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Effects of Fentanyl on Sympathetic Activation Associated with the Administration of Desflurane

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Background: **Activation of the sympathetic nervous system occurs when desflurane is inspired shortly after anesthetic induction and when the inspired concentration of desflurane is rapidly increased during steady-state periods of anesthesia. The purpose of this study was to determine the effectiveness and dose response of fentanyl pretreatment in attenuating the neurocirculatory responses to desflurane in healthy human volunteers.**

Methods: **After Institutional Research Review Board approval, three study groups were selected and, in random order, received either placebo (n = 10), a 2.5-$\mu g \cdot kg^{-1}$ intravenous bolus of fentanyl citrate followed by a continuous infusion of 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (n = 9), or a 5.0-$\mu g \cdot kg^{-1}$ intravenous bolus followed by an infusion of 2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (n = 11) before the administration of desflurane. Arterial (MAP) and central venous (CVP) pressures were measured directly, and heart rate (HR) was determined indirectly. Efferent muscle sympathetic nerve activity (SNA) was recorded from the peroneal nerve by microneurography. After neurocirculatory recordings at conscious unmedicated baseline and 12 min after fentanyl administration, anesthetic induction was carried out with 2.0 $mg \cdot kg^{-1}$ propofol and 0.2 $mg \cdot kg^{-1}$ vecuronium. Neurocirculatory measurements were repeated beginning 2 min after induction when desflurane was given *via* mask (semiclosed circle system, 6 l/min fresh gas flow, 100% O_2) in three incremental 1-min steps (3.6%, 7.2%, and 11%). Intubation occurred 10 min after propofol administration. Twenty minutes after intubation, recordings were obtained during two steady-state periods during which end-tidal concentrations had achieved 5.4% (0.75 MAC) and 11% (1.5 MAC) desflurane for at least 10 min. Data also were obtained during the rapid increase in the inspired gas concentration from 5.4% to 11% ("transition").**

Results: **Neurocirculatory variables did not differ between the three groups at conscious baseline, after fentanyl, and during steady-state periods of anesthesia. Propofol administration significantly reduced SNA and MAP. The MAP reduction was enhanced in the fentanyl-treated groups. After induction, the increases in SNA and MAP associated with the administration of desflurane by mask were not significantly reduced by fentanyl. The transition from 5.4% to 11% desflurane resulted in increases in SNA, HR, MAP, and fentanyl administration significantly attenuated the HR and MAP components. At the 11% steady-state measurement period, CVP was increased and MAP was decreased from conscious baseline, and these changes were not modified by fentanyl.**

Conclusions: **The administration of desflurane was associated with increases in SNA, HR, MAP, and CVP. Maximum sympathetic activation and hemodynamic responses occurred 4–5 min after initiating desflurane during induction and 2–3 min after increasing the inspired concentration of desflurane during the "transition" period. Although fentanyl partially attenuated the hemodynamic component in a dose-dependent fashion during the "transition" period, it did not significantly diminish the response during induction. (Key words: Anesthetics, intravenous: fentanyl. Anesthetics, volatile: desflurane. Sympathetic nervous system, measurement techniques: microneurography.)**

SYMPATHETIC nervous system activation has been observed when initially adding desflurane into the inspired gas shortly after intravenous induction of anesthesia.[1–3] This activation has been noted when the inspired concentration of desflurane exceeds 5–7% (~1.0 MAC).[2,4–6] The hemodynamic manifestations of the sympathetic activation consist of substantial increases in heart rate (HR) and blood pressure.[1–3,6] Because the properties of desflurane, such as its low solubility in blood and negligible metabolism,[7] make this agent a promising addition to the available potent inhaled anesthetic agents, effective methods to attenuate the hemodynamic perturbations produced by desflurane need to be delineated.

The purpose of this study was to determine the efficacy of two doses of the commonly used pre-induction opioid fentanyl in attenuating the sympathetic activation and subsequent hemodynamic responses associated with the administration of desflurane. In previous studies, the administration of 10 $\mu g \cdot kg^{-1}$ fentanyl before the administration of desflurane in patients undergoing anesthesia for coronary artery bypass graft

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(CABG) surgery[8] was not associated with tachycardia, hypertension, and myocardial ischemia seen in a separate study in which CABG patients were not pretreated with opioids before the administration of desflurane.[3] Because it is likely that desflurane will be employed frequently in shorter surgical procedures and outpatient procedures, smaller doses of fentanyl that might be chosen as a part of the desflurane anesthetic regimen were examined in the current study.

Methods and Materials

Institutional Research Review Board approval was obtained before the initiation of this study. Thirty healthy males, 20–34 yr of age, without systemic illnesses, and not receiving any prescription medications or taking illicit drugs were enrolled. Each subject fasted for at least 8 h before participation and none had a recent history of tobacco use. Volunteers provided written informed consent and were randomized to receive either placebo (group 1, n = 10), a 2.5-$\mu g \cdot kg^{-1}$ intravenous bolus of fentanyl citrate followed by a continuous infusion of 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (group 2, low-dose fentanyl, n = 9), or a 5.0-$\mu g \cdot kg^{-1}$ intravenous bolus of fentanyl citrate followed by a continuous infusion of 2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (group 3, mid-dose fentanyl, n = 11) before the administration of desflurane.

An 18-G catheter was placed in a forearm vein, and 7 $ml \cdot kg^{-1}$ of normal saline was given over 10 min followed by a 2.5-$ml \cdot kg^{-1} \cdot h^{-1}$ infusion. Arterial blood pressure (MAP) was measured *via* a 20-G catheter placed in the radial artery. An 18-G catheter in the superior vena cava *via* the external jugular vein was used to determine central venous pressure (CVP). Heart rate (HR) was determined from leads II and V5 of the electrocardiogram (ECG). Forearm blood flow (FBF) was determined by plethysmography whereby a Hg-in-Silastic, temperature-compensated, strain gauge was wrapped around the forearm and an upper arm blood pressure cuff was cyclically inflated (8 s on, 8 s off) to 60 mmHg while venous outflow from the hand was prevented with a wrist cuff. Forearm vascular resistance (FVR) was calculated as the ratio of MAP to FBF. An Ohmeda 5250 infrared respiratory gas monitor (Madison, WI) was employed for inspired and expired gas monitoring and was calibrated before each study with commercial tank standards.

The peroneal nerve was impaled to obtain recordings of efferent sympathetic nerve activity (SNA) directed to vascular smooth muscle of skeletal muscle blood vessels.[9,10] Briefly, the fibular head on the lateral aspect of the lower extremity was palpated and the course and location of the peroneal nerve that passes under the bony prominence was mapped using an external nerve stimulator. The site of maximum motor response was used as a guide for the percutaneous placement of two 32-G, epoxy-coated, tungsten needles. The reference needle was placed outside the nerve bundle, and the recording needle was maneuvered into a nerve fascicle. This was accomplished by delivering small electrical impulses to the needle until a motor response was observed in the distribution of the deep or superficial peroneal nerve. Neural activity was then filtered, amplified, and displayed on an oscilloscope. Characteristic, spontaneous, pulse-synchronous, muscle sympathetic nerve activity was sought by fine manipulations of the needle within the muscle nerve fascicle as described previously.[9,10]

Fentanyl infusions were maintained using a Bard infusion pump (North Reading, MA). Plasma fentanyl concentrations were determined by a commercially available radioenzymatic assay (Upjohn). The coefficient of variation of the assay was 11%.

Protocol

Twenty minutes after placement of catheters and needles, neurocirculatory data at conscious baseline were averaged over a 5-min sampling period. In opioid treatment groups, fentanyl was given through the peripheral intravenous catheter over 60 s, and 5 min later, an additional 5 min of baseline data were obtained and averaged. In an attempt to avoid hypoventilation and hypercapnia in the fentanyl groups, verbal cues were provided to maintain respiratory rate. Blood samples for arterial blood gas determination and plasma fentanyl concentration were taken after neurocirculatory measurements in awake subjects, 10 min after the initial fentanyl administration and at steady-state periods of anesthesia when end-tidal desflurane concentrations were 5.4% and 11%.

While the subjects breathed oxygen, 0.01 $mg \cdot kg^{-1}$ vecuronium was given (12 min after fentanyl administration) followed by 2 $mg \cdot kg^{-1}$ propofol and 0.2 $mg \cdot kg^{-1}$ vecuronium. Oxygen flow rates during induction were kept at 6 l/min in a semiclosed circle system, and ventilation was controlled by mask to maintain end-tidal carbon dioxide concentrations at conscious levels. Precisely 2 min after propofol administration, desflurane was added to the inspired gas

at 3.65%, increased 1 min later to 7.25%, and finally increased to 11% during the 3rd min and maintained at this level for an additional 7 min. Data were collected continuously during the 10-min induction period. Laryngoscopy and tracheal intubation were performed, ventilation was mechanically controlled with a combination air (3 l/min) and oxygen (3 l/min) mixture, and the vaporizer setting was reduced to deliver 5.4%. Twenty minutes elapsed (30 min after propofol administration) before subsequent recordings.

A 5-min data collection period at each of two steady-state periods of desflurane administration and a 5-min "transition" period were evaluated. These three measurement periods were in the following sequence: (1) steady-state end-tidal desflurane of 5.4% (0.75 MAC), (2) "transition" immediately after the vaporizer was advanced from 5.4% to 11%, and (3) 10 min after establishing end-tidal desflurane concentrations at 11% (1.5 MAC). During each steady-state recording period, alveolar ventilation was adjusted to achieve normocarbia as determined by end-tidal carbon dioxide measurements and confirmed by arterial blood gas analyses. Subjects receiving fentanyl were given 0.4 mg intravenous naloxone and 0.4 mg intramuscular naloxone at the completion of the study.

Statistical procedures consisted of repeated measures analysis of variance (ANOVA) to determine differences between groups, differences over time, and interactions between drug (fentanyl or placebo) conditions for the induction transition and steady-state periods of observation. Dunnett's *t* tests were applied when differences by ANOVA were identified. Paired and unpaired Student's *t* tests also were applied where appropriate, and significance was assigned a P value of <0.05.

Results

Induction

At conscious baseline, there were no differences in neurocirculatory variables between treatment groups except for a significantly lower CVP noted in the placebo-treated group (table 1). Neither dose of fentanyl altered resting variables (table 2).

The neurocirculatory responses to propofol administration are evident in the representative recordings shown in figure 1 and are quantified in figure 2. Propofol administration was associated with significant decreases in sympathetic outflow and blood pressure and increases in HR. Fentanyl administration before propofol did not alter the SNA response to propofol administration but did abolish the increase in HR during induction, which was associated with a significantly larger decrease in MAP in the fentanyl-treated groups (fig. 2).

The initial administration of desflurane *via* mask led to increases in SNA, HR, and blood pressure (figs. 1 and 3). This response began during the 3rd min after initiating desflurane, when end-tidal desflurane concentrations averaged 6%. Because fentanyl altered the early hemodynamic effects associated with propofol administration, the HR and blood pressure increases associated with desflurane administration were initiated from a lower baseline (fig. 2). Fentanyl did not reduce the absolute magnitude of the HR and MAP increases associated with desflurane when the changes were calculated from the propofol baseline (table 3). However, when measured from the awake baseline, HR responses were significantly reduced in the fentanyl groups. Fentanyl pretreatment did not diminish the activation of the sympathetic nervous system associated with the initial administration of desflurane (fig. 3). The activation was significantly enhanced in both fentanyl groups when compared with the placebo response. This augmented SNA response was temporally associated with significant increases in CVP in the fentanyl groups (fig. 3). Representative tracings from two subjects are displayed in figure 1. Fentanyl pretreatment reduced the HR response and delayed the MAP response but augmented the sympathetic response to desflurane.

End-tidal desflurane concentrations during each minute of induction did not differ between the three treatment groups and are averaged and displayed in figure 3. Plasma fentanyl concentrations and arterial blood gas tensions are provided in table 2. Arterial p_{CO_2} and end-tidal carbon dioxide concentrations during the administration of desflurane did not differ between groups and were within a physiologic range throughout the experimental protocol.

Steady-state

When compared to conscious baseline, increasing end-tidal concentrations of desflurane to 0.75 and 1.5 MAC were associated with significant linear and progressive increases in CVP and decreases in MAP and nonlinear but progressive decreases in FVR (fig. 4). These responses did not differ between treatment groups. Steady-state recordings of SNA at 0.75 MAC were unchanged from conscious baseline in all groups; however, at 1.5 MAC, a significant increase in SNA was

Table 1. Neurocirculatory Parameters at Conscious Baseline

	Placebo	Fentanyl, 2.5 μg/kg + 1 μg·kg⁻¹·h⁻¹	Fentanyl, 5 μg/kg + 2 μg·kg⁻¹·h⁻¹
Heart rate (beats/min)	61 ± 2	58 ± 2	62 + 2
Mean arterial pressure (mmHg)	93 ± 2	91 ± 2	92 ± 2
Central venous pressure (mmHg)	4.4 ± 0.3*	6.6 ± 0.6	5.6 ± 1.0
Forearm vascular resistance (mmHg/ml·min⁻¹ ·100 ml⁻¹)	30 ± 3	38 ± 3	36 ± 5
Sympathetic nerve activity (total activity†)	105 ± 18	106 ± 22	115 ± 17

Data are mean ± SEM.

* Significantly different from 2.5 μg/kg fentanyl, $P < 0.05$.

† Total activity = (burst frequency/100 cardiac cycles) × mean burst amplitude (μV).

noted in the placebo group. Consistent with the progressive blood pressure decline, FVR decreased with increasing desflurane administration.

Transition

At steady-state 5.4% desflurane, immediately before the transition to 11% desflurane, there were no differences in neurocirculatory variables between the three groups (fig. 5). In the placebo group, the rapid increase in the inspired desflurane concentration from 5.4% to 11% was associated with significant increases in SNA, HR, and MAP that peaked 3 min after the concentration change. Both infusion rates of fentanyl diminished the HR increase in response to the increased inspired desflurane concentration. The MAP response was significantly inhibited by the administration of the larger fentanyl dose. Similar to the induction period, sympathetic activation was largest in the fentanyl treatment groups. The enhancement of the SNA response in the fentanyl groups did not differ and was associated with increases in FVR and CVP (fig. 5).

Discussion

The current study evaluated the efficacy of fentanyl in attenuating the sympathoexcitation and hemodynamic perturbations associated with the administration of desflurane. Fentanyl altered the neurocirculatory responses to desflurane in complex ways. Fentanyl delayed but did not diminish the magnitude of the increases in blood pressure and HR and augmented the sympathetic activation and increases in CVP. A similar but more effective attenuation of the hemodynamic responses to desflurane (and a paradoxical augmentation of the sympathetic response) was observed in the fentanyl-treated subjects during the "transition" period, when the inspired concentration of desflurane was rapidly increased from 5.4% to 11%. This improved attenuation of the neurocirculatory response occurred at a time when plasma fentanyl concentrations were less (but perhaps receptor occupancy was greater) than the induction period.

Fentanyl

The possibility that fentanyl might attenuate desflurane-mediated tachycardia and hypertension has been suggested in previously cited studies. A 10-μg·kg⁻¹ dose of fentanyl given before desflurane administration in patients undergoing CABG surgery led to an uneventful perioperative course that did not differ on a hemodynamic basis when compared to patients given isoflurane.[8] In contrast, patients undergoing CABG surgery who received desflurane without prior opioid administration experienced significant hemodynamic responses and signs of myocardial ischemia that necessitated aggressive β blocker and vasodilator therapy.[3] These results suggest that 10 μg·kg⁻¹ fentanyl might modify the cardiovascular responses to desflurane administration. Because it is likely that desflurane will be employed frequently in shorter surgical procedures and outpatient procedures, smaller doses of fentanyl that might be chosen as a part of the desflurane anesthetic regimen were examined in the current study. A single bolus of fentanyl is nearly eliminated from the plasma in 60 min, therefore an infusion of fentanyl was initiated immediately after the bolus dose to maintain plasma levels of fentanyl within a therapeutic range during the later stages of this protocol.[11,12] The doses of fentanyl employed in this study resulted in plasma concentrations that were at the low end of the therapeutic range.

Table 2. Arterial Carbon Dioxide and Plasma Fentanyl Concentrations

	Conscious Baseline	5 min after Fentanyl	Steady-state Desflurane	
			5.4%	11%
P_{CO_2} (mmHg)				
Placebo	40 ± 1.2	41 ± 1.3	41 ± 1.1	40 ± 0.4
1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ fentanyl	43 ± 0.4	47 ± 1.5	40 ± 0.9*	40 ± 1.2*
2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ fentanyl	42 ± 0.8	42 ± 1.6	41 ± 0.9	41 ± 1.0
Fentanyl (ng/ml)				
1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ fentanyl	—	1.90 ± 0.33	1.00 ± 0.20	1.08 ± 0.10
2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ fentanyl	—	3.51 ± 0.47	1.68 ± 0.34†	1.57 ± 0.30†

Data are mean ± SEM.

* Significantly different from conscious baseline, $P < 0.05$.

† Significantly different from fentanyl baseline, $P < 0.05$.

Administration of fentanyl before induction produced relatively insignificant changes in neurocirculatory variables. There was a small but significant increase in Pa_{CO_2} in the low-dose fentanyl group despite verbal encouragement to maintain a constant respiratory effort. The subtle increase in carbon dioxide did not have significant effects on resting SNA, HR, and MAP. The observation that fentanyl did not reduce resting SNA is consistent with existing data demonstrating that fentanyl does not alter resting plasma concentrations of norepinephrine[13] or tonic levels of renal sympathetic nerve activity.[14] In contrast, it generally is accepted that fentanyl reduces sympathetic surges associated with noxious stimuli in a dose-dependent fashion.

Induction: Propofol

As shown previously by this laboratory, induction of anesthesia by bolus administration of propofol inhibited sympathetic neural outflow.[15] This was associated with significant reductions in blood pressure in all treatment groups that ranged from 10 to 25 mmHg (figs. 1 and 2). It also has been demonstrated that hypotension after propofol administration is partly due to its ability to relax both arterial and venous smooth muscle tone.[16] In the placebo group, HR increased more than 10 beats/min after the administration of propofol. Because sympathetic activity was inhibited during this time, it is likely that withdrawal of cardiac-vagal activity *via* baroreflex mechanisms (responding to the hypotension) contributed to this response. The increase in HR after propofol administration did not occur in the fentanyl-pretreated groups, which was associated with larger decreases in blood pressure when compared with the placebo group. The enhanced blood pressure decrease persisted for several minutes after the initial inhalation of desflurane.

Induction: Desflurane

The administration of desflurane *via* mask began 2 min after induction of anesthesia with propofol. In the placebo-treated group, a significant sympathetic activation was noted during the 3rd through 10th min after adding desflurane to the inspired gas. This was associated with increases in HR and blood pressure. The onset of the sympathetic activation during induction appeared to be delayed by several minutes when retrospectively compared to a similar group of volunteers induced with thiopental before desflurane administration.[2] This delay, which was similar in all three treatment groups, may reflect a greater ability of propofol to inhibit sympathetic outflow.[15]

In the placebo group, there was a progressive increase in blood pressure during the first 7 min of desflurane administration. This increase also occurred in the fentanyl groups but was initiated several minutes later than in the placebo group. Because the inhibition of sympathetic nerve activity was similar in the three treatment groups during the early induction period, the delayed blood pressure increase in the fentanyl groups might be attributable to the lower HR associated with the administration of fentanyl. When the data were expressed as peak individual change from the propofol baseline (table 3), there were no discernible effects of fentanyl on the maximal increases in HR and MAP associated with desflurane.

The sympathetic activation produced by desflurane peaked between the 4th and 7th min after its initiation. This was at a time when end-tidal desflurane concentrations were between 7.8% and 9.9%. During the final

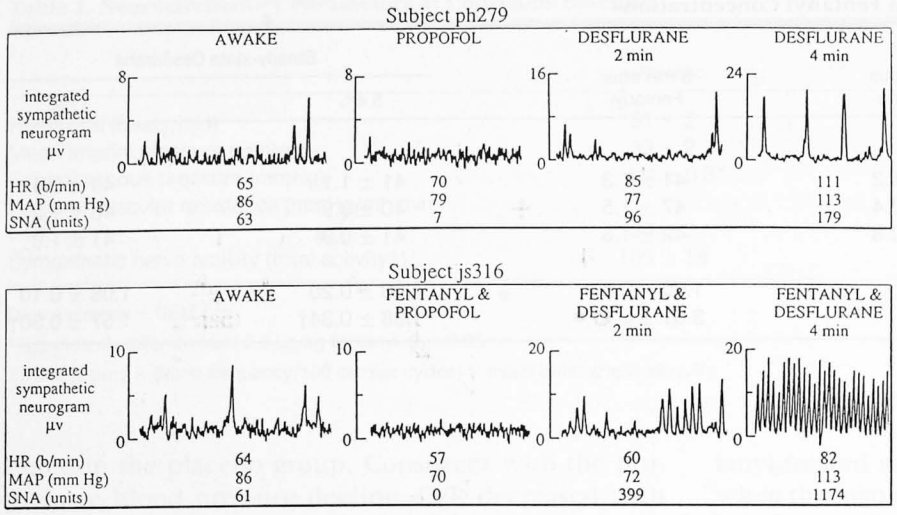

Fig. 1. Individual recordings of integrated nerve activity and hemodynamic responses from two volunteers who received desflurane. (*Top*) Tracings from a placebo study. (*Bottom*) Tracings from a subject pretreated with 5.0 $\mu g \cdot kg^{-1}$ fentanyl. Comparisons at control, 2 min after propofol administration (2 $mg \cdot kg^{-1}$), and 2 and 4 min after the mask administration of desflurane are displayed. Propofol virtually abolished sympathetic activity. An earlier and greater activation of sympathetic nerve activity with an attenuated hemodynamic response was seen in the fentanyl-treated subject.

few minutes of the 10-min induction period, there was a gradual decrease in sympathetic activity and corresponding decreases in blood pressure and HR. These later decreases in blood pressure may represent a direct relaxation of vascular smooth muscle.

The onset of sympathetic activation in the fentanyl-treated groups during the induction period followed the same time course as the placebo group; however, the magnitude of the response was larger than that noted in the placebo group. In addition, CVP increases were heightened simultaneous with the enhanced SNA response in the fentanyl groups. There is no clear-cut explanation for the greater sympathetic activation in the fentanyl-treated groups compared to the placebo group. One possibility might be that the combination of desflurane's ability to augment sympathetic outflow along with the larger unloading of arterial baroreceptors secondary to fentanyl's enhancement of the propofol-mediated hypotension led to a larger efferent sympathetic response. This observation is not spurious, because the enhanced SNA response occurred in both fentanyl groups and an augmented SNA was again observed in the fentanyl groups during the transition period (fig. 5). These data suggest that peripheral recordings of sympathetic vasoconstrictor traffic directed to vasculature within skeletal muscle bear little relationship to sympathetic drive to the heart. For example, HR increases occurred in the placebo-treated group

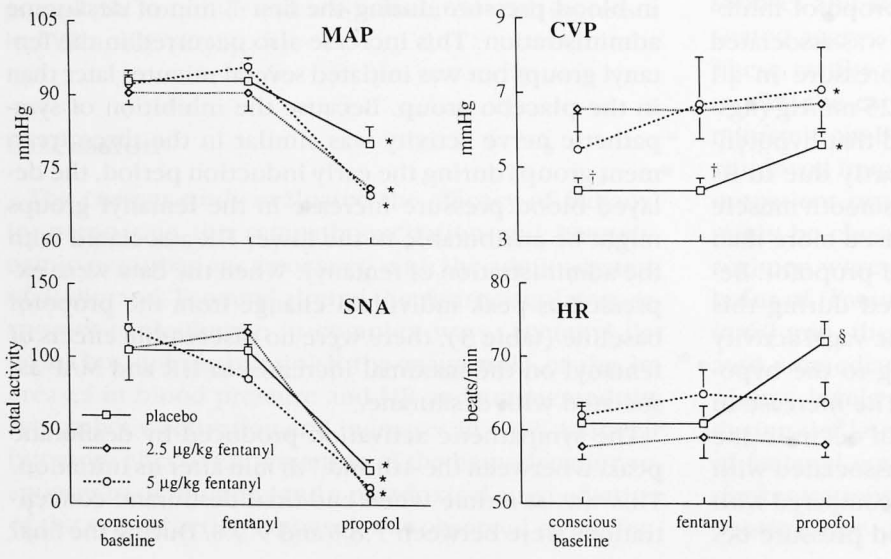

Fig. 2. Average (mean ± SEM) neurocirculatory responses to the administration of fentanyl in awake subjects and to induction of anesthesia with 2.0 $mg \cdot kg^{-1}$ propofol. After propofol induction, heart rate (HR) increased significantly more in the placebo group when compared to fentanyl-treated groups, §$P < 0.05$. †$P < 0.05$ *versus* fentanyl groups. *$P < 0.05$ *versus* respective value at conscious baseline.

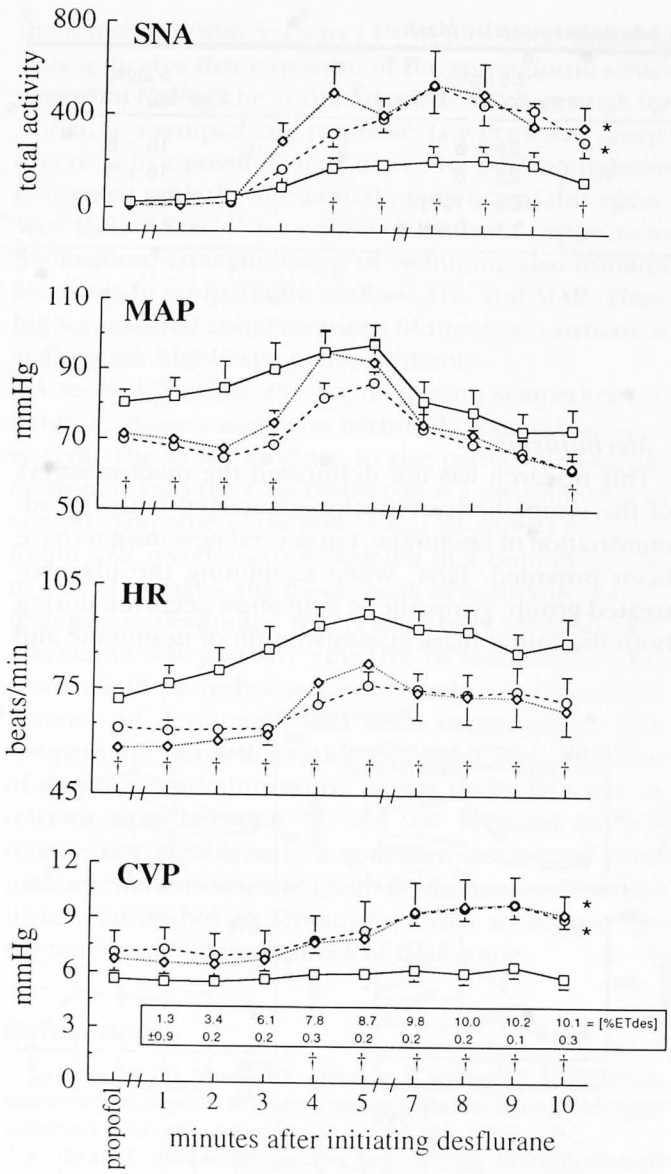

Fig. 3. Average group induction responses (mean ± SEM) of muscle sympathetic nerve activity (SNA), mean arterial blood pressure (MAP), heart rate (HR), and central venous pressure (CVP). Desflurane was initiated 2 min after propofol administration. SNA total activity = burst amplitude × burst frequency/100 cardiac cycles. *Significant interaction (by ANOVA) between the overall response in the fentanyl groups *versus* placebo ($P < 0.05$). †Significantly different values at a given time between the placebo and fentanyl groups, $P < 0.05$.

during the first several minutes after desflurane administration at a time when sympathetic neural activity was inhibited. Furthermore, large increases in SNA during the later stages of desflurane administration in the fentanyl-treated groups were associated with only minor increases in HR. The lack of a correlation of muscle SNA with HR also may be due to the predominance of cardiac vagal mechanisms in the regulation of HR in humans.[17,18] In contrast, there is a closer association between muscle SNA and vascular tone. For example, during the 2nd through 5th min of desflurane administration, sympathetic activation was maximal in the fentanyl-treated groups and was associated with abrupt increases in MAP and gradual increases in CVP (fig. 3).

Steady-state Responses

A similar, progressive decline in blood pressure at increasing steady-state concentrations of desflurane was observed in all three treatment groups. Heart rate was unchanged at 0.75 MAC desflurane; however, consistent with previous observations, 11% (1.5 MAC) desflurane was associated with an increased HR.[2,6,19] Interestingly, fentanyl did not have significant effects on the increased HR at 1.5 MAC, suggesting that the higher HR probably was not related to vagal or nociceptive mechanisms but more likely due to small increases in cardiac sympathetic outflow or circulating catecholamines. Consistent with our previous observation,[2] SNA was increased at 11% desflurane anesthesia. Increases in circulating norepinephrine also have been noted at higher MAC of desflurane.[6,20] This sympathetic activation may be due to reflex mechanisms secondary to the decreased blood pressure, or it may be due to an as yet unexplored direct effect of desflurane on central sympathetic outflow. Fentanyl did not attenuate the increased sympathetic outflow at higher steady-state concentrations of desflurane.

Steady-state measurements of forearm vascular resistance were progressively decreased with increasing MAC of desflurane. This decline was unaltered by the coadministration of fentanyl. The decrease in FVR simultaneous to large increases in SNA suggests that desflurane has potent direct effects on vascular smooth muscle.

Transition

There were significant increases in SNA, HR, and MAP during the first 5 min after the rapid increase in the inspired desflurane concentration from 5.4% to 11%. Compared to the placebo group, the fentanyl-treated groups had attenuated HR and blood pressure responses to this stimulus. The fentanyl group receiving 2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ had virtually no change in HR or blood pressure during this transition period. The sympathetic nerve responses were not attenuated by the fentanyl treatment. There were significant increases in sympa-

Table 3. Peak Changes (from Propofol Baseline) during Desflurane Administration by Mask

	Placebo	2.5 μg/kg + 1 μg·kg⁻¹·h⁻¹ Fentanyl	5 μg/kg + 2 μg·kg⁻¹·h⁻¹ Fentanyl
Δ Heart rate (beats/min)	25 ± 3	24 ± 6	16 ± 6
Δ Mean arterial pressure (mmHg)	16 ± 4	23 ± 6	16 ± 3
Δ Sympathetic nerve activity (total activity*)	187 ± 62	525 ± 150†	578 ± 112†
Δ Central venous pressure (mmHg)	0.6 ± 0.5	3.1 ± 0.4†	2.7 ± 0.7†

Data are mean ± SEM, propofol baseline depicted in figure 2

* Total activity = (burst frequency/100 cardiac cycles) × mean burst amplitude (μV).

† Significantly different from peak placebo response, $P < 0.05$.

thetic outflow that exceeded the response in the placebo group and, associated with the increased SNA, there were increases in FVR. Similar to our speculation regarding this heightened response during the induction period, this increase in sympathetic outflow may reflect the summation of two distinct mechanisms: a direct effect of desflurane (by a currently undescribed mechanism) to increase sympathetic outflow and a second, additive effect *via* the baroreflex.

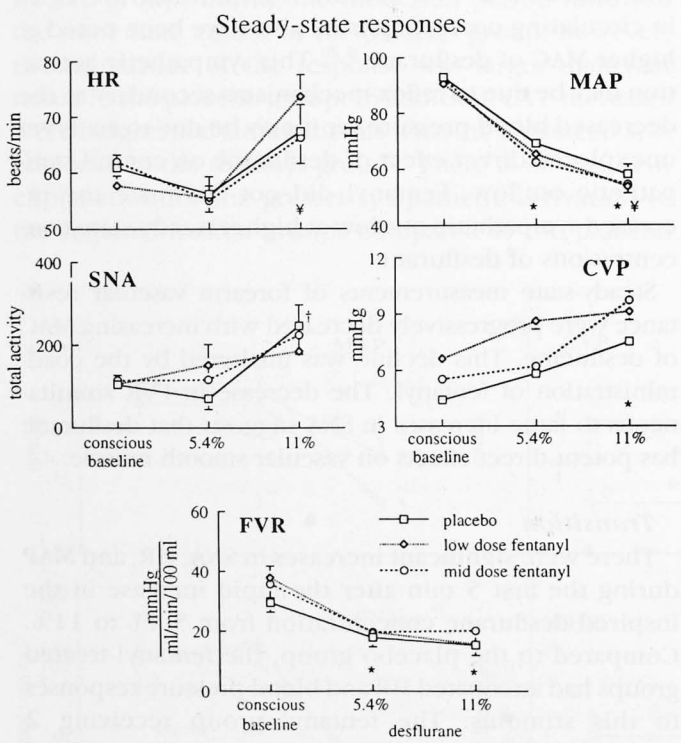

Fig. 4. Average (mean ± SEM) neurocirculatory responses at steady-state. *Significant change ($P < 0.05$) from conscious baseline in all groups. ¥Significant change from 5.4% for all groups. †Placebo response significantly changed from 5.4% desflurane.

Mechanisms

This research has not delineated the mechanism(s) of the sympathetic activation associated with the administration of desflurane, but several new insights have been provided. First, when examining the placebo-treated group, sympathetic activation occurred during both the initial mask administration of desflurane and

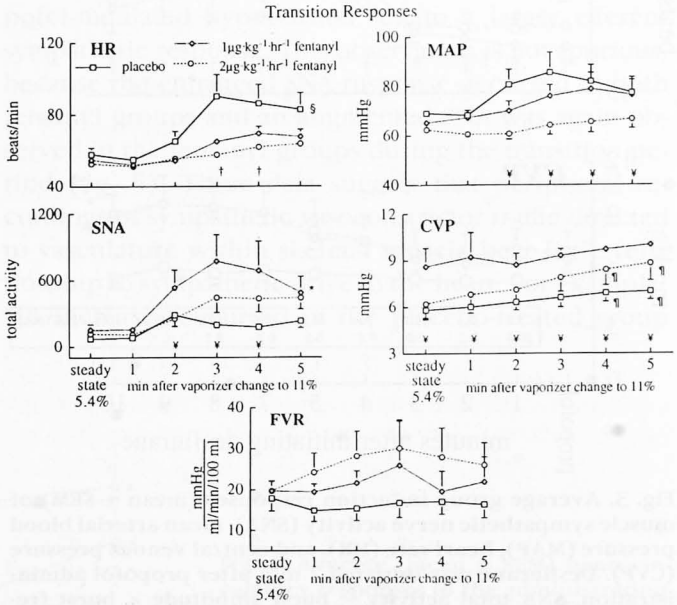

Fig. 5. Comparison of average group responses (mean ± SEM) of heart rate (HR), mean arterial pressure (MAP), sympathetic nerve activity (SNA), central venous pressure (CVP), and forearm vascular resistance (FVR) during the first 5 min of the transition from 5.4% (0.75 MAC) to 11% desflurane. SNA total activity = burst amplitude × burst frequency/100 cardiac cycles. ¶Significant change from respective value at 5.4% ($P < 0.05$). *Significant interaction (by ANOVA) between the overall response in the fentanyl groups *versus* placebo ($P < 0.05$). §Significant interaction (by ANOVA) between the overall response in the high-dose fentanyl group *versus* placebo ($P < 0.05$). Significantly different values ($P < 0.05$) at specific points in time are as follows: †placebo *versus* fentanyl groups and ¥placebo *versus* 1 μg·kg⁻¹·h⁻¹ fentanyl group.

the transition from 5.4% to 11% in intubated subjects. This indicates that exposure of the supraglottic structures, including the oropharynx, is not essential for initiating a sympathetic response. Lower airway receptors remain a possible activation site, which might be consistent with the substantial pungency of this agent. We[20] and others[5,21] have shown that brief exposure to 5% inspired concentrations of isoflurane also initiates increases in sympathetic outflow, HR, and MAP. Thus, higher inspired concentrations of these two structural analogs are highly sympathoexcitatory.

A second possible site for mediating sympathoexcitatory responses might be within the central nervous system. The rapid increase in the partial pressure of desflurane into the CNS could cause a disinhibition of central sympathetic outflow. Until an animal model is found that responds to desflurane in a fashion similar to that of humans, the mechanism of neurocirculatory response to desflurane will remain only speculative.

Fentanyl was partially effective in reducing the hemodynamic perturbations associated with the administration of desflurane. Maximum hemodynamic and sympathetic nerve activation occurred after 4–5 min of desflurane administration, when end-tidal concentrations were between 7% and 9%. Fentanyl did not reduce but significantly augmented peripheral sympathoexcitation associated with desflurane, and this had little relationship to fentanyl's ability to reduce the hemodynamic consequences of desflurane.

References

1. Fleischer LH, Young WL, Ornstein E, Smiley RS: Systemic hemodynamic changes of desflurane *versus* isoflurane during anesthetic induction (abstract). ANESTHESIOLOGY 77:A334, 1992

2. Ebert TJ, Muzi M: Sympathetic hyperactivity during desflurane anesthesia in healthy volunteers: A comparison with isoflurane. ANESTHESIOLOGY 79:444–453, 1993

3. Helman JD, Leung JM, Bellows WH, Pineda N, Roach GW, Reeves JD, III, Howse J, McEnany T, Mangano DT, The S.P.I. Research Group: The risk of myocardial ischemia in patients receiving desflurane versus sufentanil anesthesia for coronary artery bypass graft surgery. ANESTHESIOLOGY 77:47–62, 1992

4. Ostapkovich N, Ornstein E, Jackson L, Young WL: Hemodynamic changes with rapid increases in desflurane or isoflurane dose (abstract). ANESTHESIOLOGY 77:A333, 1992

5. Moore MA, Weiskopf RB, Eger EI II, Noorani M, McKay L, Damask M: Rapid 1% increases of end-tidal desflurane concentration to greater than 5% transiently increase heart rate and blood pressure in humans. ANESTHESIOLOGY 81:94–98, 1994

6. Weiskopf RB, Moore MA, Eger EI II, Noorani M, McKay L, Chortkoff B, Hart PS, Damask M: Rapid increase in desflurane concentration is associated with greater transient cardiovascular stimulation than with rapid increase in isoflurane concentration in humans. ANESTHESIOLOGY 80:1035–1045, 1994

7. Eger EI II: New inhaled anesthetics. ANESTHESIOLOGY 80:906–922, 1994

8. Thomson IR, Bowering JB, Hudson RJ, Frais MA, Rosenbloom M: A comparison of desflurane and isoflurane in patients undergoing coronary artery surgery. ANESTHESIOLOGY 75:776–781, 1991

9. Ebert TJ: Differential effects of nitrous oxide on baroreflex control of heart rate and peripheral sympathetic nerve activity in humans. ANESTHESIOLOGY 72:16–22, 1990

10. Hagbarth K-E, Vallbo AB: Pulse and respiratory grouping of sympathetic impulses in human muscle nerves. Acta Physiol Scand 74:96–108, 1968

11. McQuay HJ, Moore RA, Paterson GMC, Adams AP: Plasma fentanyl concentrations and clinical observations during and after operation. Br J Anaesth 51:543–549, 1979

12. Hengstmann JH, Stoeckel H, Schuttler J: Infusion model for fentanyl based on pharmacokinetic analysis. Br J Anaesth 52:1021–1024, 1980

13. Hicks HC, Mowbray AG, Yhap EO: Cardiovascular effects of and catecholamine responses to high dose fentanyl-O_2 for induction of anesthesia in patients with ischemic coronary artery disease. Anesth Analg 60:563–568, 1981

14. Taneyama C, Goto H, Kohno N, Benson KT, Sasao J, Arakawa K: Effects of fentanyl, diazepam, and the combination of both on arterial baroreflex and sympathetic nerve activity in intact and barodenervated dogs. Anesth Analg 77:44–48, 1993

15. Ebert TJ, Muzi M, Berens R, Goff D, Kampine JP: Sympathetic responses to induction of anesthesia in humans with propofol or etomidate. ANESTHESIOLOGY 76:725–733, 1992

16. Muzi M, Berens RA, Kampine JP, Ebert TJ: Venodilation contributes to propofol-mediated hypotension in humans. Anesth Analg 74:877–883, 1992

17. Leon DF, Shaver JA, Leonard JJ: Reflex heart rate control in man. Am Heart J 80:729–739, 1970

18. Greene NM, Bachand RG: Vagal component of the chronotropic response to baroreceptor stimulation in man. Am Heart J 82: 22–27, 1971

19. Weiskopf RB, Cahalan MK, Eger EI II, Yasuda N, Rampil IJ, Ionescu P, Lockhart SH, Johnson BH, Freire B, Kelley S: Cardiovascular actions of desflurane in normocarbic volunteers. Anesth Analg 73: 143–156, 1991

20. Ebert TJ, Muzi M: Sympathetic activation with desflurane in humans, Advances in Pharmacology. Volume 31: Anesthesia and Cardiovascular Disease. Edited by Bosnjak Z, Kampine JP. San Diego, Academic, 1994, pp 369–378

21. Yli-Hankala A, Randell T, Seppala T, Lindgren L: Increases in hemodynamic variables and catecholamine levels after rapid increase in isoflurane concentration. ANESTHESIOLOGY 78:266–271, 1993