Propofol, but not etomidate, reduces desflurane-mediated sympathetic activation in humans

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Purpose: The administration of desflurane to humans can lead to substantial activation of the neurohumoral axis. Propofol can inhibit the sympathetic response to stress. This study compared the neurocirculatory effects of induction of anesthesia with propofol with those of etomidate on desflurane-mediated sympathetic activation.

Methods: After informed consent, awake baseline recordings of heart rate (HR), mean arterial blood pressure (MAP), and efferent sympathetic nerve activity (SNA, peroneal nerve) were obtained from healthy volunteers randomly assigned to receive either 2.5 mg·kg⁻¹ propofol (n=8) or 0.3 mg·kg⁻¹ etomidate (n=7). Two minutes after iv induction, desflurane 3.6% was added to the inspired gas, and increased in consecutive minutes to 7% and 10.9%. Ventilation via mask was continued for an additional seven minutes. Normocarbica was maintained while neurocirculatory parameters were continuously recorded.

Results: There were no differences between groups at baseline. The administration of desflurane via mask after etomidate led to increases in HR, MAP and SNA. Propofol significantly reduced the MAP response and delayed and attenuated the sympatho-excitation.

Conclusion: Propofol induction reduced the sympathetic activation and hypertension associated with desflurane.

Objectif : L'administration de desflurane aux humains peut mener à une activation importante de l'axe neurohumoral. Le propofol peut inhiber la réponse du système sympathique au stress. La présente étude a comparé les effets neurocirculatoires de l'induction de l'anesthésie avec du propofol à ceux de l'étomidate sur l'activation du système sympathique par le desflurane.

Méthode : Après avoir obtenu le consentement éclairé de volontaires en bonne santé, on a pris les mesures de base, avant l'anesthésie, de la fréquence cardiaque (FC), de la tension artérielle moyenne (TAM) et de l'activité nerveuse efférente sympathique (ANS, nerf tibial antérieur), et on a réparti les sujets qui ont reçu 2,5 mg·kg⁻¹ de propofol (n = 8) ou 0,3 mg·kg⁻¹ d'étomidate (n = 7). Deux minutes après l'induction iv, on a ajouté du desflurane 3,6 % au gaz inspiré et on l'a augmenté à 7 % et 10,9 % dans les minutes suivantes. On a poursuivi la ventilation au masque pendant sept minutes de plus. La normocarbica a été maintenue pendant l'enregistrement continu des paramètres neurocirculatoires.

Résultats : Il n'y avait pas de différences intergroupe pour les mesures de base. Le desflurane administré par masque après l'étomidate a fait augmenter la FC, la TAM et l'ANS. Le propofol a réduit de façon significative la modification de la TAM et a retardé et atténué l'ANS.

Conclusion : L'induction au propofol a réduit l'activation du système sympathique et l'hypertension associée au desflurane.

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DESFLURANE differs substantially from the other volatile agents. It has an extremely low blood:gas partition coefficient (0.42) that permits rapid adjustment of the concentration of anesthesia as well as swift emergence from anesthesia.¹ These qualities make it an attractive choice for outpatient anesthesia where quick emergence with minimal fixed adjuvants is desirable. Also the low solubility should permit rapid induction of anesthesia but, because of the pungency of desflurane and the associated airway irritation, it has proved to be unsuitable for use as a sole induction agent.^{2,3} In addition, when compared with other anesthetics, desflurane produced exaggerated increases in heart rate (HR) and blood pressure (BP) and a greater incidence of myocardial ischemia during its initial administration into the inspired gases.⁴⁻⁶ A previous study from our laboratory⁴ demonstrated that these responses to desflurane are initiated by a striking activation of the sympathetic nervous system.

When used for outpatient anesthesia, it is possible that desflurane would be chosen for maintenance after the use of propofol for induction of anesthesia. We have previously documented a marked and sustained inhibition of sympathetic outflow following anesthetic induction with propofol.⁷ Despite these findings, a recent study in five volunteers suggests that propofol pretreatment prior to a sudden increase in the inspired desflurane concentration was unsuccessful in attenuating the subsequent tachycardia and hypertension.⁸ In the present study, we hypothesized that sympathoinhibitory effects of propofol would favorably modify the initial sympathetic activation produced when desflurane was introduced into the inspired gas.

Methods

After approval from the Institutional Review Board and following informed consent, 15 healthy, normotensive, male volunteers, aged 20-31 yr, were studied. These volunteers were paid and were free of systemic illness, were not receiving medications, did not take any drugs, and had fasted for at least 12 hr before testing. Each ingested 30 ml of nonparticulate antacid prior to study. Volunteers were studied while supine. Heart rate was monitored from leads II and V₅ of the ECG. A 20-gauge catheter was inserted into the radial artery for direct determination of BP. An 18-gauge catheter was inserted into a forearm vein and 5-7 ml·kg⁻¹ saline were administered before initiation of the study.

Peroneal nerve recordings

The right leg was supported and cushioned. The bony prominence at the proximal head of the fibula on the

lateral aspect of the leg was identified and marked. Brief electrical impulses (1 Hz, 3-7 mA) were delivered below this mark to identify the location of the peroneal nerve. The skin was cleansed and two 5 μ -tipped, epoxy coated, tungsten needles (TMI, Iowa City, IA) were inserted percutaneously. One needle was advanced until the tip was in an area just outside the peroneal nerve while the second was advanced into the peroneal nerve. The location of the nerve was identified by the application of brief electrical impulses (1 Hz, 0.02-0.03 mA) to the needle. A distinct muscle contraction in the distribution of the deep or superficial peroneal nerve was observed when a motor nerve fascicle within the peroneal nerve was entered. The stimulation was halted and neural activity was amplified (100,000 $\times$), band-pass filtered (200-1000 Hz), rectified and integrated. Signals common to both needles (e.g., background noise) were canceled by common-mode rejection with a custom-made preamplifier.

Characteristic bursts of efferent sympathetic nerve activity (SNA) were sought by fine manipulations of the needle within the motor nerve fascicle. The identification of these bursts and differentiation from skin sympathetic efferent nerve fibres have been described in detail elsewhere.⁹ Briefly, spontaneous bursts within the amplified signal were identified as sympathetic efferent neural activity if they occurred in pulse-synchronous groupings, generally were phase-locked to late expiratory and early inspiratory periods, were triggered by periods of low diastolic blood pressure, and preceded elevations in blood pressure. If the origin of the nerve activity could not be confirmed by the above observations, several procedures known to increase sympathetic efferent neural activity, i.e., prolonged breath holding and phases II and III of the Valsalva manoeuvre, were initiated. Bursts were identified and quantified by measuring the mean burst amplitude and the frequency of bursting expressed as bursts per 100 heart beats, so as to normalize activity based upon individual resting HRs (total activity = mean sympathetic burst amplitude $\times$ burst frequency/100 cardiac cycles). The automated system employed for these analyses was monitored by visual inspection of signals.

Experimental protocol

Once an acceptable sympathetic recording was obtained, a 10 min rest period was observed followed by five minutes of hemodynamic (HR, MAP) and neural (SNA) measurements which served as control values. The SNA, HR and MAP were averaged over the course of the five minute epoch of data collection. The face-mask was placed and O₂ 100% was administered for five minutes during spontaneous breathing. End-tidal CO₂

and post-induction inspiratory and expiratory desflurane concentrations were monitored by an infrared respiratory gas monitor (Ohmeda 5250; Madison, WI). A priming dose of $0.01 \text{ mg}\cdot\text{kg}^{-1}$ vecuronium was given, followed by induction of anesthesia with $0.3 \text{ mg}\cdot\text{kg}^{-1}$ etomidate ($n=7$) or $2.5 \text{ mg}\cdot\text{kg}^{-1}$ propofol ($n=8$), determined by random assignment, and $0.1 \text{ mg}\cdot\text{kg}^{-1}$ of vecuronium. Ventilation was controlled via the mask and without an oral airway for 10 min at a fresh gas flow of $8 \text{ L}\cdot\text{min}^{-1}$, maintaining end-tidal CO_2 concentrations at control (awake) values. Neuromuscular function was evaluated by train-of-four responses from the ulnar nerve. Exactly two minutes after intravenous induction, the vaporizer was set to desflurane 3.6%. The setting was increased to 7.2% and then 10.9% in the two subsequent one-min periods. The desflurane concentration was maintained at 10.9% for an additional five minutes. Continuous hemodynamic and nerve recordings were made throughout the 10 min induction period. Measurements of SNA, MAP and HR were averaged for each minute during minutes two - five and eight - ten after *iv* induction. Data for minutes six and seven were not obtained due to storage buffer limitations of our antiquated computer system.

Statistical procedures

Differences between baseline and induction measures of HR, MAP and SNA for each group (propofol and etomidate) were evaluated with paired *t* tests. Differences between the propofol and etomidate groups at baseline and induction were determined with unpaired *t* tests. Measures of HR, MAP and SNA made during desflurane administration were evaluated with repeated measures analysis of variance (ANOVA), with with Dunnett's post hoc analysis. A probability of $P < 0.05$ was sufficient to reject the null hypothesis.

Results

Baseline and induction

All participants were ASA physical status I, in good health, with low resting heart rates ($61 \pm 3 \text{ b}\cdot\text{min}^{-1}$, propofol group; $59 \pm 4 \text{ b}\cdot\text{min}^{-1}$, etomidate group) (mean $\pm$ SEM) and normal blood pressures (MAP, $91 \pm 3 \text{ mm Hg}$, propofol group; $99 \pm 3 \text{ mm Hg}$, etomidate group) at conscious baseline (control). One minute after *iv* induction of anesthesia, SNA, MAP and HR were averaged over the one minute immediately before breathing desflurane. These values served as the post-induction baseline (Figure 1). Results of repeated measures ANOVA demonstrated differences between groups (etomidate and propofol) for MAP and SNA ($P < 0.001$). There was an interaction for MAP ($P < 0.05$). Differences between propofol and etomidate at specific

FIGURE 1 Average neurocirculatory responses to the initial administration of desflurane by mask following anesthetic induction with either propofol or etomidate. The anesthetized baseline represents data collected two minutes after anesthetic induction but before initiation of desflurane.

§ = propofol response different from etomidate response ($P < 0.05$).

† = response different over time ($P < 0.05$).

* = response different between groups at individual time points (Dunnett's) ($P < 0.05$).

‡ = interaction between groups by repeated measures ANOVA ($P < 0.05$).

total activity = (burst frequency $\times$ mean burst amplitude)/100 cardiac cycles.

time points after induction were assessed with Dunnett's, and are indicated in the figure. Propofol caused a reduction (76%) in SNA from control. Etomidate, however, preserved SNA after induction with no change from control. Associated with these SNA effects, MAP, averaged over the two minutes after *iv* induction, decreased from control values in the propofol group ($-12 \pm 2 \text{ mm Hg}$) but not in the etomidate group ($-3 \pm 2 \text{ mm Hg}$). Heart rate was not changed from control in either group (Figure 1c) or different between the two groups.

The SNA was increased during desflurane administration in both groups, but the overall response was greater in the etomidate group (Figures 1a, 2). Peak SNA reached 309 ± 47 units during the eighth

FIGURE 2 Representative sympathetic neurograms and associated hemodynamic parameters from two subjects undergoing general anesthesia. The top tracing is from a subject who was anesthetized with 2.5 mg·kg⁻¹ propofol, which virtually abolished sympathetic nerve activity leading to a substantial reduction in blood pressure. Two minutes after initiating desflurane by mask, sympathetic activity began to return but had not substantially returned until four minutes after desflurane initiation. Activation of the sympathetic nervous system and large increases in heart rate and arterial pressure are noted. The lower tracing is from a subject anesthetized with 0.03 mg·kg⁻¹ etomidate, which did not decrease sympathetic activity or change blood pressure. The early administration of desflurane was associated with more neural activity than in the subject in whom anesthesia was induced with propofol.

minute, an increase of 218 ± 61 units over control in the etomidate group. Peak SNA in the propofol group was attenuated compared with the peak in the etomidate group, and reached only 210 ± 33 units (124 ± 30 units over control) in the fifth minute.

Desflurane induced a bi-phasic MAP response in the etomidate group with an increase over control in the early minutes, followed by decreases in the eighth to tenth minutes (Figure 1b). Peak MAP, 125 ± 4 mm Hg, was increased over conscious control ($+25 \pm 5$ mm Hg) and over anesthetized baseline ($+27 \pm 5$ mm Hg). The propofol group started from a lower MAP after *iv* induction (-12 ± 3 mm Hg), and demonstrated a more attenuated and delayed increase in MAP with desflurane to a peak of 95 ± 7 mm Hg. This peak was increased over anesthetized baseline (15 ± 5 mm Hg) but not over conscious control (3 ± 6 mm Hg). The MAP response to desflurane was different between the etomidate and the propofol groups (Figure 1b).

Desflurane caused HR increases in both groups (Figure 1c). The HRs in both the etomidate group and the propofol group were increased over conscious controls and anesthetized baselines. Peak HR occurred in minute five for both groups, reaching 106 ± 6 b·min⁻¹ (46 ± 4 b·min⁻¹ over control) in the eto-

midate group and 96 ± 5 b·min⁻¹ (35 ± 7 b·min⁻¹ over control) in the propofol group. The HR was not different between the groups at any time during desflurane administration.

Discussion

The present study indicates that propofol (2.5 mg·kg⁻¹), but not etomidate (0.3 mg·kg⁻¹), inhibits sympathetic nerve activity during the initial administration of desflurane into the inspired gas mixture. This attenuation of sympathetic activity was coincident with a substantial reduction in the hypertensive response that was consistently noted from volunteers receiving etomidate prior to desflurane. In contrast, the tachycardia associated with desflurane was not modified by propofol.

Etomidate and propofol effects

As previously reported by our laboratory, propofol has a profound effect on sympathetic outflow.⁷ Tonic levels of sympathetic nerve activity in conscious volunteers were virtually abolished by anesthetic induction with propofol and substantial reductions in blood pressure occurred. In addition, we have previously noted that propofol has an important indirect effect on arterial and venous smooth muscle leading to vascular dilatation that undoubtedly contributes to the hypotensive response to propofol.¹⁰ In contrast, anesthetic induction with etomidate maintained basal levels of sympathetic vasoconstrictor outflow and this likely contributed to the maintenance of arterial blood pressure.

Effects of desflurane

Consistent with our previous observation in healthy volunteers receiving desflurane after thiopental induction,⁴ when desflurane was given after anesthesia induction with etomidate, two- to three-fold increases in sympathetic neural outflow were observed. This was associated with substantial increases in mean pressure and heart rate. Retrospective analyses revealed only subtle differences in these responses when compared with the responses of volunteers anesthetized with thiopental in our previous study. The mechanism(s) of sympathetic activation with desflurane are uncertain. One likely explanation is that the airway irritant effects of desflurane initiate sympathetic responses.¹¹ Consistent with our previous study, we noted facial flushing, tearing, and increased airway resistance in these volunteers during the administration of desflurane.

The ability of propofol to inhibit sympathetic outflow delayed the sympathetic activation triggered by desflurane. Moreover, the total nerve activity over the

10 min induction period was reduced compared with that after etomidate. This may explain the smaller increase in arterial pressure during the initial minutes of desflurane administration. The heart rate increase produced by desflurane in volunteers in whom anesthesia was induced with etomidate was not different from that in volunteers induced with propofol. This could be due to several as yet unproved mechanisms working in unison. One mechanism could be via a desflurane-triggered increase in efferent *cardiac* sympathetic nerve activity, which might be less effectively attenuated by propofol administration. Another mechanism may involve the baroreflex, since blood pressure was substantially lower following administration of propofol. Other possible mechanisms of the preserved heart rate increase following desflurane include an effect of desflurane that promotes a withdrawal of vagal tone independent of sympathetic outflow and/or direct effects of desflurane on cardiac pacemaker cells.

These findings differ from an earlier study that employed five volunteers to study the efficacy of 2 mg·kg⁻¹ propofol in blunting sympatho-excitation, tachycardia and hypertension from desflurane.⁸ However, the design of the two studies was substantially different. The earlier study did not evaluate the induction responses to desflurane; rather, it studied volunteers during the maintenance period, after 32 min of desflurane (4%). Propofol was given either two or five minutes before a rapid increase in the inspired concentration of desflurane from 4% to 8%. They noted the increases in heart rate, blood pressure and norepinephrine in response to desflurane were preserved after propofol, but the epinephrine response was reduced. The rather simple process of increasing the inspired desflurane from 4% to 8% resulted in substantial epinephrine increases to 300 pg·ml⁻¹, but after pretreatment with 2 mg·kg⁻¹ propofol the epinephrine response was roughly halved.

We recognize several limitations of this research. One concerns the choice of subjects for study. The population that is placed at greatest risk by the substantial neurocirculatory activation associated with desflurane is that of patients with cardiac or cerebrovascular disease. However, the healthy population that was examined permitted a safe evaluation of the efficacy of propofol and etomidate to attenuate this neurocirculatory activation. Secondly, we did not study different doses of each induction agent and, therefore, are unable to derive dose-response information. Moreover, the selected doses may not be clinically relevant for all populations, but do provide general information consistent with their expected properties on the sympathetic nervous system.

In summary, the use of desflurane may be constrained by its undesirable ability to activate the sympathetic nervous system, triggering elevations in blood pressure and heart rate and thereby increasing myocardial oxygen demands. This effect seems to be consistent in volunteers induced with either thiopental or etomidate. However, the sympatho-inhibitory effects of propofol attenuate the sympatho-excitation and hypertension resulting from the initial titration of desflurane into the inspired gas shortly after induction of anesthesia. In select populations, the sympathetic inhibition afforded by propofol may prove beneficial, although it should be noted that it was ineffective in attenuating the tachycardia associated with desflurane. Considering the effect of increases in heart rate on myocardial oxygen supply and demand, the use of a beta blocking agent or an opioid also may be beneficial in attempting to prevent potential complications from desflurane after induction of anesthesia with propofol.^{12,13}

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