

## Rapid 1% Increases of End-tidal Desflurane Concentration to Greater Than 5% Transiently Increase Heart Rate and Blood Pressure in Humans

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**Background:** Large (0.5–1.0 MAC), rapid increases of desflurane to concentrations greater than 5% can transiently increase heart rate, mean arterial blood pressure (MAP), sympathetic nerve activity, and plasma epinephrine concentration. We tested the hypothesis that small (1% = 0.14 MAC), rapid increases of desflurane concentration to greater than 5% do not increase heart rate, blood pressure, and plasma catecholamine concentrations.

**Methods:** Anesthesia was induced with intravenous propofol, 2 mg/kg, in 13 healthy male volunteers, 19–33 yr of age, and ventilation was controlled to maintain normocapnia. We gave 4% end-tidal desflurane in oxygen for 32 min and then imposed successive 1% increases in end-tidal desflurane concentration, each new concentration maintained for 4 min, to a final concentration of 12%. We measured heart rate, MAP and plasma catecholamine concentrations in the awake state, after 4 min at each 1% step, and at times of peak increase of MAP ( $\geq 10\%$  change).

**Results:** Increases in heart rate and blood pressure of more than 10% occurred with 1% step-increases in only 1 volunteer at 5% desflurane but in 7–10 (MAP) and 8–12 (heart rate) of the 13 volunteers at higher desflurane concentrations. The 1%

increases in desflurane concentration to greater than 5% also transiently increased plasma epinephrine concentrations but not vasopressin concentration or plasma renin activity in those volunteers in whom MAP increased.

**Conclusions:** Small (1%) increases in desflurane concentration to and greater than 6% can transiently increase heart rate, mean arterial pressure, and plasma epinephrine concentration. These data and those from a previous study indicate that these increases occur with a lesser frequency and magnitude than those associated with a single, rapid step from 4% to 12% end-tidal desflurane. (Key words: Anesthetics, volatile: desflurane. Blood pressure. Heart: heart rate. Hormones: renin-angiotensin; vasopressin. Sympathetic nervous system, catecholamines: epinephrine; norepinephrine.)

INITIAL clinical evaluations indicated that induction of anesthesia with desflurane may be associated with increases in heart rate (HR) and mean arterial blood pressure (MAP).<sup>1–4</sup> Ebert and Muzzi<sup>5</sup> subsequently demonstrated increased HR, MAP, and muscle sympathetic nerve activity with increases in delivered desflurane concentration to greater than 6%. Weiskopf *et al.*<sup>6</sup> found that HR, MAP, and plasma catecholamine concentrations increased in response to a single, rapid increase in end-tidal desflurane or isoflurane concentration from 0.55 to 1.66 MAC but not in response to the initial wash-in of these anesthetics to 0.55 MAC. In the current study we tested the hypothesis that small (1%), rapid increases in the end-tidal concentration of desflurane do not increase HR, MAP, or plasma catecholamine concentrations. We also determined whether there is a desflurane concentration threshold for cardiovascular stimulation; and whether the cardiovascular response differs in magnitude from that associated with a large, rapid increase in desflurane concentration.

### Materials and Methods

This study was approved by the Committee on Human Research, University of California, San Francisco. In-

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# CARDIOVASCULAR STIMULATION WITH SMALL INCREASES OF DESFLURANE

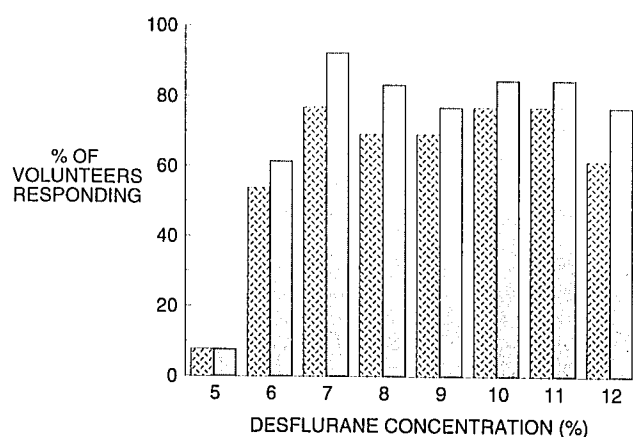


Fig. 1. Incidence of increase of mean arterial blood pressure (MAP, hatched bars) and heart rate (HR, shaded bars) ( $\geq 10\%$ ) among 13 volunteers to 1% step-increases in end-tidal desflurane concentration. A threshold for cardiovascular stimulation appears to exist at approximately 6% desflurane.

formed consent was obtained from 13 healthy male volunteers, 19–33 yr of age. We recorded HR (6-s moving average) and MAP from an intraarterial catheter (XL23 transducers, Spectramed, Oxnard, CA; ES 2000 polygraph, Gould, Hayward, CA) while volunteers were supine and unmedicated. 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, plasma catecholamine and arginine vasopressin (AVP) concentrations, and plasma renin activity (PRA).

We induced anesthesia with 2 mg/kg intravenous propofol and intubated the trachea after 0.1 mg/kg intravenous vecuronium. Normocapnia was maintained by controlled ventilation and normothermia by surface warming. End-tidal desflurane concentration was maintained at 4%, measured by an infrared spectrophotometer (Datex Ultima, Helsinki, Finland) calibrated with secondary (tank) standards which had been calibrated against primary volumetric standards by gas chromatography. A continuous electrocardiogram was recorded. Volunteers received 4% end-tidal desflurane in oxygen for 32 min, after which we imposed successive, rapid (average time to new end-tidal concentration = 27 s) 1% increases in end-tidal desflurane. Each new end-tidal concentration was maintained for 4 min. The final end-tidal concentration equalled 12% and was maintained for 16 min. We sampled blood for measurement of PRA, and plasma AVP, epinephrine and norepinephrine concentrations at the end of each 4-

min period at each end-tidal desflurane concentration. If MAP increased by more than 10%, we repeated these determinations at the time of the peak MAP.

Blood gases were determined with the use of standard electrodes. Blood samples for measurement of catecholamine concentrations (collected in heparin) and AVP and PRA determinations (both collected in ethylenediaminetetraacetic acid), were immediately placed in wet ice, and separated and frozen 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 for within-run: epinephrine 2%, norepinephrine 1%; between runs: epinephrine 7%, norepinephrine 3%. Sample values less than the limit of detection were considered as having a concentration just less than the limit of detection. AVP<sup>7</sup> and PRA<sup>8</sup> were measured by radioimmunoassay.

A hemodynamic response was defined as an increase of 10% or more in MAP or HR after step-increases compared with the values immediately before the step-increase. Values for peak MAP or peak HR (regardless of extent of increase) after each increase of desflurane concentration were compared with the values before the increase in desflurane concentration by the paired *t* test. Twelve of the 13 volunteers, on a separate occasion, received a single, rapid increase in end-tidal desflurane concentration from 4% to 12%.<sup>6</sup> Only the data for the 12 volunteers participating in both studies were used when comparing the two studies. Increases of MAP, HR, and plasma epinephrine and norepinephrine concentrations at each step-increase of desflurane concentration were compared with the same increases occurring with the single, rapid increase of desflurane concentration by the paired *t* test with Bonferroni's correction. We accepted a value of  $P < 0.05$  as statistically significant.

## Results

The increase from 4% to 5% end-tidal desflurane concentration increased HR and MAP in only 1 of the 13 volunteers (fig. 1). Increases of 1% end-tidal desflurane between 6% and 12% increased MAP in 7–10 and HR in 8–12 of the 13 volunteers. One volunteer did not respond with increased HR or MAP to any of the increases of desflurane. HR and MAP had increased in  $\geq 77\%$  of volunteers by the time 6% or 7% desflurane had been attained. The majority of volunteers re-

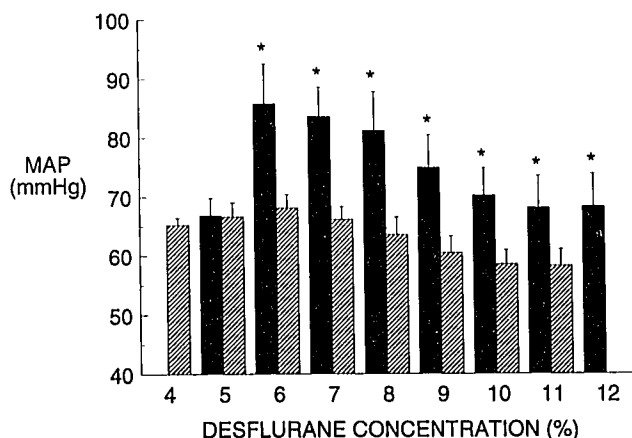


Fig. 2. Mean arterial blood pressure (MAP) in all volunteers at the peak MAP (filled bars) and 4 min (striped bars) after 1% step-increases in end-tidal desflurane concentration. MAP significantly and transiently increased after step-increases between 6% and 12% desflurane. \* $P < 0.05$  comparing peak MAP after step-increase to MAP before the increase (4-min value at previous desflurane concentration).

sponded three or more times to the eight step-increases with a 10% or greater increase in MAP or HR.

Increasing end-tidal concentration of desflurane from 4% to 5% did not significantly change MAP or HR (figs. 2 and 3). Further 1% increases significantly increased MAP and HR. Peak MAPs were  $68 \pm 5$  to  $86 \pm 7$  mmHg and peak HRs  $85 \pm 6$  to  $96 \pm 6$  beats/min. The increases in MAP or HR associated with step-increases were transient: MAP reached its peak value in  $85 \pm 4$  (mean  $\pm$  SE) s (range 71–99 s) and HR in  $112 \pm 4$  s (range 94–138 s) after the start of increase in desflurane concentration, returning to lower values by the end of the 4-min period. For the responding volunteers, one-half of the decrease in MAP or HR from the peak values to the values at 4 min occurred in  $60 \pm 4$  and  $66 \pm 4$  s, respectively. The maximum increases of MAP and HR were 20–38% of the maximum increases occurring when 12 of these 13 volunteers had been given a rapid, single step-increase of end-tidal desflurane concentration from 4% to 12%<sup>6</sup> (fig. 4).

Plasma epinephrine and norepinephrine concentrations increased significantly in those volunteers responding to step-increases of desflurane with increased MAP (figs. 5 and 6). The increase in epinephrine concentration was transient. Blood was not sampled for measurement of catecholamines at the time of peak MAP for the one volunteer responding to the increase from 4–5% desflurane. After step-increases of 1% end-tidal desflurane concentration to and above 6%, mean

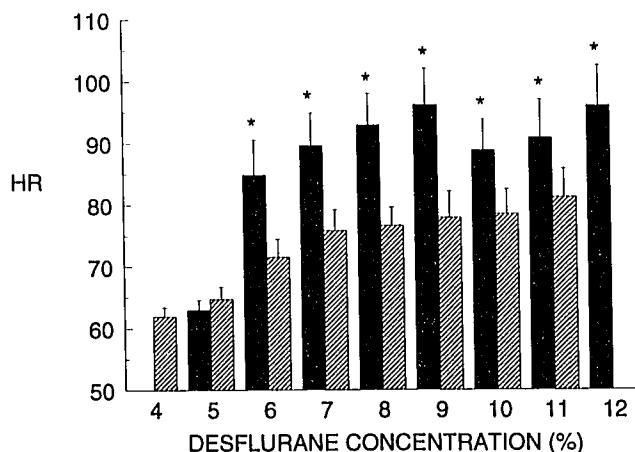


Fig. 3. Heart rate (HR) in all volunteers at the peak HR (filled bars) and 4 min (striped bars) after 1% step-increases in end-tidal desflurane concentration. HR significantly and transiently increased after step-increases between 6% and 12% desflurane. \* $P < 0.05$  comparing peak HR after step-increase to HR before the increase (4-min value at previous desflurane concentration).

plasma epinephrine concentrations ranged from  $32 \pm 9$  to  $299 \pm 161$  pg/ml (fig. 5) and mean plasma norepinephrine concentrations from  $303 \pm 36$  to  $831 \pm 122$  pg/ml (fig. 6) at times coinciding with peak MAP. No catecholamine determinations were made at times

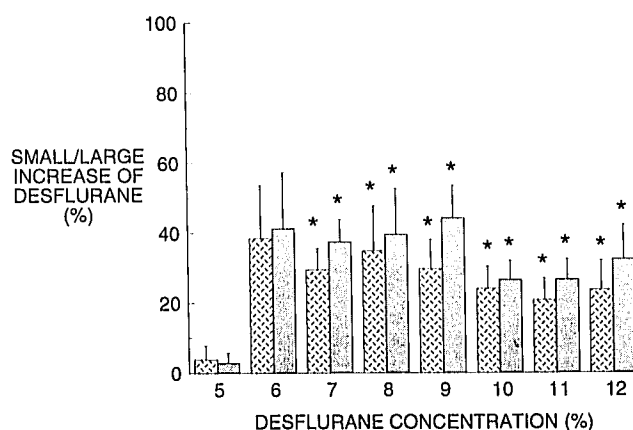
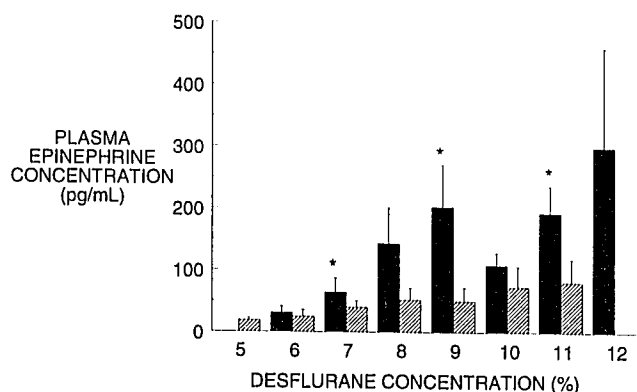


Fig. 4. Maximum increases in mean arterial pressure (MAP, hatched bars) and heart rate (HR, shaded bars) after small step-increases in desflurane concentration as a percentage of the maximum increases after a rapid increase from 4% to 12% desflurane in 12 of the 13 volunteers.<sup>6</sup> Small increases in desflurane concentration cause less cardiovascular stimulation than do large increases. \* $P < 0.05$  between small and large increases of desflurane concentration.

# CARDIOVASCULAR STIMULATION WITH SMALL INCREASES OF DESFLURANE



**Fig. 5.** Epinephrine concentration in volunteers responding hemodynamically at the peak hemodynamic response (filled bars) and 4 min (striped bars) after 1% step-increases in end-tidal desflurane concentration. Epinephrine concentration significantly and transiently increased after step-increases between 6% and 12% desflurane. Sample sizes: desflurane 5%, 1; desflurane 6%, 9; desflurane 7%, 8; desflurane 8%, 7; desflurane 9%, 8; desflurane 10%, 4; desflurane 11%, 4; and desflurane 12%, 5. \* $P < 0.05$  comparing peak epinephrine after step-increase to epinephrine before the increase (4-min value at previous desflurane concentration).

of peak MAP, by definition, for those volunteers not responding with an increase in MAP of  $\geq 10\%$ .

Plasma AVP concentration did not increase when MAP increased in response to increased desflurane concentration, and after 16 min at 1.66 MAC ( $2.5 \pm 0.6$  pg/ml) did not differ from values when the volunteers were awake ( $2.3 \pm 0.3$  pg/ml,  $P > 0.7$ ). PRA increased over the duration of the desflurane anesthetic but did not increase acutely with each rapid, step-increase.

## Discussion

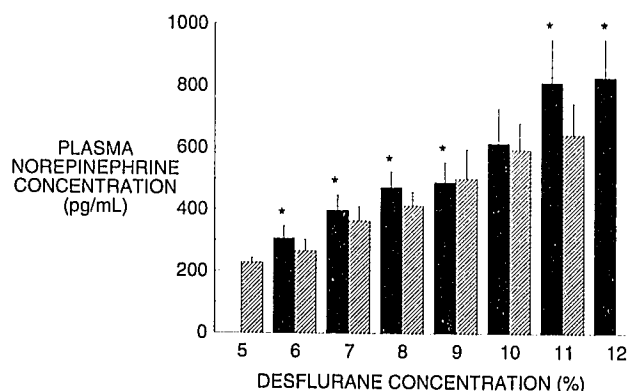
We find that 1% increases in end-tidal desflurane concentration to greater than 5% can transiently increase HR, MAP, and plasma catecholamine concentrations, but do so to a lesser extent than that after a single, rapid (approximately 60 s) step from 4% to 12% desflurane. These results are consistent with the finding that substantial, rapid increases in desflurane and isoflurane concentrations can transiently increase HR, MAP and plasma epinephrine concentrations during induction or maintenance of anesthesia.<sup>1-4,9,10</sup> Ebert and Muzi<sup>5</sup> reported slightly different results. They found increased HR and MAP and increased sympathetic nerve activity associated with an increased inspired desflurane, but not isoflurane, concentration from 1.0 to 1.5 MAC. They may have failed to find increases with iso-

flurane because they did not increase the alveolar concentration (measured as a MAC-multiple) of that agent as rapidly as they did that of desflurane. Our data and that of others suggest that attempting to treat cardiovascular stimulation provoked by a rapid increase of anesthetic concentration with an immediate further rapid increase in desflurane concentration is likely to provoke further stimulation, rather than blunt the initial response.

On a separate occasion, 12 of the 13 volunteers were also given a single, rapid increase of end-tidal desflurane concentration from 4% to 12%.<sup>6</sup> The increases in HR, MAP and plasma epinephrine and norepinephrine were substantially less with the smaller increases of end-tidal desflurane concentration as opposed to the single, large increase ( $P < 0.05$ ; paired  $t$  test).

Also consistent with previous results, we find no cardiovascular or hormonal response to 4% desflurane, nor to a step-increase from 4% to 5%. However, over one half of the volunteers responded to a step-increase to 6%. It appears that the increase to 6% end-tidal desflurane concentration defines the threshold to such a response in young, healthy volunteers, in whom the MAC of desflurane is 7.25%,<sup>11</sup> and in whom anesthesia had been induced with propofol.

The data from these 12 volunteers 16 min after having reached 12% end-tidal desflurane slowly (eight 4-min



**Fig. 6.** Norepinephrine concentration in volunteers responding hemodynamically at the peak hemodynamic response (filled bars) and 4 min (striped bars) after 1% step-increases in end-tidal desflurane concentration. Norepinephrine concentration significantly increased after step-increases between 6% and 12% desflurane. Sample sizes: desflurane 5%, 1; desflurane 6%, 9; desflurane 7%, 8; desflurane 8%, 7; desflurane 9%, 8; desflurane 10%, 4; desflurane 11%, 4; and desflurane 12%, 5. \* $P < 0.05$  comparing peak norepinephrine after step-increase to norepinephrine before the increase (4-min value at previous desflurane concentration).

steps) did not differ from the data 16 min after the same desflurane concentration had been reached rapidly (in approximately 60 s), except for a slightly greater HR after the slow steps (slow *vs.* fast increase: MAP  $58 \pm 3$  *vs.*  $59 \pm 4$  mmHg; HR  $86 \pm 4$  *vs.*  $80 \pm 4$ ,  $P < 0.05$ ; plasma epinephrine concentration  $56 \pm 9$  *vs.*  $60 \pm 14$  pg/ml; plasma norepinephrine concentration  $612 \pm 44$  *vs.*  $609 \pm 59$  pg/ml; AVP  $2.5 \pm 0.6$  *vs.*  $2.4 \pm 0.4$  pg/ml; PRA  $21 \pm 2$  *vs.*  $16 \pm 2$  ng angiotensin I/ml/2 h). That is, although rapidly imposing 12% end-tidal desflurane resulted in a single, brief, sympathetic and cardiovascular response, whereas slow, repetitive increases of anesthetic concentrations resulted in smaller, repetitive sympathetic and hemodynamic responses, these values were similar 16 min after equivalent anesthetic concentrations had been achieved.

We did not investigate the basis for the stimulation found. The rapidity of response suggests an action on airways, lungs, or rapidly perfused tissue. Increasing the end-tidal desflurane concentration rapidly by 1% required the use of inspired concentrations which were approximately 3% greater than the end-tidal values. These larger increases may have stimulated receptors in the airways or lungs. Increased epinephrine concentrations could have resulted from decreased reuptake, a direct effect of desflurane on the adrenal gland, or central sympathetic stimulation of the adrenal. The rapidity and transient nature of the catecholamine response to increase in desflurane concentration favor the two latter possibilities. That volunteers experienced repeated catecholamine responses in conjunction with the step-increases suggests that depletion of catecholamines available for release does not take place under these conditions.

The absence of increase of plasma AVP concentration at any time of increased MAP in response to 1% increase of desflurane differs from our finding in these volunteers when MAP increased in response to a large increase of desflurane.<sup>6</sup> This could be a direct result of a lesser increase of desflurane, or a result of the lesser increase of plasma epinephrine. The absence of increased AVP likely contributed to the lesser increase in MAP than when these volunteers were exposed to a single, large increase of desflurane.

Blood was only sampled for determination of plasma catecholamine concentrations during a given 4-min period for volunteers responding to that 1% step-in-

crease in desflurane concentration with an increase in MAP of  $\geq 10\%$ . Thus, we cannot assess whether increases in plasma catecholamine concentrations correlated with hemodynamic changes or whether the former may have increased without increases in the latter.

In conclusion, we find that 1% increases in end-tidal desflurane concentration transiently increase HR, MAP, and plasma epinephrine concentration; that this stimulation has a threshold of approximately 6% end-tidal desflurane; and that the magnitude of the response to any single, small step-increase is considerably less than the magnitude of response to a single, larger increase of desflurane concentration.

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