± 2 cm; means ±
SE) after obtaining informed consent and the approval of the protocol by the University of California, San Francisco Committee on Human Research. No volunteer had undergone general anesthesia within 6 months of this study or had taken medications within 7 days, alcohol for at least 2 days, or food or drink within 9 h of the study.

After skin infiltration with less than 1 ml 1% lidocaine, peripheral venous and radial arterial cannulae were inserted, before administration of any other drugs, on the 1st study day. On subsequent study days, the arterial cannulae were inserted after induction of anesthesia. Mean systemic arterial blood pressure (MAP) (transducer calibrated with a mercury manometer before and after each study; 23XL, Gould Statham, Oxnard, CA) and HR were recorded continuously by a digital polygraph (ES 2000, Gould, Cleveland, OH). Awake values for MAP and HR 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), and plasma catecholamines (collected in heparin, immediately placed in wet ice, separated, and frozen at −70°C until measured by high-performance liquid chromatography).

One minute after induction of anesthesia with 2 mg/kg intravenous propofol, desflurane in oxygen was administered to produce and sustain an end-tidal concentration of 0.55 MAC (4.0%). The trachea was intubated after intravenous administration of vecuronium 0.1 mg/kg. Additional intravenous vecuronium, 0.02 mg/kg, was administered before increasing the desflurane concentration (described below) when four 2-Hz stimuli produced three or four twitches. Anesthetic concentration was measured continuously at the proximal orifice of the tracheal tube by an infrared spectrometer (Datem Ultima, Helsinki, Finland). A 20-ml dead space was inserted to assure accurate sampling of end-tidal gas. We calibrated the spectrometer before and after each study by secondary (tank) standards, which in turn were calibrated against primary (volumetric) standards by gas chromatography.

Mechanical ventilation of the volunteers’ lungs maintained normocapnia, and surface warming with heated air maintained normothermia throughout the study. Study days for each volunteer were separated by at least 1 week.

**Experimental Sequences**

Each volunteer was anesthetized four or five times, using four different experimental sequences which tested whether repetitive increases of desflurane concentration attenuated cardiovascular and sympathetic responses.

**Sequence 1: Effect of Repetitive Increases at 32-Minute Intervals (Nine Volunteers).** Desflurane anesthesia was maintained at 0.55 MAC for 32 min, at which time all measurements were repeated. We then increased the end-tidal desflurane concentration rapidly (within 1 min) to 1.1 MAC (8%) and maintained this concentration for 10 min.

Arterial blood was sampled 1, 2, 4, and 8, min after reaching 1.1 MAC. After 10 min at 1.1 MAC, end-tidal anesthetic concentration was rapidly reduced to 0.55 MAC. At 32 min after return to 0.55 MAC, all cardiovascular measurements were repeated and blood was sampled for analysis of catecholamine concentrations, and the end-tidal concentration was, again, increased to 1.1 MAC, maintained for 10 min, then decreased to 0.55 MAC, maintained for 32 min, and then, for a third time, increased to 1.1 MAC, and maintained for 10 min. Measurements were repeated, as before, with each of these cycles.

**Sequence 2: Effect of Interval Length Between Initial and Second Increase of Desflurane Concentration (Five Volunteers, Selected Randomly).** Desflurane anesthesia was maintained at 0.55 MAC for 32 min, at which time all measurements were repeated. End-tidal concentration of desflurane was increased to 1.1 MAC, as above, and maintained for 10 min, measurements repeated, and desflurane concentration then decreased to 0.55 MAC. After 10 or 75 min (randomly assigned), cardiovascular measurements were repeated and, as before, desflurane concentration was increased to 1.1 MAC, and maintained for 10 min. All procedures were repeated, at least 1 week later, except that the interval between the first and second increase of desflurane concentration (10 or 75 min) was the one not used previously.

**Sequence 3: Effect of Duration of Anesthesia.** To control for duration of anesthesia, four of the volunteers (randomly selected) were anesthetized another time, at least 1 week later. All procedures were similar except that desflurane concentration was increased only once, at a time equivalent to that of the second increase of desflurane in experimental sequence 1 (75 min).

**Sequence 4: Effect of Background of 60% Nitrous Oxide.** The first two steps of the first sequence were repeated in a background of 60% nitrous oxide, in four volunteers.
When an increase of desflurane concentration increased HR or MAP less than 10%, to test for sympathetic responsiveness, we applied a percutaneous supramaximal 60-s 100-Hz tetanic stimulus to the volunteer's ulnar nerve. Blood for measurement of plasma catecholamine concentrations was sampled 1 min before and after the electrical stimulus.

**Catecholamine Analyses**

Plasma for analysis of epinephrine and norepinephrine concentrations were stored at −70°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 within trials were epinephrine 2% and norepinephrine 1% and between trials were epinephrine 7% and norepinephrine 3%. Sample values less than the limit of detection were considered as having a concentration just below the limit of detection.

**Statistical Analyses**

**Sequence 1.** Data among the three successive increases of desflurane concentration were compared by analysis of variance with repeated measures and the Newman-Keuls method of multiple comparisons or by paired $t$ test with Bonferroni’s correction.

**Sequence 2.** Data from the second increases of desflurane concentration (10, 32, or 75 min; the 32 minute data are from sequence 1) were compared by analysis of variance with repeated measures and Newman-Keuls method of multiple comparisons, or by paired $t$ test with Bonferroni correction.

**Sequence 3.** Data from the initial increase of desflurane concentration after 75 min was compared with data from the initial increase of desflurane concentration after 32 min (sequence 1) by analysis of variance with repeated measures and Newman-Keuls method of multiple comparisons, or by paired $t$ test with Bonferroni correction.

**Sequence 4.** Using paired $t$ tests, data from the initial increase and second increase of desflurane concentration were compared with data for comparable increases from sequence 1.

When data from sequences 2, 3, or 4 were compared with data from sequence 1, only the data from those volunteers participating in both sequences was used. In all instances statistical significance was accepted at $P < 0.05$. Data are presented as means ± SE.

**Results**

Arterial carbon dioxide tension and pH throughout all experimental sequences did not differ from awake values (39.8 ± 0.7 mmHg and 7.404 ± 0.07, respectively). Arterial oxygen tension during anesthesia was always greater than 500 mmHg, except when nitrous oxide was included in the background gas, in which case arterial oxygen tension was not less than 150 mmHg.

**Sequence 1**

All volunteers responded to the initial increase of desflurane with increases in HR, MAP, and plasma catecholamine concentrations (fig. 1). The second and third rapid increases of desflurane concentration provided markedly attenuated increases of HR, MAP, and plasma catecholamine concentrations compared to the initial increase ($P < 0.05$; fig. 1). Results for the second and third increases did not differ from each other ($P > 0.05$). As a percentage of the initial increase, the second and third increase of desflurane concentration increased MAP by 16 ± 6% and by 2 ± 7%, HR by 21 ± 6% and by 18 ± 9%, plasma epinephrine concentration by 12 ± 6% and by 4 ± 4%, and plasma norepinephrine by 72 ± 13% and by 58 ± 11%, respectively (fig. 2). The third increase of desflurane did not cause significant changes in any measured variable at the time of maximal stimulation. Five of the nine volunteers had no increases in HR, and seven of the nine had no increase in MAP, whereas five of nine did not have an increase in plasma epinephrine concentration, and in all volunteers plasma norepinephrine concentration increased after the second and third increases of desflurane concentration.

**Sequence 2**

Data at 32 min of 0.55 MAC desflurane and during the initial increase on the 2 experimental days did not differ from the data at similar times of sequence 1 or from each other. Compared with the effect of the initial increase, increases of desflurane concentration 10 and 75 min after the initial increase of desflurane concentration attenuated the increases of HR, MAP, and plasma catecholamine concentrations ($P < 0.05$; fig. 3), but did not differ from each other ($P > 0.05$). When the second increase of desflurane followed the first by 10 min, the change in MAP was $−1% ± 2%$, HR $7% ± 2%$, and plasma epinephrine concentration $0% ± 0%$ of the change after the initial increase of desflurane concen-

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plasma epinephrine and norepinephrine concentrations did not differ from those after the initial desflurane concentration increase of sequence 1 or sequence 2 (fig. 5).

**Sequence 4**

When the first increase of desflurane concentration of sequence 1 was accomplished in a background of steady-state 60% nitrous oxide, the response was similar to that when the background gas was oxygen, except for a smaller increase in MAP (51 ± 4 vs. 35 ± 12 mmHg; P < 0.02). In the presence of 60% nitrous oxide, the response to subsequent desflurane increase was attenuated: there were no significant changes in HR or plasma epinephrine concentration, and MAP decreased, rather than increased (fig. 6).

Supramaximal tetanic stimulation of the ulnar nerve increased HR (before stimulation 61 ± 2 to after stimulation 88 ± 3 beats/min; P < 0.0001), and MAP (before stimulation 71 ± 2 to after stimulation 88 ± 3 mmHg; P < 0.0001) but not plasma concentrations of epinephrine (before stimulation 28 ± 5 to after stimulation 25 ± 6 pg/ml; P > 0.05) or norepinephrine (before stimulation 214 ± 13 to after stimulation 215 ± 26 pg/ml; P > 0.05) when rapidly increased desflurane concentration did not increase HR or MAP.

In summary, an initial rapid increase of the desflurane concentration to 1.1 MAC produces greater cardiovas-
REPEATED INCREASES OF DESFLURANE BLUNT STIMULATION

Fig. 3. Second increase of desflurane concentration 10, 32, or 75 min after the first increase resulted in similarly attenuated responses of mean arterial blood pressure (MAP), heart rate (HR), and plasma epinephrine concentration (data not shown). Data are means ± SE. † P < 0.05 versus initial response.

Discussion

The results of the current study confirm that a rapid increase in the concentration of desflurane\textsuperscript{1-4} or isoflurane\textsuperscript{2,5,6} to concentrations greater than 1 MAC elicits a transient sympathetic response with attendant increases in HR, MAP, and circulating catecholamine concentrations. The increases in MAP, HR, and plasma epinephrine concentration found in our volunteers in response to an increase in end-tidal desflurane from 4% to 8% equaled that of similar volunteers subjected to an increase from 4% to 12%,\textsuperscript{2} suggesting that we had provided a supramaximal stimulus. In contrast to the substantial initial response, subsequent step increases of desflurane concentration produced minimal circulatory responses despite a capacity to mount such a response as demonstrated by HR and MAP increases with supramaximal ulnar stimulation.

These findings are consistent with the hypothesis that desflurane (and other anesthetics) stimulate a receptor (such as in the airway) that adapts rapidly to a strong stimulus and that remains adapted for a substantial period of time. We measured a duration of adaptation of at least 75 min. Moore \textit{et al.}\textsuperscript{3} observed that small increases in desflurane concentration every 4 min (in several instances the next step occurred before the evidence of stimulation had subsided completely) each can produce increases in HR, MAP, and circulating concentrations of epinephrine and norepinephrine. Their finding appears to suggest that maximal adaptation occurs only after imposition of a more substantial stimulus or after the response is completed.

Our finding of an attenuated or absent response to an increase in desflurane concentration but a substantial cardiovascular response to electrical stimulation of the ulnar nerve suggests that the adaptation does not result from a change in the efferent side of the reflex. The absence of an increase of plasma catecholamine concentration from ulnar nerve stimulation suggests the possibility that attenuation of the response to rapidly increased desflurane concentration resulted from diminished adrenal secretion. Stimulation of the ulnar nerve followed the step increases in desflurane. A finding that ulnar nerve stimulation before increasing the concentration of desflurane caused plasma catecholamine concentrations to increase would support the possibility of subsequent suppression of adrenal secretion by the step increase in desflurane. We did not test this possibility.

Plasma epinephrine, MAP and HR exhibited parallel transient changes with each increase in desflurane concentration, attenuated with the second and third steps.

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Fig. 4. In five volunteers, increases of mean arterial blood pressure (MAP), heart rate (HR), and plasma epinephrine concentration (EPI) were similarly attenuated when the second increase of desflurane occurred 10, 32, or 75 min after the initial increase of desflurane to 8%. Data are means ± SE. † P < 0.05 versus initial response.
response to increase of desflurane concentration. Second, when the background gas was 60% nitrous oxide, the initial response was similar to that when the background gas was oxygen, except for a smaller increase of MAP in the presence of nitrous oxide. As with oxygen, the background gas, the second response was attenuated when nitrous oxide was the background gas.

In an editorial, Lowenstein wondered why we did not see evidence of cardiovascular stimulation in our initial administration of desflurane to volunteers. Our current findings suggest the answer and a point of some clinical importance: after the increased HR and MAP resulting from an initial rapid increase of desflurane concentration.

In contrast, plasma norepinephrine concentration increased in a delayed manner at each step. In some volunteers, norepinephrine increased in the absence of any increase in epinephrine or MAP. In these volunteers, a decrease in MAP always occurred. These findings suggest that neural sympathetic activity (as represented by plasma uptake of overflow of norepinephrine from the synaptic cleft) resulted in part as a response to the increase in epinephrine and in part as a response to the ensuing hypotension.

There were two additional findings of this study. First, the duration of anesthesia (up to at least 75 min) preceding the initial step to 8% did not alter the initial

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concentration subside (in our initial studies we induced anesthesia with high concentrations of desflurane but made no systematic measurements of cardiovascular variables). Subsequent rapid increases of desflurane concentration may not elicit sympathetic-mediated cardiovascular stimulation.

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