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Propofol Fails to Attenuate the Cardiovascular Response to Rapid Increases in Desflurane Concentration

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Background: A rapid increase in desflurane concentration to greater than 1 MAC transiently increases heart rate, arterial blood pressure, and circulating catecholamine concentration. Because propofol decreases sympathetic outflow, it was hypothesized that propofol would blunt these responses.

Methods: To test this hypothesis, five healthy male volunteers were studied three times. After induction of anesthesia with 2 mg · kg⁻¹ propofol, anesthesia was maintained with 4% end-tidal desflurane in oxygen (0.55 MAC) via an endotracheal tube for 32 min. On separate occasions, in random order, either no propofol or 2 mg · kg⁻¹ propofol was administered either 2 or 5 min before increasing end-tidal desflurane concentration from 4% to 8%.

Results: Without propofol pretreatment, the increase to 8% desflurane transiently increased heart rate (from 63 ± 3 beats/min to 108 ± 5 beats/min, mean ± SEM; $P < 0.01$), mean arterial pressure (from 73 ± 1 mmHg to 118 ± 6 mmHg; $P < 0.01$), and epinephrine concentration (from 14 ± 1 pg · ml⁻¹ to 279 ± 51 pg · ml⁻¹; $P < 0.05$). There was no significant change in norepinephrine concentration (from 198 ± 37 pg · ml⁻¹ to 277 ± 46 pg · ml⁻¹). The peak plasma epinephrine concentration was attenuated by each propofol pretreatment (158 ± 35 pg · ml⁻¹, propofol given 2 min before, and 146 ± 41 pg · ml⁻¹, propofol given 5 min before; $P < 0.05$), but neither propofol pretreatment modified the cardiovascular or norepinephrine responses.

Conclusions: Although able to blunt the increase in epinephrine concentration, propofol 2 mg · kg⁻¹ propofol does not attenuate the transient cardiovascular response to a rapid increase in desflurane concentration to greater than 1 MAC. (Key words: Anesthetics, intravenous: propofol. Anesthetics, volatile: desflurane. Blood pressure. Heart: heart rate. Sympathetic nervous system, catecholamines: epinephrine; norepinephrine.)

CLINICAL reports^{1,2} initially suggested and controlled studies³⁻⁵ demonstrated that rapid increases in desflurane concentration to greater than 1 MAC can cause transient sympathetic activation with increases in heart rate and blood pressure. These responses may increase the risk of myocardial ischemia in patients with ischemic heart disease.¹

Fentanyl, clonidine, and esmolol attenuate but do not completely block the desflurane-induced cardiovascular stimulation.⁶ Clonidine and esmolol were associated with subsequent hypotension, and clonidine increased postanesthetic drowsiness,⁶ properties that limit the usefulness of clonidine and esmolol for the purpose of attenuating desflurane-induced cardiovascular stimulation.

To develop a clinically useful strategy to prevent the transient desflurane-induced cardiovascular stimulation, we examined the capacity of propofol to blunt the cardiovascular response. We hypothesized that the sympathetic inhibition associated with propofol⁷ would attenuate the cardiovascular response to desflurane. When used for induction of anesthesia, propofol reportedly diminishes the cardiovascular response to an increase in desflurane during induction of anesthesia.⁸ We also hypothesized that the time of propofol administration may be important, because injection of propofol may trigger a transient cardiovascular response. Accordingly, we studied propofol administration two times before increasing the desflurane concentration.

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Methods

With approval of the University of California, San Francisco, Committee on Human Research and with written informed consent, we studied five healthy male volunteers, aged 23 ± 1 yr (mean \pm SEM). No volunteer had general anesthesia within 6 months of the study, medications within 7 days, alcohol for 2 days, or food or drink within 9 h of each study.

Anesthesia was induced with $2 \text{ mg} \cdot \text{kg}^{-1}$ propofol; $0.1 \text{ mg} \cdot \text{kg}^{-1}$ vecuronium facilitated tracheal intubation. One minute after induction of anesthesia, desflurane in oxygen was administered to produce and sustain an end-tidal concentration of 0.55 MAC (4%) for 32 min, as previously described.³ Throughout the study, inspired and end-tidal oxygen, carbon dioxide, and desflurane concentrations were measured by an infrared spectrometer (Datex Ultima, Helsinki, Finland). Gases were sampled at the proximal orifice of the endotracheal tube, and a 40-ml deadspace protected the end-tidal gas from contamination by inflow of fresh gas. The spectrometer was calibrated before and after each study. We used secondary (tank) standards, which had been calibrated by gas chromatography against primary (volumetric) standards, to calibrate for desflurane. Mechanical ventilation provided normocapnia, and surface warming with heated air (Bair Hugger, Augustine Medical, Eden Prairie, MN) sustained normothermia.

Each volunteer had intravenous and radial artery canulae inserted after skin infiltration with 1% lidocaine (the arterial catheter was placed after induction of anesthesia). Mean systemic arterial pressure (Gould Stratham 23XL transducer, calibrated with a mercury manometer before and after each study) and heart rate were recorded continuously by a digital polygraph (Gould model ES 2000).

The volunteers were anesthetized on three occasions, each separated by at least 5 days. After 32 min at 4% end-tidal desflurane, we increased the end-tidal concentration to 8% within 1 min and maintained this concentration for 10 min. To accomplish this rapid change, we used inflow rates of $6 \text{ l} \cdot \text{min}^{-1}$ and increased the inspired concentration to 12–14% desflurane. Tidal volume and respiratory rate were not altered. The volunteers received (in random order) either no propofol or $2 \text{ mg} \cdot \text{kg}^{-1}$ propofol 2 or 5 min before the increase in desflurane concentration. Injections of propofol were made over the course of 1 min into a free-flowing stream of lactated Ringer's solution directed through an 18-G catheter placed in the antecubital vein. We

determined that the injection caused little or no pain during induction of anesthesia.

Arterial blood was sampled, for measurement of pH, P_{O_2} , P_{CO_2} (by standard electrodes), and plasma catecholamines, before the administration of propofol on the occasions propofol was given, immediately before the increase in desflurane concentration, and at 1 min after reaching 8% end-tidal desflurane concentration. Plasma for assay of catecholamine concentration was stored at -70°C until thawed for analysis. Plasma catecholamine concentrations were determined by high-performance liquid chromatography, with detection limits of $14 \text{ pg} \cdot \text{ml}^{-1}$ for epinephrine and $25 \text{ pg} \cdot \text{ml}^{-1}$ for norepinephrine.

Coefficients of variation within trials were 2% epinephrine and 1% norepinephrine and between trials were 7% epinephrine and 3% norepinephrine. Sample values less than the limit of detection were considered as having a concentration just below the limit of detection.

Data obtained before and after the increases in desflurane within groups were compared with repeated measures analysis of variance, and data from each group receiving propofol before the desflurane increase were compared to the control data (desflurane administered in oxygen without propofol) using paired *t*-tests with Bonferroni correction. Data are reported as mean \pm SEM on all occasions. Statistical significance was accepted at $P < 0.05$.

Results

In the absence of pretreatment with propofol, the increase to 8% desflurane transiently but consistently increased heart rate and mean arterial pressure. Heart rate increased from 63 ± 3 beats/min to a peak of 108 ± 5 beats/min ($P < 0.01$). Mean arterial pressure increased from 73 ± 1 mmHg to a peak of 118 ± 6 mmHg ($P < 0.01$; fig. 1). Plasma epinephrine increased from $14 \pm 1 \text{ pg} \cdot \text{ml}^{-1}$ to $279 \pm 51 \text{ pg} \cdot \text{ml}^{-1}$ ($P < 0.05$), and plasma norepinephrine did not change significantly ($198 \pm 37 \text{ pg} \cdot \text{ml}^{-1}$ to $277 \pm 46 \text{ pg} \cdot \text{ml}^{-1}$; $P > 0.05$; fig. 2).

Administration of $2 \text{ mg} \cdot \text{kg}^{-1}$ propofol during 4% end-tidal desflurane anesthesia 2 min before the desflurane increase, transiently increased heart rate from 68 ± 4 beats/min to 89 ± 7 beats/min ($P < 0.05$). Mean arterial pressure did not change significantly (78 ± 5 mmHg to 96 ± 8 mmHg; $P > 0.05$) when propofol was given 2 min before the desflurane increase. When pro-

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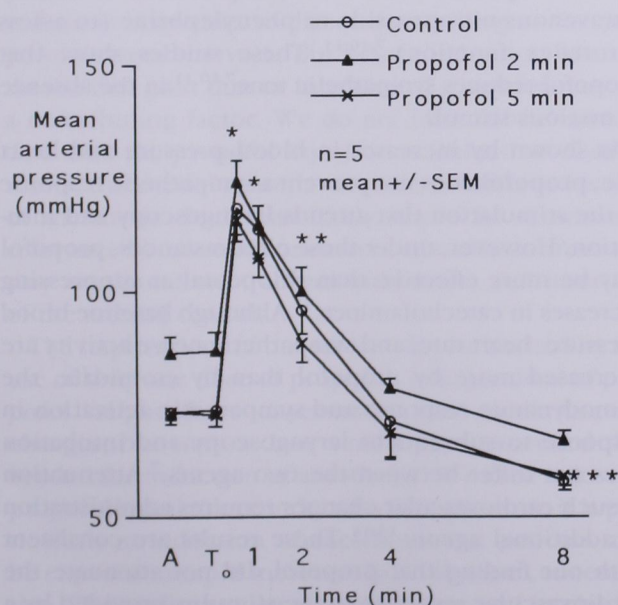
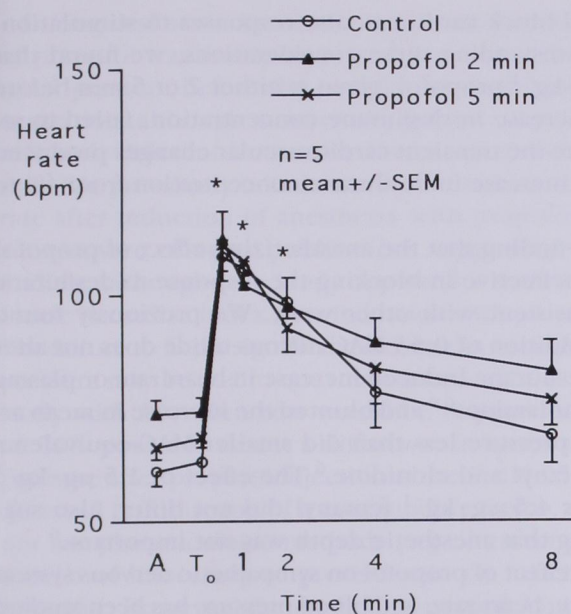


Fig. 1. A rapid increase in desflurane concentration in the control group produced an increase in heart rate and mean arterial pressure, compared to values at 32 min of 4% end-tidal desflurane (* $P < 0.01$; ** $P < 0.05$). Mean arterial pressure was significantly reduced in the control group at 8 min after the increase in desflurane, compared to the value at 32 min of 4% end-tidal desflurane (** $P < 0.01$). There were no significant differences between the groups before the desflurane increase. Propofol in a concentration of $2 \text{ mg} \cdot \text{kg}^{-1}$ at both times of administration did not alter the increase in heart rate or mean arterial pressure after a rapid increase of end-tidal desflurane concentration. A = value at 32 min of 4% end-tidal desflurane; T₀ = value at first breath of increased concentration.

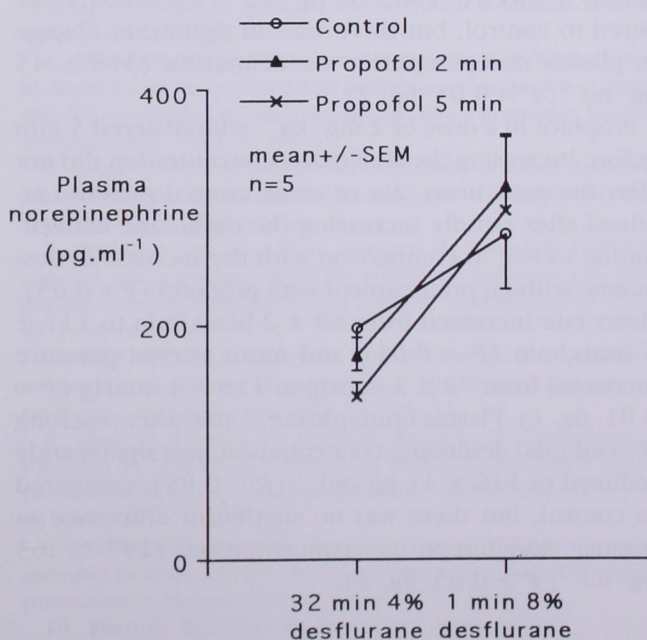
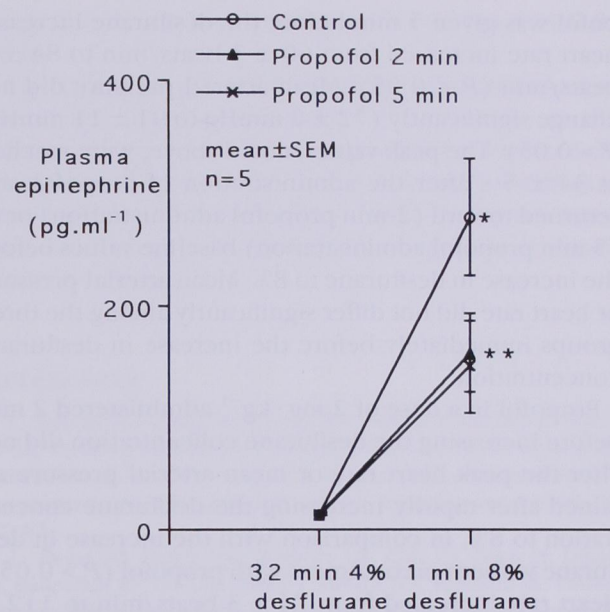


Fig. 2. In the control group, plasma epinephrine increased significantly from 32 min of 4% end-tidal desflurane to 8 min of 8% end-tidal desflurane (* $P < 0.05$). Plasma epinephrine at 8 min of 8% end-tidal desflurane was significantly reduced in both propofol groups compared to control (** $P < 0.05$). There was no significant difference in norepinephrine concentration after the increase in desflurane concentration within or between the groups.

propofol was given 5 min before the desflurane increase, heart rate increased from 60 ± 3 beats/min to 84 ± 9 beats/min ($P < 0.05$). Mean arterial pressure did not change significantly (72 ± 2 mmHg to 91 ± 11 mmHg; $P > 0.05$). The peak values, noted above, were reached at 34 ± 5 s after the administration of propofol and returned toward (2-min propofol administration) or to (5-min propofol administration) baseline values before the increase in desflurane to 8%. Mean arterial pressure or heart rate did not differ significantly among the three groups immediately before the increase in desflurane concentration.

Propofol in a dose of $2 \text{ mg} \cdot \text{kg}^{-1}$ administered 2 min before increasing the desflurane concentration did not alter the peak heart rate or mean arterial pressure attained after rapidly increasing the desflurane concentration to 8%, in comparison with the increase in desflurane without pretreatment with propofol ($P > 0.05$). Heart rate increased from 74 ± 3 beats/min to 112 ± 6 beats/min ($P < 0.01$), and mean arterial pressure increased from 86 ± 4 mmHg to 124 ± 4 mmHg ($P < 0.01$; fig. 1). Plasma epinephrine, 1 min after reaching 8% end-tidal desflurane concentration, was significantly reduced to $158 \pm 35 \text{ pg} \cdot \text{ml}^{-1}$ ($P < 0.05$), compared to control, but there was no significant change in plasma norepinephrine concentration ($318 \pm 45 \text{ pg} \cdot \text{ml}^{-1}$; $P > 0.05$; fig. 2).

Propofol in a dose of $2 \text{ mg} \cdot \text{kg}^{-1}$ administered 5 min before increasing the desflurane concentration did not alter the peak heart rate or mean arterial pressure attained after rapidly increasing the desflurane concentration to 8%, in comparison with the increase in desflurane without pretreatment with propofol ($P > 0.05$). Heart rate increased from 68 ± 2 beats/min to 111 ± 6 beats/min ($P < 0.01$), and mean arterial pressure increased from 72 ± 2 mmHg to 116 ± 4 mmHg ($P < 0.01$; fig. 1). Plasma epinephrine, 1 min after reaching 8% end-tidal desflurane concentration, was significantly reduced to $146 \pm 41 \text{ pg} \cdot \text{ml}^{-1}$ ($P < 0.05$), compared to control, but there was no significant difference in plasma norepinephrine concentration ($297 \pm 63 \text{ pg} \cdot \text{ml}^{-1}$; $P > 0.05$; fig. 2).

Discussion

Propofol reportedly decreases sympathetic nerve activity, reduces vascular resistance, is associated with hypotension, and attenuates baroreceptor reflex mechanisms.⁷ One might also speculate that the additional anesthesia conferred by administration of propofol

would block cardiovascular responses to stimulation. Notwithstanding these considerations, we found that $2 \text{ mg} \cdot \text{kg}^{-1}$ propofol, given at either 2 or 5 min before the increase in desflurane concentration, failed to attenuate the transient cardiovascular changes produced by an increase in desflurane concentration from 4% to 8%.

The finding that the anesthetizing effect of propofol was ineffective in blocking the response to desflurane is consistent with other work. We previously found that addition of 0.55 MAC nitrous oxide does not alter the desflurane-induced increase in heart rate or plasma catecholamines^{6,9} and blunted the increase in mean arterial pressure less than did smaller MAC-equivalents of fentanyl and clonidine.⁶ The effect of $1.5 \text{ } \mu\text{g} \cdot \text{kg}^{-1}$ versus $4.5 \text{ } \mu\text{g} \cdot \text{kg}^{-1}$ fentanyl did not differ, also suggesting that anesthetic depth was not important.⁶

The effect of propofol on sympathetic nervous system activity, heart rate, and blood pressure has been studied in volunteers and patients not undergoing stimulation, other than perturbations of blood pressure induced by intravenous nitroprusside or phenylephrine (to assess baroreflex function).^{7,10,11} These studies show that propofol reduces sympathetic tone^{7,10,11} in the absence of noxious stimuli.

As shown by increases in blood pressure and heart rate, propofol does not prevent a sympathetic response to the stimulation that attends laryngoscopy and intubation. However, under these circumstances, propofol may be more effective than thiopental at suppressing increases in catecholamines.¹² Although baseline blood pressure, heart rate, and sympathetic nerve activity are decreased more by propofol than by etomidate, the hemodynamic response and sympathetic activation in response to subsequent laryngoscopy and intubation does not differ between the two agents.⁷ Attenuation of such cardiovascular changes requires administration of additional agents.^{13,14} These results are consistent with our finding that propofol did not attenuate the cardiovascular response to the stimulus provided by a rapid increase in desflurane concentration. The magnitude of the cardiovascular response after such a rapid increase in desflurane concentration does not differ from that found after a 4–12% increase,³ suggesting that the increase to 8% elicits a maximal response. We also have found that the cardiovascular response after a 4–8% end-tidal desflurane increase is similar to that found with application of 100 Hz supramaximal stimulation of the ulnar nerve¹⁵ or the response to endotracheal intubation³ during desflurane anesthesia.

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During desflurane anesthesia, we found that injection of propofol transiently increased heart rate. Mean arterial pressure before the increase in desflurane concentration, although numerically greater, was not significantly different from values before propofol injection. We previously noted a transient increase in heart rate after induction of anesthesia with propofol.³ We are unaware of other publications suggesting such a finding, although one study reported a transient increase in cardiac index after induction with propofol.¹⁶ The failure to find a significant increase in mean arterial pressure may be due to our small sample size. A repeat study with 10 volunteers would be required to have an 80% power to detect a difference in mean arterial pressure after propofol injection at the $P < 0.05$ level. To avoid introduction of a confounding factor, we did not use pharmacologic methods (e.g., intravenous injection of lidocaine) to prevent pain on injection of propofol. However, the method of propofol injection before the increase in desflurane was the same as at induction of anesthesia, and we are confident from the volunteer responses to direct questioning as the propofol entered the vein, but before induction of anesthesia, that pain due to injection of propofol was not a contributing factor. We do not have cardiovascular data after the propofol injection at induction of anesthesia; the arterial cannula was inserted after induction of anesthesia. Such data likely would be of minimal relevance because of concurrent stimulation from airway manipulation, tracheal intubation, and insertion of the arterial cannula.

The implications of our results may be limited by the use of only one dose of propofol. A larger dose of propofol might have attenuated the cardiovascular changes, but such a dose would have exceeded that needed for induction of anesthesia. We used a dose of propofol equal to our induction dose, because it is particularly at induction of anesthesia that patients may be exposed to rapid increases in desflurane concentration. The cardiovascular response to tracheal intubation is not different for induction doses of 2–3.5 mg · kg⁻¹ propofol.¹⁴ Thus, we have no reason to suspect that increasing the propofol dose would have modified the cardiovascular response found in this study. The failure of this study to find a significant attenuation of the cardiovascular response after a rapid increase in desflurane concentration, following pretreatment with propofol, may be attributed to the small sample size. However, a repeat study with 50 volunteers would be required to have an 80% power to detect a difference in the peak

heart rate or mean arterial pressure at the $P < 0.05$ level.

In conclusion, propofol diminishes sympathetic tone during the unstimulated state.^{7,10,11} However, in this study, we found that, although propofol attenuated the epinephrine response to a rapid increase in desflurane concentration to greater than 1 MAC, it did not attenuate the transient cardiovascular response in young healthy volunteers.

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