Sympathetic Responses to Induction of Anesthesia in Humans with Propofol or Etomidate

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Anesthetic induction with propofol commonly results in hypotension. This study explored potential mechanisms contributing to hypotension by recording cardiovascular responses including sympathetic neural activity from patients during induction of anesthesia with propofol (2.5 mg · kg⁻¹ plus 200 μg · kg⁻¹ · min⁻¹) or, for comparison, etomidate (0.5 mg · kg⁻¹ plus 15 μg · kg⁻¹ · min⁻¹). Twenty-five consenting, nonmedicated, ASA physical status 1 and 2, surgical patients were evaluated. Measurements of R-R intervals (ECG), blood pressure (radial artery), forearm vascular resistance (plethysmography), and efferent muscle sympathetic nerve activity ([MSNA] microneurography: peroneal nerve) were obtained at rest and during induction of anesthesia. In addition, a sequential bolus of nitroprusside (100 μg) followed by phenylephrine (150 μg) was used to obtain data to quantify the baroreflex regulation of cardiac function (R-R interval) and sympathetic outflow (MSNA) in the awake and anesthetized states. Etomidate induction preserved MSNA, forearm vascular resistance, and blood pressure, whereas propofol reduced MSNA by 76 ± 5% (mean ± SEM), leading to a reduction in forearm vascular resistance and a significant hypotension. Both cardiac and sympathetic baroslopes were maintained with etomidate but were significantly reduced with propofol, especially in response to hypotension. These findings suggest that propofol-induced hypotension is mediated by an inhibition of the sympathetic nervous system and impairment of baroreflex regulatory mechanisms. Etomidate, conversely, maintains hemodynamic stability through preservation of both sympathetic outflow and autonomic reflexes. (Key words: Anesthetics, intravenous: propofol; etomidate. Anesthetic techniques: induction. Autonomic nervous system: sympathetic. Blood pressure. Measurement techniques: forearm plethysmography; sympathetic microneurography. Reflexes: baroreceptors; pressoreceptors.)

ETOMIDATE AND PROPOFOL both are rapid-acting sedative agents used for the induction of general anesthesia. Administration of etomidate produces minimal changes in hemodynamics, whereas propofol induction decreases arterial pressure. Published reports have not agreed as to the mechanism of propofol-mediated hypotension, but several mechanisms may be involved. Propofol has been shown to decrease preload, afterload, and contractility. Several investigators have attributed the arterial and venous-dilating properties of propofol to its direct effect on vascular smooth muscle. It has been shown to reduce tonic levels of sympathetic activity. It is noteworthy that etomidate also has been shown to decrease sympathetic activity in rabbits and appears to reduce myocardial contractility both in vivo and in vitro models. These data contrast with the clinical observation of hemodynamic stability after administration of etomidate to humans. To our knowledge, published human studies have not examined sympathetic function during etomidate administration. One goal of the present study was to directly examine sympathetic neural function in humans, with microneurography, during etomidate administration and to compare the observed responses to those noted during administration of induction doses of propofol.

The maintenance of hemodynamic stability during induction of anesthesia is not only dependent on the basal "tone" of the autonomic nervous system, but is also importantly influenced by baroreceptor reflex regulation of autonomic outflow influencing cardiac function and peripheral vascular resistance. Propofol has been shown to decrease the baroreceptor slope relating blood pressure to heart rate in animals. Others have suggested that in humans propofol maintains the baroslope but shifts the operating point of the baroreflex curve to lower pressures. In contrast, relatively little work has focused on the effects of etomidate on the baroreceptor reflex. However, if in fact etomidate does reduce myocardial function and basal sympathetic "tone" as suggested by animal studies, then the observed hemodynamic stability after etomidate induction in humans might be related to preserved or augmented baroreflex mechanisms. Thus, a second goal of the present research was to evaluate baroreflex regulation of cardiac function (R-R interval) and peripheral resistance (by sympathetic microneurography) after propofol or etomidate induction in patients.

Materials and Methods

Twenty-five healthy, normotensive men, ages 21 to 71 yr (mean age 39 yr) scheduled for elective surgery were studied. Each signed consent forms that previously had been approved by the Institution's human research review committee. Research participants were not receiving medications with cardiac or vasoactive properties. Each
patient fasted for at least 12 h prior to testing. Patients were instrumented and studied while supine. Heart rate was monitored from leads II and V5 of the electrocardiogram. A 20-G catheter was inserted into a radial artery for direct determination of arterial blood pressure, and an 18-G catheter was inserted into a forearm vein and used for fluid and drug administration. Each subject received 10 ml·kg⁻¹ saline prior to initiation of the study.

Subjects underwent a trial exposure to the baroreceptor stress test. This was carried out by injecting 100 µg sodium nitroprusside through the intravenous catheter; approximately 60 s later, during peak hypotension, a 150-µg bolus of phenylephrine was injected to restore blood pressure and to elevate it slightly above baseline for 1 to 2 min. This process resulted in a broad range of blood pressure perturbations and permitted a quantitative analysis of the acute baroreceptor reflex regulation of both cardiac intervals and efferent sympathetic nerve activity directed to skeletal muscle blood vessels.²⁴ Forearm blood flow was measured by Hg-in-Silastic plethysmography, and forearm vascular resistance was calculated as the ratio of mean arterial pressure to forearm blood flow.²⁴

PERONEAL NERVE RECORDINGS

After the trial baroreceptor test, 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, 30–40 V, 150 mA) were delivered below this mark to identify the location of the peroneal nerve. The skin was then cleansed, and two 5-µm-tipped, epoxy-coated tungsten needles (TMI Electronics, Iowa City, IA) were inserted. One needle was advanced to an area just outside the peroneal nerve; the second needle was advanced into the peroneal nerve. The location of the nerve was identified by applying brief impulses (1 Hz, 0.3–0.7 V, 150 mA) to the needle. When a muscle fascicle within the peroneal nerve was entered, a distinct muscle contraction in the distribution of the deep or superficial peroneal nerve was noted. The stimulation was halted, and neural activity was amplified (100,000 ×). Signals common to both needles (e.g., background noise) were cancelled in a custom-made preamplifier by common-mode rejection. Characteristic bursts of sympathetic efferent activity were sought by fine manipulations of the needle within the motor nerve fascicle. The identity of these bursts and their distinction from activity occurring in skin sympathetic efferent nerve fibers have been described in detail elsewhere.²⁵,²⁶

PROCEDURES

Once an acceptable sympathetic recording was obtained, a 10-min quiet rest period was observed, followed by 6 min of hemodynamic measurements. A blood sample was obtained from the arterial catheter for blood gas analysis. Subjects then underwent the baroreceptor stress test. A face mask was gently placed and 100% O₂ administered for a period of 5 min. End-tidal carbon dioxide and nitrogen concentrations were monitored by mass spectrometry. A priming dose of vecuronium (0.01 mg·kg⁻¹) was given and followed by anesthetic induction with either etomidate (0.3 mg·kg⁻¹) or propofol (2.5 mg·kg⁻¹). Ventilation was assisted through the mask and without an oral airway while 0.15 mg·kg⁻¹ of vecuronium was given. A continuous intravenous infusion of anesthetic began immediately after induction (200 µg·kg⁻¹·min⁻¹ for propofol or 15 µg·kg⁻¹·min⁻¹ for etomidate). Continuous hemodynamic measurements were made for 4 min after induction. End-tidal carbon dioxide concentrations were kept at identical levels to those recorded during spontaneous awake ventilation. Four minutes after induction, another blood gas sample was obtained, and the baroreceptor stress test was repeated. Upon completion of this test, vecuronium (0.1 mg·kg⁻¹) was given and when neuromuscular blockade was adequate, tracheal intubation was performed.

ANALYSIS

Consecutive hemodynamic measurements were compared between groups with repeated measures analysis of variance. Specific time points were compared with Dunnett’s procedure. Baroreceptor regulation of cardiac function (R-R intervals) and sympathetic nerve activity were determined by plotting blood pressure against the corresponding dependent variable. The linear portion of the sigmoid relationship between systolic blood pressure and R-R interval and the linear portion of the relationship between diastolic blood pressure and sympathetic nerve activity were determined by computer as previously described²⁷ and used to calculate baroslopes. The sigmoid relationship between systolic pressure and R-R interval often revealed a hysteresis (i.e., the relationship during decreasing blood pressure did not superimpose on the data obtained during the subsequent increase in pressure). Therefore, R-R interval responses to decreasing pressure were analyzed separately from responses during increasing pressure. A hysteresis was not evident in evaluating the diastolic pressure–muscle sympathetic nerve activity (MSNA) relationship.

Awake and anesthetized baroslopes were compared with Student’s t tests. Probability values that were less than 0.05 were considered sufficient to reject the null hypothesis. Hemodynamic and MSNA responses to laryngoscopy and tracheal intubation were recorded from five subjects in the etomidate group and eight subjects in the propofol group. The peak R-R interval and blood pressure response were chosen, and the sympathetic ac-
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TABLE 1. Awake, Supine Baseline Neurocirculatory Parameters

<table>
<thead>
<tr>
<th></th>
<th>Etomidate Group</th>
<th>Propofol Group</th>
<th>Sympathetic Activity</th>
<th>Etomidate Group</th>
<th>Propofol Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>R–R interval (ms)</td>
<td>966 ± 50</td>
<td>975 ± 51</td>
<td>Bursts</td>
<td>35.0 ± 6.5</td>
<td>24.9 ± 3.2</td>
</tr>
<tr>
<td>Systolic pressure (mmHg)</td>
<td>140.6 ± 3.3</td>
<td>131.9 ± 4.3</td>
<td>100 Cardiac cycles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic pressure (mmHg)</td>
<td>69.4 ± 2.6</td>
<td>66.6 ± 1.8</td>
<td>Bursts</td>
<td>21.6 ± 5.5</td>
<td>15.4 ± 1.9</td>
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<tr>
<td>Forearm vascular resistance (units)</td>
<td>26.0 ± 2.9</td>
<td>30.1 ± 3.5</td>
<td>Total activity</td>
<td>34.3 ± 7.1</td>
<td>26.7 ± 5.6</td>
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Data are means ± SEM. Total activity = integrated burst frequency per 100 cardiac cycles multiplied by the average burst amplitude (microvolts); units = mmHg + ml⁻¹ · 100 ml⁻².

Results

There were no differences in age (41 ± 5 yr vs. 37 ± 4 yr, mean ±SEM), height (176 ± 2 vs. 176 ± 2 cm), and weight (79 ± 4 vs. 81 ± 2 kg) in the etomidate and propofol groups. In addition, ASA physical status (etomidate ASA 1, n = 4, and ASA 2, n = 5; propofol ASA 1, n = 9, and ASA 2, n = 7) and baseline values of R–R interval, systolic and diastolic pressure, and forearm vascular resistance did not differ between groups (table 1). The average resting MSNA parameters tended to be lower in the propofol group, but these differences were not statistically significant. Arterial pH, PO₂, and PCO₂ were similar in both groups while awake. Average pH and PCO₂ in all patients while awake was 7.4 ± 0.01 and 39.1 ± 1.2 mmHg, and 4 min after induction of anesthesia during mask ventilation the average pH was 7.4 ± 0.01 and the average PCO₂ was 41.9 ± 1.3 mmHg (P > 0.05). Arterial PO₂ averaged 135 ± 25 mmHg in awake patients and increased to 374 ± 26 mmHg during administration of 100% O₂ by mask (P < 0.01). We have previously observed unchanged hemodynamic indices and baroreflex responses in healthy volunteers who first breathed room air and later breathed 100% O₂ (unpublished observations).

Administration of etomidate produced an average change in R–R interval (−67 ± 25 ms), which was one third of that noted during protocol induction (−161 ± 22 ms; fig. 1). This translates to a 4-beat · min⁻¹ increase in heart rate with etomidate and a 12-beat · min⁻¹ increase with propofol. Both systolic and diastolic blood pressures were well maintained with etomidate but were decreased during administration of propofol (systolic, 132 ± 4.3 to 105 ± 4 mmHg, and diastolic, 66 ± 2 to 59 ± 2 mmHg; fig. 1). Likewise, MSNA was well preserved with etomidate but was markedly reduced with propofol (average reduction of 76 ± 5%; fig. 2). There was a significantly greater decrease in forearm vascular resistance produced by propofol than by etomidate (fig. 3).

Representative recordings from two patients receiving sodium nitroprusside while awake and after induction of anesthesia are shown in figure 4. Declining blood pressure provoked reflex sympathetic activation that was preserved in the patient receiving etomidate but nearly abolished in the patient receiving propofol. Cardiac (R–R interval) baroslopes, an index of reflex gain, are shown in figure 5. Slopes from awake and anesthetized periods were separately derived in six patients: for decreasing pressures. Etomidate induction did not alter cardiac baroslopes. Propofol produced a small reduction in the cardiac baroslope obtained during increasing blood pressure but produced a more marked attenuation in gain with decreasing pressures. In figure 6, the sympathetic baroslopes are shown. In the etomidate group, this slope averaged −4.7 ± 0.5 (bursts × amplitude/mMmHg) in awake patients and was not significantly reduced after etomidate administration (−3.7 ± 0.8). Propofol, in contrast, produced a nearly 4-fold reduction (−70 ± 16%) in the baseline sympathetic baroslope (fig. 6). Responses to laryngoscopy and tracheal intubation are demonstrated in figure 7. Despite different baseline blood pressure, heart rate, and nerve activity under anesthesia, the hemodynamic response and sympathetic activation that occurred during intubation were similar in subjects anesthetized with etomidate or propofol.

Discussion

Cardiovascular homeostasis is in large part mediated by the sympathetic nervous system, which modulates heart rate, myocardial contractility, arterial resistance, and venous capacitance. Thus, knowledge of how anesthetic agents modify sympathetic activity is essential for understanding subsequent cardiovascular responses. This study demonstrates, in humans, that propofol decreases tonic sympathetic nerve activity. Moreover, propofol appears to attenuate greatly the baroreflex changes in sympathetic activity that occur in response to blood pressure perturbations. This contrasts markedly from responses noted during administration of etomidate, in which both tonic
outflow to blood vessels within skeletal muscle in awake, nonpremedicated surgical patients. Sympathetic vasoconstrictor outflow to skeletal muscle blood vessels is primarily regulated by baroreceptor afferent information but may be substantially modified by central integration and processing of diverse neural inputs. In previous studies from

and baroreflex regulation of sympathetic activity are well preserved.

In this study, sympathetic microneurography was used to obtain direct recordings of sympathetic vasoconstrictor

FIG. 1. Hemodynamic responses to anesthetic induction with either propofol (2.5 mg/kg) or etomidate (0.5 mg/kg). Propofol produced a greater tachycardia and a larger decline in blood pressure compared to responses during etomidate induction. †P < 0.05 and *P < 0.01 compared to etomidate responses (ANOVA).

FIG. 2. Muscle sympathetic nerve activity was significantly decreased in patients induced with propofol compared to those receiving induction doses of etomidate. This figure includes graphs expressing sympathetic traffic in three different units as explained in the legend of table 1. *P < 0.05 compared to the etomidate group.
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FIG. 3. Propofol produced a larger decrease in forearm vascular resistance compared to etomidate. *P < 0.05.

etomidate may reduce cardiac function. For example, comparisons of the direct cardiac effects of equianesthetic doses of thiopental and etomidate have been made in isolated (and therefore denervated) cardiac tissue. Etomidate reduced myocardial contractility but did so to a lesser extent than thiopental. This observation is at variance with the clinical finding of hemodynamic stability after administration of etomidate to humans. The present study helps explain this discrepancy. The ability of etomidate to sustain stable cardiovascular hemodynamics when administered to humans is most likely related to its ability to maintain sympathetic outflow and baroreceptor responsiveness. In light of data that demonstrate that etomidate reduces cardiac function in isolated heart preparations, the preservation of autonomic function during etomidate administration in neurally intact humans appears essential to the maintenance of myocardial function, cardiac output, and blood pressure.

The unperturbed sympathetic activity during etomidate administration in humans is at variance with the results of Hughes and MacKenzie, who observed decreases in sympathetic activity in decerebrate rabbits given etomidate. However, because these animals were maintained with a background anesthetic of halothane and were par-

patient ST235 Etom

nitroprusside while awake

nitroprusside during etomidate

patient DH162 Prop

nitroprusside while awake

nitroprusside during propofol

FIG. 4. Representative recordings from two patients receiving sodium nitroprusside while awake (baseline) and 5 min after induction of anesthesia. The reflex augmentation in sympathetic traffic that occurs in response to the hypotension is clearly shown in both patients while awake and in the patient receiving etomidate. However, these reflex responses are virtually abolished in the patient who received propofol. Also note that baseline nerve activity during anesthesia with etomidate and propofol are quite different. Etomidate did not reduce neural activity to the extent that propofol did (note beginning segment of the nitroprusside during anesthesia tracings).
alyzed with gallamine, the observed autonomic changes during etomidate administration might have been substantially modified.

In contrast to our observations during administration of etomidate, induction of anesthesia with propofol significantly decreased arterial blood pressure despite careful preinduction hydration of each patient. Although this finding is consistent with those of most previous studies, controversy exists as to the mechanism(s) of hypotension. Lepage et al. used gated radionuclide ventriculography and invasive cardiac monitoring to show that propofol reduced several indicators of preload but did not alter myocardial contractility.5 We and others have demonstrated that propofol-mediated decreases in cardiac preload are, in part, attributable to augmentations in venous compliance.11,12,39 In contrast, several studies suggest that propofol reduces myocardial contractility.8,9 Muller et al. used transesophageal echocardiography to show that administration of propofol to humans had negative inotropic effects.8 Finally, decreases in afterload have also been suggested as a mechanism whereby propofol causes hypotension.8,6,7 For example, in patients with a Jarvik-7 artificial heart and fixed cardiac output, propofol has been shown to reduce blood pressure by direct arterial (and venous) vasodilation.10 These vascular changes were not believed to be due to alteration in sympathetic tone because there were no changes in plasma epinephrine or norepinephrine concentrations. However, plasma nor-

**FIG. 5.** Cardiac baroreceptor slopes derived from the relationship between systolic pressure and R-R interval. The top graphs demonstrate the R–R interval responses to increasing blood pressure. The standard error bars represent the variation about systemic pressure and R–R interval among the entire group. The regression line is the average slope or gain from subjects while awake and during anesthesia. The average group baroslopse is also shown in the small inset histogram. The slope units are milliseconds per mmHg. The heart rate responses to decreasing blood pressure are depicted in the lower half of this figure. Propofol induced a significant reduction (flattening) of the cardiac baroslopes to both rising pressure (*P < 0.05) and declining pressures (**P < 0.01 compared to awake response). In contrast, etomidate did not alter the slope of the relationship between R–R interval and systolic pressure during periods of increasing pressure or decreasing pressure. This is noted by the parallel regression lines.

**FIG. 6.** Sympathetic baroreceptor slopes derived by relating diastolic pressure to muscle sympathetic nerve activity (MSNA). Propofol produced a pronounced inhibition of the sympathetic baroreflex depicted in the left portion of the graph by a flattening of the slope. The inset demonstrates the average baroslopes from patients while awake and after induction of anesthesia with propofol or etomidate. The average baroslope was markedly decreased in subjects receiving propofol (**P < 0.01 vs. awake slope).
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Intubation Response

![Graph showing R-R interval and mean arterial pressure responses to intubation]

**Fig. 7.** Hemodynamic and neural responses to laryngoscopy and tracheal intubation in patients anesthetized with either etomidate or propofol. Preintubation baseline numbers differed significantly between groups (*P < 0.01). The absolute change in these parameters produced by intubation was similar in both groups. This is demonstrated by the parallel hemodynamic and neural responses between groups.

epinephrine concentrations alone may be inadequate for assessing the sympathoinhibitory effects of anesthetic agents because these concentrations are a function of norepinephrine release into, and clearance from, the circulation. In addition, the analytical methods used to determine plasma levels of norepinephrine are subject to error.

Sympathetic microneurography is a more precise method for directly assessing regional sympathetic activity during anesthesia. Seligren et al. used microneurography in eight premedicated patients (rectal diazepam) anesthetized with propofol and maintained on isoflurane. Administration of propofol was associated with a 34% decrease in MSNA. Our results in nonpremedicated patients show a greater decrease in MSNA (75%) and demonstrates a neuroeffect response to the reduced MSNA, i.e., a reduced forearm vascular resistance. The ability of propofol to reduce MSNA, forearm vascular resistance, and blood pressure is similar but more dramatic than that of approximately equal anesthetic doses of thiopental, as previously studied in this laboratory. This suggests that the sympathoinhibition that occurs during propofol administration importantly contributes to the subsequent hypotension. In fact, propofol-mediated decreases in sympathetic activity might be the unifying mechanism that explains all of the various observations of previous investigators, i.e., increased venous compliance, decreased contractility, and decreased afterload. We remain uncertain as to the contribution of direct vascular smooth muscle relaxation to propofol-mediated hypotension, but it undoubtedly plays a role.

Although tonic activity of the autonomic nervous system is important for maintaining blood pressure equilibrium, the baroreceptors play a critical role in buffering perturbations in arterial pressure. They, therefore, importantly contribute to homeostatic equilibrium. For example, if propofol reduces MSNA and lowers blood pressure but preserves reflex responses to a further change in blood pressure, then equilibrium will be maintained, albeit reset to a lower operating point. Baroreflex control of cardiac function (heart rate) has been previously studied during propofol and etomidate administration. These studies, however, have been difficult to interpret. Several were performed on heavily instrumented, surgically manipulated animals with various anesthetics used as a baseline. Other studies carried out in humans used patients pretreated with morphine and maintained on nitrous oxide. The central nervous system and cardiovascular effects of these adjuvant drugs and their potential interactions with propofol or etomidate may have influenced one or many of the components of the baroreflex arc, thereby making interpretation difficult. The present study used volunteers scheduled for elective surgery who were not receiving vasoactive medications and who were not premedicated. An additional limitation of many past studies of baroreflex function under intravenous anesthesia is that only heart rate responses to increasing blood pressure were examined.
In humans, baroreflex control of cardiac function is primarily mediated through fluctuations in cardiac vagal activity.\textsuperscript{[2,3]} Our study demonstrates that propofol significantly attenuates baroreflex regulation of cardiac intervals. This reduction in reflex gain is more pronounced when examining heart rate responses to hypotension than when examining responses to hypertension. In contrast, etomidate induction produced virtually no change in the cardiac reflex responses to increasing or decreasing blood pressures.

In this study, we also quantitate a second important limb of the baroreflex, \textit{i.e.}, sympathetic vasoconstrictor outflow. The slope of the relationship between diastolic pressure and MSNA is an index of the sensitivity of the baroreceptor regulation of the sympathetic nervous system.\textsuperscript{[23,27,34]} Propofol produced a marked attenuation of the sympathetic baroslope, while etomidate preserved the response. The combination of reduced tonic levels of sympathetic activity and an impaired reflex sympathetic response (and direct vasodilatation\textsuperscript{[10,11]}) could result in a sustained reduction in blood pressure during propofol anesthesia.

Finally, we quantitated the peak hemodynamic response to laryngoscopy and tracheal intubation in a subset of patients and determined the amount of sympathetic activity that immediately preceded this peak (fig. 7). The magnitude of the response was similar in all subjects receiving either propofol or etomidate. Although baseline blood pressure and MSNA were reduced after propofol induction, the increased MSNA during intubation raised blood pressure to preinduction levels. In contrast, a similar increase in MSNA in subjects receiving etomidate in which blood pressure was not reduced resulted in a marked hypertension.

We recognize several limitations of our research. We did not study different doses of each induction agent and therefore are unable to generate dose–response information. Instead, we chose to use the usual and commonly administered induction dose of etomidate and propofol. The choice of a maintenance infusion rate was based on pharmacokinetic properties of each anesthetic. These were calculated to maintain relatively high plasma concentrations of each agent following the induction bolus. This enabled us to obtain baroreflex data 4 min after induction without the confounding effects of “lightening” of anesthesia.

In summary, propofol-mediated hypotension is due in part to an inhibition of the sympathetic nervous system and to an impairment of baroreflex mechanisms. Etomidate, conversely, maintains hemodynamic stability through preservation of both sympathetic outflow and autonomic reflexes.

References