Cardiovascular Stimulation Induced by Rapid Increases in Desflurane Concentration in Humans Results from Activation of Tracheopulmonary and Sysemic Receptors


Background: It was hypothesized that stimulation of rapidly adapting airway receptors produces the transient (2–4 min) circulatory responses to rapid increases in desflurane concentrations greater than 6%. Accordingly, it was reasoned that increasing the concentration of desflurane in one lung, without altering the concentration of desflurane in systemic blood, should cause cardiovascular stimulation, whereas once the airway receptors had adapted to the stimulation, an initial increase in the systemic concentration of desflurane should have little effect.

Methods: After placement of a double-lumen endotracheal tube in four volunteers and establishment of a steady-state level of 4% desflurane in both lungs, the desflurane concentration was rapidly increased from 4% to 8% in one lung while decreasing it in the other, thereby obviating any increase in the systemic desflurane blood concentration (confirmed by analysis). After returning the desflurane end-tidal concentration to 4% in both lungs, this process was repeated for the contralateral lung thereby having exposed both lungs to 8% desflurane without increasing the systemic desflurane concentration. After returning desflurane concentration to 4%, it was increased in both lungs simultaneously to 8% and consequently in blood to 8% of an atm.

Results: Rapid increases in desflurane concentrations in either lung, but not blood, significantly increased heart rate (17 ± 5 beats/min, mean ± SE, P < 0.05) and mean arterial blood pressure (15 ± 5 mmHg, P < 0.05), but a greater increase in heart rate (43 ± 5 beats/min, P < 0.05) and mean arterial blood pressure (46 ± 11 mmHg, P < 0.05) occurred when both lungs were exposed simultaneously to rapidly increased desflurane concentration for the second time within 90 min. This result did not differ from the increase occurring on another day when both lungs and blood were exposed for the first time that day to 8% desflurane (heart rate 40 ± 7 beats/min, P = 0.8; mean arterial blood pressure 40 ± 5 mmHg, P = 0.5).

Conclusions: It was concluded that at least two sites respond to a rapid increase in desflurane concentrations greater than 6%: one site in the airways and/or lungs, and at least one other in a highly perfused tissue(s). The systemic site contributes more importantly. (Key words: Airways; receptors. Anesthesics, volatile; desflurane. Autonomic nervous system. Cardiovascular actions: blood pressure; heart rate. Sympathetic nervous system.)

A rapid increase in desflurane or isoflurane to a concentration greater than approximately 1 minimum alveolar concentration (MAC) can transiently increase sympathetic activity, plasma epinephrine concentration,2-3 vasopressin secretion,4 heart rate, and arterial blood pressure.1-8 The mechanism(s) underlying these increases is unknown, but the transient nature of the responses indicates a mechanism that rapidly adapts. Ebert and Muzi1 and we previously hypothesized2-3 that the afferent limb of the response includes airway receptors, and we further hypothesized that these receptors are rapidly adapting.5 Supporting this hypothesis was the rapidity of onset of the response (less than 90 s), the rapidity of the decay (4 min) in the response, and our finding that repetitive increases of end-tidal desflurane to concentrations exceeding 6% evoked much smaller sympathetic and cardiovascular responses than those evoked by the initial increase of desflurane concentration.5 In the current study, we tested this hypothesis (that the receptors are in the trachea or lungs) by increasing the concentration of desflurane in the airways and lungs without concomitantly increasing the

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concentration of desflurane in systemic blood, and hence, other tissues. We then tested the effect of increasing the concentration in both airways and systemic blood. We reasoned that if rapid adaptation of pulmonary receptors results from the stimulation provided by the initial increases in desflurane, we should see a circulatory response to the stimulation of each lung but no response to a second increase in desflurane. Alternatively, if the receptors transducing this response lie in the systemic circulation then the individual initial increases should produce no circulatory response, but the second (systemic) increase should produce the response.

**Methods**

We studied four healthy male volunteers (age 24.5 ± 0.7 yr; weight 69.9 ± 3.8 kg; height 178.4 ± 1.2 cm; mean ± SE), while supine, with informed consent and 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. 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%) for 32 min. The trachea was intubated with either a single-lumen (control) or a double-lumen tube (position checked by differential spirometry and auscultation) after administration of 0.1 mg/kg intravenous vecuronium. After skin infiltration with less than 1 ml 1% lidocaine, a radial arterial cannula was inserted. Additional vecuronium (0.02–0.03 mg/kg intravenous) was administered before increasing the desflurane concentration (see sequences, later) when four 2-Hz stimuli of an ulnar nerve produced any twitches. When a double-lumen tube was inserted, each lumen was connected by a separate circuit to a separate anesthesia machine with a separate mechanical ventilator. Anesthetic concentration was measured continuously at the proximal orifice of both lumena of the endotracheal tube by two separate infrared spectrometers (Datex Ultima, Helsinki). A 20-ml dead space was attached to each lumen of each endotracheal or endobronchial tube to prevent contamination of end-tidal gas with inspired gas. Each spectrometer was calibrated before and after each study by secondary (tank) standards, which in turn were calibrated against primary (volumetric) standards using gas chromatography. Mechanical ventilation of the volunteers’ lungs maintained normocapnia, and surface warming with heated air maintained normothermia throughout the study.

Mean systemic arterial blood pressure (Gould Statham 23XL transducer, Oxnard, CA, calibrated with a mercury manometer before and after each study), heart rate, and desflurane concentration at the orifice of each endotracheal or endobronchial tube lumen were recorded continuously by a digital polygraph (Gould model ES 2000, Cleveland, OH). Arterial blood was sampled for measurement of pH, P O₂, and P CO₂ (by standard electrodes) before each increase of desflurane concentration, and for measurement of desflurane concentration immediately before and 0.5, 1, and 2 min after each increase in desflurane concentration. Desflurane blood partial pressure was measured to ensure that it did not exceed 5.5% of an atm when the desflurane concentration was increased in only one lung.

Each volunteer was anesthetized twice, each instance separated by at least 1 week.

**Control.** Twenty-seven minutes after reaching 0.55 MAC desflurane (4.0% end-tidal), 2 mg/kg propofol was administered intravenously. Five minutes later, the end-tidal desflurane concentration was increased rapidly (within 60 s) to 1.1 MAC (8%) and sustained at that concentration for 10 min.

**Experimental.** The aim of this portion of the study was to increase the concentration of desflurane in one lung to 8% (a concentration known to cause cardiovascular stimulation when administered to both lungs) without altering the systemic desflurane concentration.

Twenty-seven minutes after reaching 0.55 MAC desflurane (4.0% end-tidal via both lumens of the endotracheal tube), 0.7 mg/kg propofol was administered intravenously. Four minutes later, the inspired concentration of desflurane delivered to one lung (randomly assigned) was decreased to 0% to obviate a subsequent increase in systemic desflurane concentration. One minute later (32 min after reaching 0.55 MAC desflurane) the end-tidal concentration of desflurane in the other lung was rapidly increased (within 60 s) to 8.0%. These two separate pulmonary desflurane concentrations were maintained for 10 min, after which the end-tidal desflurane concentration in both lungs was returned to 0.55 MAC (4.0%).

After 5 min at 4% desflurane, another intravenous dose of 0.7 mg/kg propofol was given and the aforementioned procedure was repeated, except that the concentrations of desflurane were increased and decreased.
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in the opposite lungs. As before, this desflurane concentration was maintained for 10 min, after which the concentrations in both lungs were restored to 4.0% end-tidal concentration.

Finally, again after 5 min another intravenous dose of 0.7 mg/kg propofol was given and 5 min later, the concentration of desflurane was increased rapidly (within 60 s) in both lungs simultaneously to 8.0% and maintained at this concentration for 10 min.

**Blood Desflurane Partial Pressure Analysis.** Blood desflurane partial pressure was determined as previously described,\(^9\) for each sample, in duplicate. Briefly, immediately after anaerobically drawing each sample of arterial blood, a measured quantity of the blood was placed in an evacuated, airtight (with a polytetrafluoroethylene stopper) flask of known volume. Flasks were incubated in a 37°C water bath for 2 h, after which the desflurane concentration in the gas phase was determined by gas chromatography.\(^9\) The gas chromatograph was calibrated using secondary (tank) standards that had been calibrated against primary (gravimetric) standards.

**Statistical Analyses.** Data are presented as mean ± SE. Peak changes in heart rate and mean arterial blood pressure after increases of desflurane concentration in each lung separately were compared with each other by \(t\) test. Because these responses did not differ (\(P > 0.05\)) the data were grouped for further analysis. The statistical power was low (0.4) for detection of a difference between the responses from the lungs individually; however, we calculated from the variability and averages obtained in the current study that a sample size of more than 50 volunteers would have been required to detect a difference with 80% probability. There was no apparent trend: of the three volunteers for whom we had a complete data set, two had greater responses from the left lung and one had a greater response from the right lung. Peak changes in heart rate and mean arterial blood pressure after increase of desflurane concentration in one lung (and not blood) and both lungs (and blood) were compared by \(t\) test with similar data after similar change in desflurane concentration in both lungs on another occasion (control). Bonferroni’s correction was applied where appropriate. Statistical significance was accepted as \(P < 0.05\).

**Results**

Arterial \(\text{pCO}_2\) and \(\text{pH}\) throughout all experimental sequences did not differ from awake values (38.0 ± 0.8 mmHg, 7.437 ± 0.006, respectively; mean ± SE). Arterial \(\text{PO}_2\) during anesthesia always exceeded 500 mmHg.

We did not incorporate data from one single-lung increase of desflurane because the blood desflurane partial pressure in this case exceeded 5.5% of an atm, a value that was our a priori limit because it approximates the threshold for stimulation.\(^3\) For the remaining data, measured end-tidal, inspired, and blood desflurane partial pressures are shown in figures 1 and 2, demonstrating that we maintained constant desflurane blood partial pressure at 4% when desflurane concentration was increased in only one lung, but that desflurane blood partial pressure appropriately increased to 8% of an atm when desflurane concentration was increased simultaneously in both lungs.

Before increasing desflurane concentration, heart rate was 61 ± 2 beats/min and mean arterial blood pressure was 70 ± 1 mmHg, and did not differ from the values obtained before propofol administration (we had waited 5 min after administration of propofol to allow for return to previous values) nor among the four times before increasing desflurane concentration. Heart rate increased by 40 ± 7 beats/min and mean arterial blood pressure by 40 ± 3 mmHg after the increase of end-tidal desflurane concentration to 8% in both lungs (control). Increasing end-tidal desflurane concentration to 8% in only one lung, while maintaining desflurane blood partial pressure unchanged (fig. 1) pro-

![Fig. 1. Rapidly increased end-tidal desflurane concentration to 8% in one lung (I, \(\Delta\), [To ↑]); while inspired desflurane concentration in the other lung is decreased [D, \(\bigtriangledown\)] to 0, [To ↓]).](image)

Data are mean ± SE.
Fig. 2. Increasing end-tidal concentration to 8% in both lungs simultaneously (○, △; L, left lung; R, right lung) similarly increases desflurane blood partial pressure (●). Data are mean ± SE.

duced a smaller change in heart rate (17 ± 5 beats/min; P < 0.05; 43% of control) and mean arterial blood pressure (15 ± 5 mmHg; P < 0.05; 38% of control) than did increasing systemic desflurane partial pressure (control; fig. 3). The time to maximal increase of heart rate and blood pressure were similar (P > 0.05) when the desflurane increases were applied to one lung (heart rate, 86 ± 15 s; mean arterial blood pressure, 75 ± 8 s) or two lungs (heart rate, 82 ± 3 s; mean arterial blood pressure, 69 ± 9 s).

In the experimental group, increases in desflurane to 8% were imposed independently to each lung before a final increase to both lungs simultaneously. When end-tidal desflurane concentration was increased to 8% in both lungs simultaneously, and hence the partial pressure in systemic blood to 8% of an atm (fig. 2), the increase in heart rate (43 ± 5 beats/min; 108% of control) and mean arterial blood pressure (46 ± 11 mmHg; 115% of control) did not differ (P > 0.05) from the increases seen when the systemic desflurane partial pressure was increased to 8% of an atm, without first having increased the concentration in each lung separately (control; fig. 3).

Discussion

The increases in heart rate and blood pressure in the current “control” experiments were similar to those observed in other volunteers. Consistent with the two possibilities (hypotheses) outlined at the beginning of this article, our data indicate (1) that at least two receptor sites determine desflurane-induced sympathetic stimulation: one in the airways or lungs, and at least one other in highly perfused tissue(s); and (2) that the latter contributes more importantly than the former. The increases in heart rate and blood pressure resulting from the unilateral pulmonary increases in desflurane in the absence of a systemic increase in desflurane indicate the existence of a tracheal–pulmonary site. Our previous findings indicate that if a pulmonary site were the only one transducing the effect of the increase in desflurane concentration, pretreatment of each lung with 8% desflurane should have attenuated the impact of any subsequent increases in desflurane. That is, we anticipated from one of our hypotheses (that the receptors are in the trachea or lungs) that the third increase to 8% desflurane, the one in which the systemic increase was imposed, should not have produced a greater cardiovascular response than did the unilateral pulmonary increases to 8% desflurane. The current data do not support this hypothesis, demonstrating instead an important systemic transducer for the effect of a rapid increase in desflurane concentration. When both

Fig. 3. When one lung (1L) is exposed to a rapid increase of end-tidal desflurane concentration to 8%, heart rate (HR) and mean arterial blood pressure (MAP) increase, but significantly less (*P < 0.05) than after a similar increase of both lungs on another occasion (C; control). A second exposure of both lungs (simultaneously) to a rapid increase of desflurane concentration, while blood partial pressure is increased for the first time (2L), produces an increase in heart rate and mean arterial blood pressure, which do not differ from a similar exposure of both lungs on another occasion (C). Data are mean ± SE.
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lungs were exposed to end-tidal 8% desflurane for the second time within 90 min of the first exposure (third desflurane increase on the experimental day), the cardiovascular response did not differ from the control response. Because a second increase in lung and blood desflurane partial pressure to 8% of an atm within 2 h of the first increase produces a markedly attenuated cardiovascular response, the absence of such attenuation in this study suggests that a systemic receptor provides the more important contribution.

An alternative explanation is also possible: that the summation of responses from the two lungs individually is not linear, but that the response from the two together is greater than the sum of the individual responses; and that the site(s) of integration and of attenuation of repeated desflurane increases is at a central location(s), rather than in the airways or lungs. Our experiments cannot eliminate this possibility completely.

A test of the alternative hypothesis could have been accomplished by a variant of our basic experiment. In the variant, the concentration of desflurane in one lung (preferably the left because it offers a lesser surface area for stimulation) would be increased from 4% to 12% rather than 8%. As in the original study, the concentration in the other lung would be decreased to a low value. We previously demonstrated that the response to an increase to 8% applied to both lungs did not differ from that to 12% applied to both lungs. Thus, if the transduction occurs in the lung, and if this summed centrally, there should not be a response to an increase in one lung to 12%. However, such an increase should cause an increase in the systemic partial pressure of desflurane that would reach the threshold for stimulation. If transduction occurs in a tissue perfused by the systemic circulation, a response should be seen that approximates the control response. Although we did not intend such a study, in fact this result was obtained in one volunteer whose data were separated from those obtained in the other volunteers. The data for the one volunteer were separated because although only one lung was ventilated with 8% desflurane, the blood partial pressure exceeded our predetermined limit of 5.5% of an atm. The result was a transient increase in heart rate and blood pressure that approximated the increase seen in the control study.

Additional data also argue against central integration of pulmonary stimulation causing the resultant increases in heart rate and blood pressure. If this were the case, then heart rate and blood pressure should increase within a few seconds of the stimulus arriving at the receptor site(s). Consistent with such a stimulus response temporal relationship, a supramaximal tetanic stimulus produces an increased heart rate and blood pressure (increase >10% of baseline) in 6 ± 1 s (analysis of previous data obtained after stimulating volunteers with a supramaximal tetanic stimulus, after having previously increased desflurane concentration 3 times within 2 h). However, the increase of heart rate and blood pressure produced by a bilateral increase in desflurane concentration begins 30 s after the first breath of increased desflurane concentration. This interval is consistent with the time required for desflurane to circulate from the lungs to a central location plus time for an adequate increase in the tissue concentration of desflurane. A more rapid cardiovascular change should result from direct stimulation of pulmonary receptors transmitting to the brain for processing. Thus, we are inclined to discard the notion of central integration as an explanation of our findings.

Did we study too few subjects to support the conclusions we reached? We argue that the numbers were sufficient to provide statistically significant results with no suggestion of a trend for a lesser response after the second airway-pulmonary and first blood increase, than for the control. The data were sufficient to test our hypothesis; thus, we felt compelled to terminate the study without exposing additional volunteers to potential complications.

We administered propofol before each increase in desflurane concentration because decreasing the concentration of desflurane in one lung to 0% might have decreased blood and brain desflurane concentration to a level that permitted volunteer recall (MAC: awake for desflurane is 2.4%. The dose of propofol administered (2 mg/kg in the control group) does not affect the cardiovascular response to a rapid increase of desflurane. Thus, the smaller dose (0.7 mg/kg) given 5 min before each of the three independent increases in desflurane in the experimental group would not be expected to influence the results. Indeed, if propofol attenuates the response to desflurane, the smaller dose given in the experimental group should have exaggerated the responses to the single-lung increases in desflurane, and the larger dose should have decreased the response in the control subjects.

The relatively small increase in heart rate and blood pressure after exposure of only one lung to increases in desflurane concentration might have resulted from...
small systemic increases in desflurane concentration and not from increases in pulmonary desflurane concentration. That is, one might interpret our data as suggesting that all of the effects resulted from stimulation of systemic receptors. However, Moore et al. found that rapidly increasing end-tidal desflurane from 4% to 5% produced increases in heart rate or blood pressure in only one of ten volunteers. In addition, one of our volunteers had small increases of heart rate and blood pressure when blood desflurane concentration decreased during exposure of a single lung to an increased desflurane concentration.

We suggest the following explanation for the data obtained in this and previous reports. In adult humans, a rapid increase in desflurane concentration greater than 6% transiently increases sympathetic activity, heart rate, and blood pressure by stimulating both pulmonary and systemic receptors. Of these, the systemic receptors provide the greater effect. Given the brief time between the imposition of higher desflurane concentration and the circulatory responses (60 s), the systemic receptor(s) must be highly perfused. Finally, we speculate that the attenuated increases in heart rate and blood pressure associated with repeated increases in desflurane (previous report) result from attenuation of responses from systemic but not pulmonary receptors. This suggestion follows from the magnitude of the responses to the isolated stimulation of pulmonary receptors in the current study, a magnitude that equaled the magnitude of the responses after repetitive stimulation in a previous study. Such an interpretation would imply that the rapidly adapting pulmonary receptors, but not the systemic receptors, can reset after a period of time.

References

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