Desflurane-mediated Sympathetic Activation Occurs in Humans Despite Preventing Hypotension and Baroreceptor Unloading

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Background: Increasing concentrations of desflurane result in progressive decreases in blood pressure (BP) and, unlike other currently marketed, potent volatile anesthetics, heightened sympathetic nervous system activity. This study aimed to determine whether baroreflex mechanisms are involved in desflurane-mediated sympathetic excitation.

Methods: Healthy volunteers were anesthetized with desflurane (n = 8) or isoflurane (n = 9). Heart rate (HR; measured by electrocardiograph), blood pressure (BP; measured by arterial catheter), and efferent sympathetic nerve activity (SNA; obtained from percutaneous recordings from the peroneal nerve) were monitored. Baroreflex sensitivity was evaluated at baseline while volunteers were conscious and during 0.5, 1, and 1.5 minimum alveolar concentration (MAC) anesthesia *via* bolus injections of nitroprusside (100 µg) and phenylephrine (150 µg) to decrease and increase BP. To prevent the BP decline with increasing depths of anesthesia, phenylephrine was infused to maintain mean BP at the 0.5 MAC level.

Results: The HR, BP, and SNA were similar between the groups at the conscious baseline measurement. Efferent SNA did not change during higher MAC of isoflurane, but it increased progressively as desflurane concentrations were increased beyond 0.5 MAC, despite maintaining BP at the 0.5 MAC value with phenylephrine infusions (P < 0.05). Cardiac baroslopes (based on changes in HR) were progressively and similarly decreased with increasing concentrations of isoflurane and desflurane (P < 0.05). Sympathetic baroslopes (based on SNA) decreased with increasing isoflurane concentrations but were maintained with increasing concentrations of desflurane; the response was significantly different between groups.

Conclusions: The increase in basal levels of SNA with increasing concentrations of desflurane persisted despite "fixing" BP and thus is probably not due to hypotension and unloading of the baroreceptors. Further, the preservation of reflex increases in SNA to nitroprusside during desflurane indicates that desflurane preserves one component of the baroreflex in humans when BP is "fixed." (Key words: Autonomic nervous system; blood pressure; heart rate; isoflurane; sympathetic microneurography; sympathetic pressoreceptors; volatile anesthetics.)

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DESFLURANE differs from its parent ether molecule isoflurane by only one atom. Despite this subtle chemical change, desflurane has several properties that are markedly different than those of isoflurane. One of these properties is the ability of desflurane to increase the activity of the sympathetic nervous system at higher steady state concentrations.[1-3] Because this response appears to be unique to humans, the mechanism of the sympathetic excitation from desflurane has been difficult to discern. Several common factors that increase human sympathetic activity include pain, psychological or surgical stress, and the baroreceptor reflex responses to hypotension.[4] Because increasing concentrations of the volatile anesthetics progressively decrease blood pressure (BP), we hypothesized that a possible explanation for desflurane-mediated augmentation of sympathetic nervous system activity at higher steady state concentrations might be a better preservation or sensitization of the baroreflex control system. This might heighten the sympathetic response to the usual decrease in BP that occurs as the depth of anesthesia is increased.

In this study, we titrated phenylephrine to prevent the decrease in BP (and presumably the baroreceptor unloading) usually associated with increasing concentrations of volatile anesthetics. We used sympathetic microneurography to record directly from the sympathetic nervous system of humans.[5] We hypothesized

that by preventing the BP decrease associated with higher concentrations of desflurane, the usual increase in sympathetic outflow also would be prevented. For comparison, we conducted an identical protocol in volunteers who were anesthetized with isoflurane. Finally, we activated the baroreflex by applying brief hypotensive and hypertensive challenges at several different depths of anesthesia to determine whether the gain of the baroreceptor reflex during desflurane was modified in a different way than the baroreflex gain during equipotent concentrations of isoflurane.

Materials and Methods

After the Human Research Review Committee approved our study, we obtained informed consent from 15 men and 2 women aged 20–28 yr. Volunteers were healthy, normotensive, free of systemic illness, were not receiving medications, did not take any illicit drugs, and had fasted for at least 8 h before testing. Each volunteer received only one anesthetic.

On the morning of the study, the volunteers received 30 ml oral sodium bicitrate. While positioned supine, electrodes for the electrocardiogram were applied, and peripheral intravenous and radial arterial catheters and microneurographic needle electrodes were inserted as described elsewhere.[1,6] Basal heart rate (HR), BP, and efferent muscle sympathetic nerve activity (SNA) directed to blood vessels within skeletal muscle were recorded at rest, after a 20-min accommodation period after instrumentation. This was followed by baroreceptor testing. The baroreflex test consisted of a 100-μg bolus of sodium nitroprusside given through the intravenous catheter, followed 60 s later by a 150-μg bolus of phenylephrine. This resulted in a 10–20% decrease in BP and a 10–20% increase in BP above the baseline before nitroprusside administration. These changes in BP cause a brief unloading and loading of the baroreceptors. Beat-by-beat evaluations of BP, HR, and SNA were performed during this test period and analyzed off-line to derive the sensitivity of the reflex control of HR and SNA, as described later here and elsewhere.[5] This test was repeated after hemodynamic parameters returned to baseline (usually 5 min later).

After conscious baseline measurements, standard ASA monitors were applied, and the volunteers breathed 100% oxygen for 5 min. Anesthesia was induced with propofol (2.5 mg/kg) and vecuronium (0.1 mg/kg). The anesthetic was randomly assigned to be isoflurane (n = 9) or desflurane (n = 8). After tracheal intubation and mechanical ventilation to maintain normocarbia, the anesthetic gas was titrated to achieve 0.5 minimum alveolar concentration (MAC) anesthesia (end-tidal concentrations of 0.65% isoflurane or 3.65% desflurane). After a 30-min equilibration to allow for washout of propofol and tissue saturation with the anesthetic gas, hemodynamic and sympathetic measurements were obtained, and the baroreceptor stress was repeated twice in a manner similar to that used for the awake measurements.

Phenylephrine was titrated to maintain mean arterial pressure (MAP) at the level recorded at 0.5 MAC as the anesthetic depth was increased gradually to 1 MAC (1.15% isoflurane, 7.25% desflurane) and then to 1.5 MAC (1.7% isoflurane, 11% desflurane). A 20-min equilibration period was allowed before repeating basal measurements and reflex testing at each anesthetic depth. Fresh gas flow rates were adjusted to achieve the target end-tidal anesthetic concentration within the first 5 min of the 20-min period. End-tidal anesthetic and carbon dioxide concentrations were monitored continuously using a calibrated infrared spectrometer.

Electrocardiograph signals were computer processed to identify R spikes and measure the R-R intervals in milliseconds. Efferent nerve signals were amplified ($\times 100,000$), band-pass filtered (200–2,000 Hz), rectified, and integrated (150 ms moving average) to produce a processed nerve signal. Individual bursts of integrated nerve activity were identified by computer and confirmed manually. Sympathetic nerve activity was identified by previously defined criteria.[6,7] This activity has been shown to be similar in upper and lower, ipsilateral and contralateral extremities.[6] Because muscle blood flow is 40% of resting cardiac output, recordings of muscle SNA represent an important window on neural control of blood pressure. Sympathetic nerve activity was quantified as the number of integrated bursts that occur during 100 heart beats. Integrated bursts also vary in amplitude based on the varying recruitment of sympathetic fibers with each heart beat. Therefore, we also define muscle SNA as total activity, which is the average burst amplitude (μV) measured over the sampling period multiplied by the number of bursts per 100 heart beats. Although the total amount of SNA is best expressed by combining both amplitude and duration, the amplitude of sympathetic bursts can be unpredictably altered by a subtle movement of the needle within the nerve. Thus both units of quantification are reported.

To evaluate baroreflex responses, cardiac baroslopes were derived by plotting R-R interval (in milliseconds) against mean arterial pressure (MAP) during BP changes induced by bolus administrations of nitroprusside and phenylephrine. The linear portion (slope) of the sigmoid relation was derived for periods of decreasing and increasing BP. This slope served as the measure of baroreflex sensitivity or "gain." The MAP immediately before the bolus administration of nitroprusside and the lowest recorded MAP resulting from its administration were recorded.

Sympathetic baroslopes were derived from the muscle SNA response to lowered diastolic pressure. The sympathetic response is meaningful to determine only during the nitroprusside perturbation (*i.e.*, decreasing BP) because, as pressure increases just a few millimeters of mercury above baseline, nerve activity quickly decreases to zero, and a slope cannot be obtained. The choice of MAP and diastolic pressure as the ordinates in the regression analyses was based on published data that show that these variables are the primary determinants of arterial baroreflex neuroeffector responses in healthy persons.[8] Baroreceptor tests were performed in duplicate at each anesthetic level, and the derived baroslopes at each anesthetic level were averaged because there were no differences between the two trials.

Steady state data were averaged for the 5-min collection period and presented as means ± SD. Steady state measurements and baroslopes with increasing depth of anesthesia were compared by repeated measures analysis of variance between isoflurane and desflurane. Probability values <0.05 indicated statistical significance.

Significant time effects were further evaluated by Dunnett's *post hoc* analysis. If there was a significant interaction term in the analysis of variance, Fisher's protected least significant difference was applied to determine differences at specific anesthetic concentrations.

Results

Table 1 shows hemodynamic and SNA measures at conscious baseline and during steady state periods of anesthesia with either isoflurane or desflurane. There were no differences in resting variables between anesthetic groups while awake. At 0.5 MAC anesthesia, HR was unchanged, but muscle SNA and MAP decreased significantly and similarly between the two groups (fig. 1). The addition of a phenylephrine drip during anesthesia at 1 and 1.5 MAC resulted in no significant change in MAP, systolic or diastolic pressures from 0.5 MAC (fig. 1). Sympathetic nerve activity progressively and significantly increased as desflurane concentrations were increased beyond 0.5 MAC, despite the maintenance of MAP (fig. 1).

With BP fixed, cardiac (HR) baroslopes were progressively diminished with increasing anesthetic depth and were not different between the anesthetics (fig. 2). At 1 MAC, the cardiac baroslope derived from the decreasing pressure stimulus was reduced by 53 ± 23% and 34 ± 33% with isoflurane and desflurane, respectively. At 1 MAC, the cardiac baroslope derived from the increasing pressure stimulus was reduced by 26 ± 31% and 38 ± 20% with isoflurane and desflurane, respectively. Sym-

Table 1. Baseline and Steady-State Neurocirculatory Parameters

		Conscious Baseline	0.5 MAC	1.0 MAC	1.5 MAC
Heart rate (beats/min)	Iso	62 ± 8	62 ± 7	63 ± 10	61 ± 16
	Des	68 ± 9	67 ± 18	66 ± 24	75 ± 20§
Mean arterial pressure* (mmHg)	Iso	87 ± 4	65 ± 6†	63 ± 6†	62 ± 10†
	Des	86 ± 8	66 ± 4†	67 ± 6†	65 ± 7†
Sympathetic nerve activity (bursts/100 cardiac cycles)	Iso	24 ± 7	8 ± 4†	14 ± 13‡	10 ± 9†‡
	Des	33 ± 15	14 ± 10†	30 ± 13§	47 ± 27§
Sympathetic nerve activity (total activity)	Iso	176 ± 174	76 ± 141†	82 ± 137†	85 ± 142†
	Des	153 ± 92	45 ± 43†	110 ± 96§	194 ± 196

Iso = isoflurane; Des = desflurane.

Data are mean ± SD. Total activity = (burst frequency × mean burst amplitude)/100 cardiac cycles.

* Mean arterial pressure was maintained ("fixed") at 0.5 minimum alveolar concentration (MAC) levels during increasing anesthesia depth.

† $P < 0.05$ from conscious baseline.

‡ $P < 0.05$ between anesthetics.
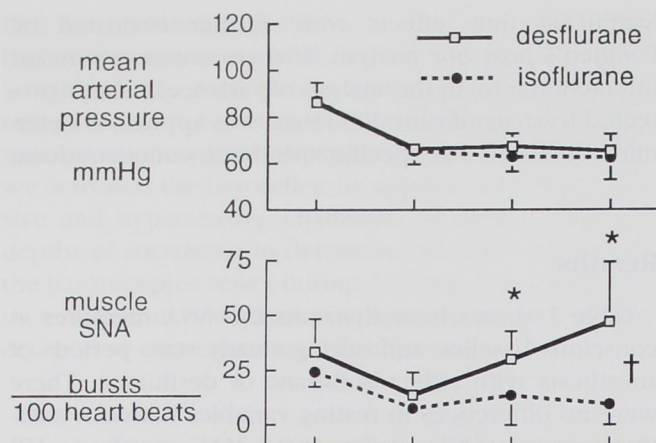
§ $P < 0.05$ change from 0.5 MAC.

Fig. 1. Blood pressure and sympathetic nerve responses at baseline while volunteers were conscious and during three depths of anesthesia. The mean arterial pressure is maintained at the level achieved during 0.5 minimum alveolar concentration (MAC) by titrating phenylephrine as outlined in Materials and Methods section. Muscle sympathetic nerve activity progressively increases with increasing depth of desflurane anesthesia. Data are means ± SD; * Significant change from 0.5 MAC. † Significant difference between anesthetics. ($P < 0.05$.)

pathetic baroslopes were attenuated (became less negative) with increasing isoflurane depth but were maintained (no significant change from awake baseline values) with increasing concentrations of desflurane (fig. 3). The differences between anesthetics in the sympathetic baroreflex sensitivity were significant at all depths of anesthesia. The decrease in MAP as a result of nitroprusside administration was similar between isoflurane and desflurane at 0.5 and 1.5 MAC but not at 1 MAC ($P < 0.05$). Nitroprusside decreased MAP by 21 ± 5 mmHg, 19 ± 3 mmHg, and 20 ± 3 mmHg during desflurane anesthesia and by 24 ± 6 mmHg, 23 ± 4 mmHg, and 23 ± 4 mmHg during isoflurane anesthesia (means ± SD).

Discussion

The current study provides two new insights into the sympathetic excitation associated with higher concentrations of desflurane. First, increasing basal levels of SNA with increasing steady state levels of desflurane anesthesia may not be attributed to preserved or heightened reflex responses to hypotension. Mean arterial pressure was "fixed" and increasing levels of SNA still were observed at higher concentrations of desflurane. Second, desflurane, and not isoflurane, was associated

with a preserved reflex sympathetic response to an acute hypotensive stimulus. The explanation for these two findings may not be mutually exclusive, as we will explain.

The baroreceptor reflex consists of several components including the receptors, afferent and efferent nerves, central integration sites, peripheral ganglia, and the neuroeffector site. Many, if not all, of these sites can be influenced by volatile anesthetics.[9-11] Past studies in the canine model have indicated that most volatile anesthetics attenuate most of these components of the baroreflex.[9-11] However, some volatile anesthetics enhance or "sensitize" the baroreceptor while attenuating overall the effector response of the reflex.[9] The complexity of anesthetic action on individual "segments" of the baroreflex makes it difficult to speculate on the apparent absence of a baroreflex contribution to the heightened SNA response during increasing desflurane concentrations. One untested possibility might be that
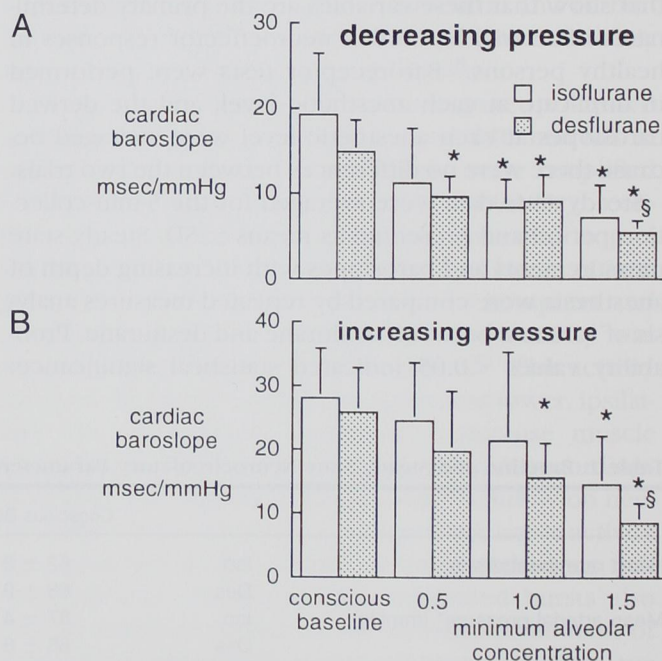

Fig. 2. Arterial baroreflex sensitivity (baroslope) during (*A*) decreasing pressure from a nitroprusside challenge and (*B*) increasing pressure due to administration of a phenylephrine bolus. Cardiac baroslopes were taken during conscious rest and three steady-state minimum alveolar concentration (MAC) levels for isoflurane and desflurane. During 1 and 1.5 MAC anesthesia, mean arterial pressure was fixed at the level recorded during 0.5 MAC. Values are plotted as a millisecond change in R-R interval per millimeters of mercury change in mean arterial pressure. Data are means ± SD. * Significant change from conscious baseline. § Significant change from 0.5 MAC. ($P < 0.05$.)
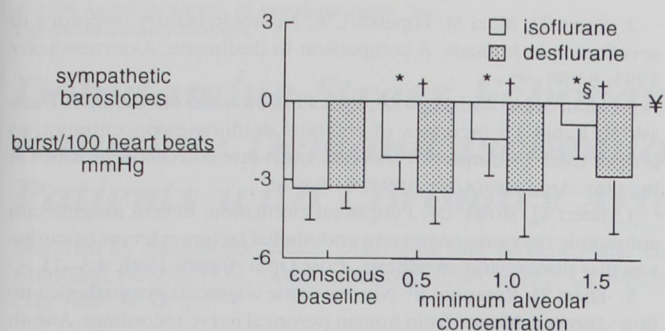
Fig. 3. Sympathetic baroslopes were taken during conscious rest and at three steady-state minimum alveolar concentration (MAC) levels for isoflurane and desflurane. During 1 and 1.5 MAC anesthesia, mean arterial pressure was fixed at the level recorded during 0.5 MAC. Values are plotted as a change in burst activity per millimeters of mercury change in diastolic pressure. A negative slope indicates that sympathetic nerve activity increases with decreasing blood pressure. Alternatively, as pressure increases, the nerve activity diminishes and baroslopes approach zero. In addition, as baroreceptor sensitivity decreases, a given change in pressure produces no change in sympathetic nerve activity. Data are means ± SD. * Significant change from conscious baseline. § Significant change from 0.5 MAC. † Significant difference between anesthetics. ¥ Significant interaction. ($P < 0.05$.)

compared with isoflurane, desflurane desensitizes the baroreceptors, resulting in less afferent traffic for a given BP. This would be perceived as baroreceptor unloading and would result in more efferent SNA. This seems unlikely because the increase in SNA in the present study in which BP was "fixed" was similar to the increase in SNA in our earlier studies during which BP was not maintained.[1,12] Another possibility is that desflurane increases sympathetic outflow by stimulating receptors in or near the airway, and this seems more likely based on findings from our previous investigation.[13]

Increasing the complexity of implicating or absolving the baroreflex in the sympathetic excitation with desflurane are findings from recent studies in which two types of receptors within the baroreceptor were identified in animals.[14] The type I baroreceptors are primarily involved in controlling afferent nerve traffic in response to dynamic changes in pressure, but they appear to have little role in regulating baseline BP. Conversely, type II baroreceptors have a greater influence on basal BP but are less involved in responses to acute changes in BP.[14] If these distinctions exist in humans, we could speculate that desflurane may affect these receptor types in unique ways. For example, the preservation of reflex increases in SNA to sodium nitroprusside-induced hypotension might be due to preserved type I receptor function.

If SNA is higher at increasing depths of desflurane anesthesia and if desflurane preserves the SNA to an acute hypotensive stimulus, then we would expect that resting BP during desflurane might be higher than during equipotent concentrations of isoflurane. Further, desflurane might be considered the preferred anesthetic when the potential for rapid blood loss (and subsequent decreases in BP) exists. These assumptions may, however, be flawed. First, the direct effects of the volatile anesthetics on vascular smooth muscle and cardiac contractility appear to override the ability of heightened SNA and preserved reflex increases in SNA to maintain BP during desflurane anesthesia. In our earlier work, we found that the BP decreases with increasing concentrations of desflurane are identical to those that occur at equipotent concentrations of isoflurane and sevoflurane, despite higher levels of SNA with desflurane.[1,2,15] Second, an earlier study of baroreflex sensitivity in which BP was not "fixed" during increasing concentrations of desflurane anesthesia failed to show that reflex SNA responses were preserved. Instead, we found a progressive decrease in the reflex sympathetic responses as the anesthetic depth was increased.[12] This might be explained by a complex interplay between baroreceptor types influenced not only by the dynamic changes in receptor firing but also by the static pressure level. In the present study, we measured the maximal decreases in MAP due to nitroprusside at each of the three anesthetic levels for each of the two anesthetics. We could not consistently show that the preserved reflex increase in SNA during deeper levels of desflurane anesthesia translated to a lesser reduction in MAP than during isoflurane anesthesia. The decrease in MAP due to nitroprusside was the same during 0.5 and 1.5 MAC isoflurane and desflurane. Only during 1 MAC did we find that desflurane lessened the MAP decrease to nitroprusside compared with isoflurane.

The question addressed in the current study should not be confused with a separate question of the mechanism of sympathetic excitation after rapid increase in the inspired concentration of desflurane. When desflurane is given *via* face mask in rapidly increasing concentrations shortly after anesthetic induction, or when the inspired concentration of desflurane is rapidly increased in intubated humans, tachycardia, hypertension, and, in some cases, myocardial ischemia have been observed.[1,16] We found that this response is mediated through marked increases in sympathetic nervous system activity.[1,2] Further, substantial increases in stress hormones, including epinephrine and vasopressin, have

been observed.[3,17] We and others have theorized that this stress response is reflex in origin and is due to stimulation of receptors in or near the airways due to the high pungency of desflurane.[13,18] This dynamic response probably does not involve the baroreceptors because their activation by increased blood pressure would work to attenuate the hypertension and tachycardia from the airway stimulus.

One finding that was not central to our research goal was that increasing steady state concentrations of isoflurane did not increase HR when BP was "fixed" with phenylephrine. This contrasts to our earlier work in volunteers in which HR was significantly and progressively increased as blood pressure was decreased with increasing depth of isoflurane anesthesia.[1] An early study from this investigative group focused on baroreflex function with isoflurane, and the results suggested that tachycardia during isoflurane anesthesia might be explained by a better preservation of reflex control of HR compared with enflurane and halothane.[19] The absence of increasing HRs when BP decreases are prevented during deeper depths of isoflurane anesthesia further supports the possible role of the baroreflex in mediating the higher HRs during isoflurane anesthesia.

In summary, basal levels of SNA that increase with increasing concentrations of desflurane are probably not a result of hypotension and unloading of the baroreceptors because they persisted despite fixed BP levels. Although we cannot rule out the possibility that the response is caused by desensitization of the baroreceptor, a more likely explanation is that desflurane stimulates nonbaroreceptor sites within or near the airway. In contrast to isoflurane, the preservation of reflex increases in efferent SNA in response to an acute hypotensive stimulus during desflurane anesthesia suggests that, under the conditions of a fixed BP, desflurane preserves at least one component of the baroreflex in humans. The site or sites where isoflurane inhibits and desflurane preserves reflex sympathetic function remain unknown.

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