A Comparison of Baroreflex Sensitivity during Isoflurane and Desflurane Anesthesia in Humans

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Background: Desflurane anesthesia has been associated with heart rate (HR) and sympathetic nerve activity (SNA) responses that differ from those during isoflurane anesthesia. Whether these differences are due to better preservation by desflurane of the baroreceptor reflex control of HR or SNA in humans was examined.

Methods: Baroreflex sensitivity was assessed in 18 volunteers anesthetized with either desflurane or isoflurane. Measurements of HR, blood pressure (BP), and effenter SNA (percutaneous recordings from the peroneal nerve) were made, and baroreflex sensitivity was evaluated at conscious baseline and during 0.5, 1.0, and 1.5 MAC anesthesia. Baroreflex responses were triggered by bolus intravenous injections of nitroglycerin (100 μg) and phenylephrine (150 μg). The linear portions of the baroreflex curves relating HR to mean arterial pressure and relating SNA to diastolic pressure were determined to obtain cardiac and sympathetic baroslopes, respectively.

Results: Cardiac (HR) baroslopes were equally diminished as increasing MAC of both anesthetics. Sympathetic baroslopes were preserved at 0.5 MAC isoflurane but diminished at 0.5 MAC desflurane. Higher MAC produced equal depression of sympathetic baroslopes with both anesthetics.

Conclusions: Increasing MAC of desflurane and isoflurane anesthesia results in similar and progressive decreases in BP but dissimilar SNA and HR responses. These differences are not explained by disparate effects of these anesthetics on the baroreceptor reflex control of SNA or HR. (Key words: Anesthetics, volatile: desflurane; isoflurane. Autonomic nervous system: blood pressure; heart rate; sympathetic pressoreceptors. Techniques: sympathetic microneurography.)

DESFLURANE is the newest volatile anesthetic agent marketed in the United States, and like isoflurane, it produces vasodilation and appears to have similar cardiovascular properties. However, recent data indicate that there are substantial differences between the hemodynamic actions of isoflurane and desflurane, especially with respect to the autonomic nervous system.

At 0.5 MAC anesthesia, desflurane produces decreases in blood pressure (BP) similar to those caused by isoflurane but does not trigger an increased heart rate (HR) as does isoflurane. At 1.5 MAC, sympathetic outflow and circulating norepinephrine levels are greater in subjects receiving desflurane than isoflurane despite similar declines in BP at this level of anesthesia. Whether these differences are attributable to unique effects of desflurane on baroreflex control mechanisms regulating autonomic outflow is unknown.

The baroreflex system is an important, short-term, pressure-regulating system that maintains blood flow to vital organs in the face of variations in hemodynamics. The functional performance of the baroreflex feedback system can be assessed by studying the response to a hypotensive challenge. There are two main effector limbs by which the reflex maintains BP. The first is the cardiac limb, in which BP perturbations induce reflex changes in the cardiac interval, thereby altering HR and cardiac output. This response is mediated primarily through the vagus or the parasympathetic branch of the autonomic nervous system. The second effector limb of the baroreflex is the sympathetic nervous system. BP changes trigger reflex adjustments in peripheral sympathetic outflow that regulate vascular tone. Both effector limbs can be directly quantified by measuring the change in HR or effenter sympathetic nerve activity (SNA) in response to a given change in BP.

Although the hemodynamic effects of the general anesthetics have been extensively investigated in both humans and animals, the effects of these agents on the baroreflex control of HR, BP, and SNA have been reported in only a few studies. Halothane, enfurane, and isoflurane all diminish baroreflex sensitivity.

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In this study, we compared the effects of desflurane and isoflurane on autonomic limbs of the baroreflex in young healthy volunteers by perturbing the baroreceptors with hypo- and hypertensive stimuli. We chose young volunteers rather than surgical patients because this allowed controlled, reproducible stimuli and responses that were not influenced by other medications, stresses, or pathologic processes.

Methods and Materials

After Human Research Review Committee approval, 18 healthy, normotensive, male volunteers (aged 20–31 yr) provided informed consent and were instrumented with electrocardiogram, peripheral intravenous and radial arterial catheters, and microneurographic needle electrodes, as described elsewhere. Subjects fasted for at least 12 h before the study but received 30 ml of oral sodium bicarbonate as a precautionary measure. Subjects received 5–7 ml·kg⁻¹ of intravenous saline before measurements. Basal HR, BP, and efferent SNA directed to blood vessels within skeletal muscle were recorded at rest after a 20-min accommodation period following instrumentation.

Electrocardiogram signals were processed by computerized identification of R spikes and measurement of RR intervals. Efferent nerve signals were amplified (×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 over 5-min epochs at each steady-state anesthetic level. Sympathetic nerve activity was identified by previously defined criteria. This activity has been shown to be similar in upper and lower, ipsilateral and contralateral extremities. Because muscle blood flow is 40% of resting cardiac output, recordings of muscle SNA represent an important window on neural control of BP. SNA is often quantified as the number of bursts per minute. A better method to express SNA is by quantitating the number of integrated bursts that occur every 100 heartbeats, because the integrated bursts of SNA are pulse-synchronous with the electrocardiogram, and HR varies widely over the stress period. Integrated bursts also vary in amplitude based on the recruitment of sympathetic fibers each heartbeat. Thus, 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 heartbeats. Because the amplitude of sympathetic bursts can be altered by unpredictable/unwanted needle movement within the nerve, both methods of quantification are reported.

Baroreceptor Testing

The activity from the baroreceptors was altered via drug-induced, sequential hypo- and hypertensive challenges. A bolus injection of sodium nitroprusside (100 μg) was followed 60 seconds later by a bolus injection of phenylephrine (150 μg). These doses were designed to produce a range of BP values within physiologically acceptable limits. The doses chosen caused pressure to be decreased by about 15 mmHg and then increased approximately 10 mmHg above control levels. Sodium nitroprusside and phenylephrine were employed because of their direct acting effects with minimum direct influence on the reflex pathways under study.

Procedures

After recording neurocirculatory parameters at conscious baseline and the response to the baroreceptor challenge, subjects breathed oxygen, and anesthesia was induced with 100 mg thiopental (to reduce mydriatic responses), followed immediately by 0.3 mg·kg⁻¹ etomidate and 0.2–0.25 mg·kg⁻¹ vecuronium to facilitate intubation. After tracheal intubation, the anesthetic was randomly chosen to be either isoflurane (n = 9) or desflurane (n = 9). Anesthesia was maintained with isoflurane or desflurane at 0.5 (0.6 or 3.6%), 1.0 (1.2 or 7.2%), or 1.5 (1.8 or 10.9%) MAC in a randomized fashion. End-tidal anesthetic and carbon dioxide levels were continuously monitored (infrared spectrometry, Ohmeda, W1). Ventilation was adjusted to maintain P CO₂ at 38–40 mmHg, which was confirmed at each anesthetic level by an arterial blood gas measurement. After 30 min of equilibration to allow the effects of the induction agents to subside, steady-state and baroreceptor stress measurements were repeated at the first MAC setting. The anesthetic depth was adjusted to the next randomized level, and another 20-min equilibration period was allowed before additional measurements were repeated. Flow rates were adjusted to achieve the target end-tidal anesthetic concentration within the first 10 min of the 20-min period.

Cardiac baroslopes were derived by plotting RR interval versus mean arterial pressure (MAP) over the stress period induced by nitroprusside and phenylephrine (fig. 1). To more easily manage the large number of points and nonbaroreceptor-mediated variations of RR interval (due to respiration and arousal), RR interval data were averaged before plotting in figure 1. The relation was fit to the regression of the general form of increasing and decreasing decreasing flow rates due to regression of the general form of increasing and decreasing flow rates due to decreasing decreasing flow rates due to...
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Cardiac Baroslope Derivation

![Cardiac Baroslope Derivation Diagram](image)

**Fig. 1.** Derivation of cardiac baroslopes. (Top) Individual data points from a 165- subjects file in which bolus sodium nitroprusside (SNP) is given, followed 60 s later by a bolus of phenylephrine (Phe). Note that the decreasing and increasing paths are not identical, and thus, these slopes are analyzed separately. Data are averaged over 2 mmHg blood pressure increments, and then the best fit line is drawn to the linear portion of the response: left side for decreasing pressure and right side for increasing pressure. The X on each graph represents the mean heart rate and blood pressure before drug administration.

Abaroslope was altered via hypertensive challenge. Subjects were designed to be either isoflurane or desflurane. Anesthesia was induced via 0.5 (0.6 or 0.7) MAC of isoflurane and carboxygenation (in-duced by ventilation of nitrogen). After intubation was achieved, arterial blood pressure was measured to allow for proper baroslope. Steady-state arterial pressure was noted before the baroslope was performed (aesthetic depth). Abaroslope was created in a 10 min period using bolus injections of sodium nitroprusside (SNP) and phenylephrine (Phe) (Table 1). RR interval

![Cardiac Baroslope Derivation Diagram](image)

data were averaged for each sequential 2 mmHg of BP before plotting RR interval versus MAP, as shown in figure 1. The linear portions of the typically sigmoid relation were derived by computer after visual selection of the general region of interest. The HR response to increasing BP did not typically overlay the response to decreasing BP, an effect known as hysteresis. (This may be due to a differential baroreflex response based on the direction of pressure change.) Therefore, the linear portions of the response curve were fitted to separate lines by regression analysis for both falling and rising pressure responses, as shown in figure 1. Similar sympathetic baroslopes were created from the SNA response to lowered diastolic pressure. The sympathetic response represents primarily the falling pressure response, because as pressure was elevated above baseline, nerve activity was shut off. The choice of MAP and diastolic pressure as the ordinate in the regression analyses was based on published data demonstrating that these variables are the primary determinants of arterial baroreflex neuroeffector responses in healthy humans.

Consecutive hemodynamic and neural measurements were compared by analysis of variance for repeated measures, and paired comparisons were made with Dunnett's t test. Differences between baroslopes derived under isoflurane and desflurane anesthesia were compared by analysis of variance for repeated measures. Probability values less than 0.05 were considered sufficient to reject the null hypothesis for all comparisons.

**Results**

The hemodynamic measurements at conscious baseline and during steady-state levels of anesthesia are displayed in table 1 and are consistent with what has been described previously by this laboratory in this population. In two subjects receiving isoflurane at 1.5 MAC, MAP decreased below 50 mmHg, and baroreflex testing was not performed. Their data were dropped from the final study analysis and are not included in the presentation. The awake, resting HR, MAP, and SNA were similar between groups. Increasing MAC of isoflurane resulted in significant increases in HR from conscious baseline. Conversely, 0.5 and 1.0 MAC desflurane did not result in changes in HR, but 1.5 MAC desflurane was associated with significant increases in HR similar to the isoflurane group (table 1). Resting MAP was significantly reduced in a dose-dependent fashion by both anesthetics, and there were no differences between anesthetics. SNA initially decreased at 0.5 MAC desflurane and gradually increased at higher MAC. Although SNA at 0.5 MAC isoflurane also decreased from conscious baseline, it did not significantly increase with higher MAC, and at 1.5 MAC, it was significantly lower than equivalent isoflurane.

Awake cardiac and sympathetic baroslopes were similar between groups (table 2). In all cases, cardiac baroslopes derived during decreasing pressure were less than responses to increasing pressure. Isoflurane and desflurane produced similar decreases in cardiac baroslopes in response to the increasing and decreasing pressure stimuli (fig. 2). The sympathetic slopes differed between anesthetics only at the 0.5 MAC level, with isoflurane showing a preserved slope and desflurane a decreased response (table 2 and fig. 3). Baroslopes decreased in magnitude with increasing anes-

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Table 1. Baseline and Steady-state Neurocirculatory Parameters

<table>
<thead>
<tr>
<th></th>
<th>Conscious Baseline</th>
<th>0.5 MAC</th>
<th>1.0 MAC</th>
<th>1.5 MAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>57 ± 2.4</td>
<td>65 ± 1.7*</td>
<td>68 ± 2.1*</td>
<td>71 ± 2.5*†§</td>
</tr>
<tr>
<td>ISO</td>
<td>56 ± 3.2</td>
<td>60 ± 4.6</td>
<td>60 ± 3.7</td>
<td>72 ± 5.0*†§</td>
</tr>
<tr>
<td>DES</td>
<td>92 ± 1.6</td>
<td>79 ± 3.6*</td>
<td>68 ± 1.8†</td>
<td>56 ± 3.9†§</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>90 ± 2.1</td>
<td>74 ± 3.2*</td>
<td>64 ± 2.6†</td>
<td>48 ± 2.5†§</td>
</tr>
<tr>
<td>Sympathetic nerve activity (bursts/100 cardiac cycles)</td>
<td>19 ± 2.5</td>
<td>12 ± 2.8*</td>
<td>18 ± 6.3‡</td>
<td>24 ± 6.8†</td>
</tr>
<tr>
<td>ISO</td>
<td>30 ± 3.9</td>
<td>26 ± 8.4</td>
<td>46 ± 9.9†</td>
<td>57 ± 9.9†</td>
</tr>
<tr>
<td>DES</td>
<td>26 ± 2.3</td>
<td>15 ± 5.1*</td>
<td>18 ± 4.8</td>
<td>29 ± 13.1</td>
</tr>
<tr>
<td>Sympathetic nerve activity (total activity)</td>
<td>40 ± 7.7</td>
<td>21 ± 5.3*</td>
<td>39 ± 8.9†</td>
<td>57 ± 14.3</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
Total activity = (burst frequency × mean burst amplitude)/100 cardiac cycles; ISO = isoflurane; DES = desflurane.
* P < 0.05 from respective conscious baseline.
† P < 0.05 change from 0.5 MAC.
‡ P < 0.05 between anesthetics.
§ P < 0.05 change from 1.0 MAC.

Thusic depth except for isoflurane at the 0.5 MAC level, as mentioned above.

Discussion

In this study, we assessed the ability of the baroreceptor reflex to respond to hypotensive stresses during increasing MAC levels of desflurane and isoflurane anesthesia. From previous work, we learned that most volatile anesthetics suppress the ability to reflexively adjust BP and HR in response to BP perturbations. Seagard et al., in their work with dogs, reported that volatile anesthetics act at several sites along the baroreceptor pathway to produce these results, including the baroreceptors, afferent and efferent nerve pathways, central nervous system, peripheral ganglia, and heart. Although most components of the baroreflex were suppressed by volatile anesthetics,

Table 2. Arterial Baroreceptor Sensitivity (Baroslope) Responses to Increasing and Decreasing Blood Pressure Perturbations

<table>
<thead>
<tr>
<th>Cardiac Baroslopes</th>
<th>Decreasing Pressure</th>
<th>Increasing Pressure</th>
<th>Sympathetic Baroslopes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoflurane</td>
<td>Desflurane</td>
<td>Isoflurane</td>
<td>Desflurane</td>
</tr>
<tr>
<td>Baseline</td>
<td>17.0 ± 3.1</td>
<td>22.2 ± 2.4</td>
<td>29.5 ± 3.4</td>
</tr>
<tr>
<td>0.5 MAC</td>
<td>8.9 ± 1.4</td>
<td>11.7 ± 2.1†</td>
<td>24.9 ± 5.7</td>
</tr>
<tr>
<td>1.0 MAC</td>
<td>5.8 ± 1.2†</td>
<td>9.9 ± 2.0*</td>
<td>14.6 ± 2.0*</td>
</tr>
<tr>
<td>1.5 MAC</td>
<td>2.1 ± 0.6†</td>
<td>3.9 ± 0.8†</td>
<td>6.8 ± 1.8†</td>
</tr>
<tr>
<td>Sympathetic Baroslopes</td>
<td>Isoflurane</td>
<td>Desflurane</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>-8.5 ± 2.7</td>
<td>-8.5 ± 1.4</td>
<td></td>
</tr>
<tr>
<td>0.5 MAC</td>
<td>-9.6 ± 2.3</td>
<td>-5.0 ± 1.2†§</td>
<td></td>
</tr>
<tr>
<td>1.0 MAC</td>
<td>-4.7 ± 1.6†</td>
<td>-4.1 ± 1.3*</td>
<td></td>
</tr>
<tr>
<td>1.5 MAC</td>
<td>-2.4 ± 1.4†</td>
<td>-2.6 ± 0.9*</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SEM (baroslopes as described in the text).
Cardiac baroslopes = mmHg; sympathetic baroslopes = total activity/mmHg.
* P < 0.05 from respective conscious baseline.
† P < 0.05 change from 1.0 MAC.
‡ P < 0.05 change from 0.5 MAC.
§ P < 0.05 between anesthetics when compared as change from baseline.

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they found that baroreceptor afferent activity was increased with deeper anesthetic levels.\textsuperscript{10} The increased inhibitory afferent activity was thought to partially account for the decrease in BP observed with these agents.

Several observations suggest that baroreflex control of the circulation may differ during desflurane anesthesia compared to isoflurane. Although preliminary work by Stekel et al.\textsuperscript{22} suggests that the reflex mesenteric vascular response of rabbit to baroreceptor stimulation or inhibition is similarly attenuated by desflurane, halothane, and isoflurane, observations in humans suggest that isoflurane and desflurane might have dissimilar effects on the reflex control of the circulation. We\textsuperscript{2} and others\textsuperscript{1,3} have shown that equip-MAC concentrations of isoflurane and desflurane produce similar decreases in BP. However, isoflurane produces a moderate increase in HR at 0.5 MAC, whereas desflurane does not change HR. Moreover, despite similar BP decreases at 1.5 MAC, desflurane is associated with a greater level of SNA and greater plasma norepinephrine concentrations than those seen with isoflurane.\textsuperscript{2,3} One possible explanation for these differences has been that isoflurane preserves baroreflex function at low MAC concentrations, allowing for reflex increases in HR in response to hypotension, whereas at 1.5 MAC desflurane, the inhibitory afferent nerve traffic from baroreceptors is impaired, leading to augmented sympathetic outflow.

In the current study, the cardiac baroreceptor reflex was decreased similarly and in a graded fashion by both anesthetic agents, suggesting a reduced ability to increase HR for any given decrease in pressure. Despite similar decreases in BP, isoflurane was associated with
an increase in HR at 0.5 MAC, and desflurane was not. This effect cannot be attributed to differences in cardiac baroreflex responsiveness. However, the sympathetic baroslopes were preserved at 0.5 MAC desflurane but decreased at similar levels of desflurane. This finding might explain the early tachycardia in response to isoflurane at 0.5 MAC but would not explain the disparate SNA responses at deeper anesthetic levels. If the sympathetic reflex activity were responsible for the increased HR response, one would expect a similar magnitude of HR increase for both agents at the 1.0 MAC level when baroreflex function was diminished similarly. The inability to directly relate changes in sympathetic baroslopes with alterations in basal HR at different anesthetic depths is related in part to human baroreflex physiology: The regulation of HR is almost entirely via activation or withdrawal of parasympathetic activity to the SA node. Thus, the differences in steady-state HR response produced by these two agents cannot be explained by differences in sympathetic baroreflex responsiveness.

A second reason that baroreflex activity may not correlate with basal levels of HR and BP can be found in the structure of the baroreceptor HR control system. The observed differences in HR at various depths of anesthesia were made at steady-state, but the reflex measurement technique was in response to a stress on the system at each steady-state anesthetic concentration. The dynamic testing procedures that we employed may not appropriately assess the autonomic influences on basal HR or SNA under anesthesia but instead reflect the ability to oppose acute pressure changes at these new set-points. Such a distinction between basal autonomic activity versus rapid reflex adjustments in autonomic outflow has been strengthened by recent findings of Seagard and colleagues of two distinct sets of carotid baroreceptor afferent cell types. Type I cells are generally quiescent but respond briskly to dynamic pressure changes and can quickly reset to operate at new pressure thresholds. Type II cells are tonically active, fire in proportion to the absolute pressure, and slowly reset. Whether type I or II cells in the carotid baroreceptors have differential effects on efferent vagal or SNA responses has not been determined; however, we conjecture that isoflurane and desflurane might similarly alter the activity of dynamic type I cells to depress the acute reflex response to pressure changes with increasing depth of anesthesia. Furthermore, the slower reacting, tonic limb of the baroreflex arc (perhaps mediated by type II cells) may be dissimilarly altered by desflurane and isoflurane, leading to different basal HR and SNA with increasing anesthetic concentrations.

Clinically, our data confirm the ability of volatile anesthetics to progressively suppress the acute reflex response to hypo- or hypertensive stimuli with increasing anesthetic depth, and the effect appears to be greater for decreasing versus increasing pressure responses. In addition to attenuating the neural reflexes, isoflurane and desflurane lower BP by direct effects on vascular smooth muscle. This would alter vascular dispensability and deformation of the vessel wall containing the baroreceptor sensors, as demonstrated previously in dogs, where controlled pressure stimuli resulted in enhanced afferent nerve activity from baroreceptors during isoflurane administration compared to control conditions. In the human model, it is virtually impossible to evaluate the direct effects of isoflurane and desflurane on the vascular wall containing baroreceptors and on the afferent profile from these sites during pressure loading and unloading conditions. In summary, we found a graded depression of both pressor and depressor cardiac baroslopes with increasing anesthetic depth, and there were essentially no differences between isoflurane and desflurane. There was a similar depression of sympathetic baroslopes with increasing MAC, with the exception that low-dose isoflurane maintained sympathetic reflexes near awake levels. These findings do not explain the different steady-state HR and SNA responses to isoflurane and desflurane anesthesia.

References


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