Effects of anesthetic and sedative agents on sympathetic nerve activity

Xiao Liu, MD,† Perry L. Rabin, BS,† Yuan Yuan, MD,† Awaneesh Kumar, MD,† Peter Vasallo III, BS,† Johnson Wong, BS,† Gloria A. Mitscher, RN,† Thomas H. Everett IV, PhD, FHRS,* Peng-Sheng Chen, MD, FHRS†

From the *Krannert Institute of Cardiology and Division of Cardiology, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana, and †Division of Anesthesiology, Xiangya Hospital, Central South University, Chang Sha, China.

BACKGROUND The effects of sedative and anesthetic agents on sympathetic nerve activity (SNA) are poorly understood.

OBJECTIVE The purpose of this study was to determine the effects of commonly used sedative and anesthetic agents on SNA in ambulatory dogs and humans.

METHODS We implanted radiotransmitters in 6 dogs to record stellate ganglion nerve activity (SGNA), subcutaneous nerve activity (ScNA), and blood pressure (BP). After recovery, we injected dexmedetomidine (3 μg/kg), morphine (0.1 mg/kg), hydromorphone (0.05 mg/kg), and midazolam (0.1 mg/kg) on different days. We also studied 12 human patients (10 male; age 68.0 ± 9.1 years old) undergoing cardioversion for atrial fibrillation with propofol (0.77 ± 0.18 mg/kg) or methohexital (0.65 mg/kg) anesthesia. Skin sympathetic nerve activity (SKNA) and electrocardiogram were recorded during the study.

RESULTS SGNA and ScNA were significantly suppressed immediately after administration of dexmedetomidine (P = .000 and P = .000, respectively), morphine (P = .011 and P = .014, respectively), and hydromorphone (P = .000 and P = .012, respectively), along with decreased BP and heart rate (HR) (P < .001 for each). Midazolam had no significant effect on SGNA and ScNA (P = .248 and P = .149, respectively) but increased HR (P = .015) and decreased BP (P = .004) in ambulatory dogs. In patients undergoing cardioversion, bolus propofol administration significantly suppressed SKNA (from 1.11 ± 0.25 μV to 0.77 ± 0.15 μV; P = .001), and the effects lasted for at least 10 minutes after the final cardioversion shock. Methohexital decreased chest SKNA from 1.59 ± 0.45 μV to 1.22 ± 0.58 μV (P = .000) and arm SKNA from 0.76 ± 0.43 μV to 0.55 ± 0.07 μV (P = .001). The effects lasted for at least 10 minutes after the cardioversion shock.

CONCLUSION Propofol, methohexital, dexmedetomidine, morphine, and hydromorphone suppressed, but midazolam had no significant effects on, SNA.

KEYWORDS Anesthetic agents; Cardioversion; Propofol; Skin sympathetic nerve activity; Stellate ganglion nerve activity

Introduction

Anesthetic and sedative agents are frequently used during electrophysiological studies. Their use may reduce arrhythmia inducibility and increase the need to use isoproterenol or hemodynamic support.1–3 Although anesthetic agents are known to exert significant effects on synapses and axons of mammalian sympathetic ganglia,4 the quantitative effects of anesthetic agents on sympathetic nerve activity (SNA) of ambulatory animals or human patients remain unclear. Stellate ganglion (SG) is known to be an important source of cardiac sympathetic innervation. Stellate ganglion nerve activity (SGNA) is important in arrhythmogenesis and blood pressure (BP) control.5,6 Subcutaneous sympathetic nerve activity (ScNA) recorded in ambulatory dogs closely correlates with SGNA.7 Both SGNA and ScNA are associated with spontaneous onset of ventricular tachycardia in a canine model.8 Subsequently we developed a new method (neuECG) to simultaneously record electrocardiogram (ECG) and superficial skin sympathetic nerve activity (SKNA) using conventional ECG patch electrodes in dogs and in humans.9,10 The availability of these recording methods provided us with an opportunity to directly determine the effects of anesthetic and sedative agents on SNA. The purpose of the present study was to test the hypothesis that commonly used intravenous anesthetic and sedative agents can suppress...
SNA in normal ambulatory dogs and in humans with atrial fibrillation (AF) undergoing direct current cardioversion.

**Methods**

Animal experiments were performed with approval of the Institutional Animal Care and Use Committee of the Indiana University and conformed to the Guide for the Care and Use of Laboratory Animals. Human studies were performed with approval of the Institutional Review Board of the Indiana University. All human subjects gave written informed consent to participate in the study.

**Animal studies**

*Surgical preparation*

Six adult mongrel dogs (4 male and 2 female; weight 25–35 kg) underwent sterile surgeries with isoflurane inhalation anesthesia. A D70-CCTP radiotransmitter manufactured by Data Sciences International (DSI, St. Paul, MN) was implanted to record left SGNA, left thoracic ScNA, and intravascular BP from the descending aorta. The dogs were allowed to recover for 2 weeks before commencement of baseline ambulatory recording.

**Injection of anesthetic and sedative agents**

All agents were given by single intravenous injection during the daytime. We tested only 1 drug per day to allow complete washout before the next drug was injected. The dosages were based those reported in the literature. (1) Dexmedetomidine: Dosage for sedation when combined with inhalation anesthesia was 2 μg/kg for dogs.11 Based on our experience, 3 μg/kg is an effective dose for sedation in dogs when used alone. (2) Morphine: 0.2 mg/kg was used for heavy sedation in dogs undergoing thoracic skin incisions.12 However, our target was moderate sedation, and 0.1 mg/kg was adequate. (3) Hydromorphone: 0.05 mg/kg bolus injection was selected based on the literature.13 (4) Midazolam: 0.2 mg/kg was used as coinduction agent for dogs.14 We used 0.1 mg/kg injection to achieve medium sedation without depressing respiration. The implanted radiotransmitter has a sampling rate limited to 1000 Hz. Their recordings from SG and subcutaneous space were high-pass filtered at 150 Hz to display SGNA and ScNa, respectively. The same electrical signals from the subcutaneous electrodes were then low-pass filtered at 100 Hz to display ECG.

**Clinical studies**

We performed an observational study in 12 patients with persistent AF undergoing cardioversion as part of their standard care. There were 10 men and 2 women (average age 68.0 ± 9.1 years; average body mass index 32.5 ± 7.5 kg/m²). Eleven were given propofol, and 1 was given methohexitol before cardioversion. We performed 2 channels of neuECG recordings using methods described in a previous report.15 A pair of bipolar electrodes was placed on the left and right subclavian area to simulate ECG lead I. A second pair of bipolar electrodes was placed on the right upper arm. ECG and SKNA were simultaneously recorded by a ME6000 recorder (Biomation, Almonte, Ontario, Canada) with a sampling rate of 10,000/s starting at least 5 minutes before sedative administration and continued until 10 minutes after cardioversion.

**Statistical analysis**

Nerve activity recordings were analyzed using custom-written software. For dogs, nerve activities were quantified by integrating the absolute value of the filtered signal over 20-second windows (iSKNA). The integrated nerve activities were then divided by the total number of samples in each window (20,000) to calculate the average stellate ganglion nerve activity (aSGNA) and average subcutaneous nerve activity (aScNA). BP waveforms were analyzed by the software for automatic detection of systolic BP and diastolic BP. For clinical studies, the electrical signals were bandpass filtered from 500–1000 Hz to display nerve activities. The same signals were then bandpass filtered between 0.5 and 150 Hz to display surface ECG. Average SKNA (aSKNA) was the integrated nerve activity over 5-second windows divided by 50,000, which is the total number of samples within that window. Unless otherwise indicated, all quantitative data are expressed as mean ± SD. Paired Student t tests were used to compare the means. Repeated measures analysis of variance (ANOVA) was performed individually to compare overall differences among different time points after the injection of each agents. Statistical analysis was performed using IBM SPSS Statistics 24 (SPSS Inc, Chicago, IL). Two-sided P ≤ .05 was considered significant.

**Results**

**Effect of anesthetic/sedative agents on sympathetic nerve activity in dogs**

The dogs became quiet and lied down after all drug injections, but they remained conscious without respiratory suppression. Figure 1A shows a typical example of a recording showing the effects of dexmedetomidine on nerve activity. Dexmedetomidine eliminated all SGNA and most ScNA bursts about 2 minutes after injection. BP and heart rate (HR) showed continuous reduction before they recovered 20 minutes later. Figure 1B shows the continuous 28-minute mean values of SGNA, ScNa, mean arterial blood pressure (mBP), and HR in this same dog. Figure 2 shows the typical effects of morphine (Figure 2A), hydromorphone (Figure 2B), and midazolam (Figure 2C). Both morphine and hydromorphone decreased SGNA and ScNa about 2 minutes after the injection, along with reduction of BP and HR. Nerve activity, BP, and HR recovered about 25 minutes after injection. In comparison, little change of SNA was observed after midazolam injection. Of note, midazolam injection was transiently followed by decreased BP but increased HR, suggesting that baroreflexes were intact immediately after injection.

Figure 3 summarizes the effects of drugs on all dogs studied. The ordinate shows the ratios of SGNA, ScNa, BP, and
HR to baseline. After injection of dexmedetomidine, SGNA decreased to 76% ± 17% of baseline in 2 minutes (P = .027), to a maximum of 41% ± 6% of baseline at 5 minutes (P = .005). ScNA also decreased to 75% ± 12% of baseline in 3 minutes (P = .04), which is about 1 minute later than the reduction of SGNA. Maximum reduction was to 58% ± 12% of baseline at 10 minutes after injection (P = .032). SGNA recovered to 90% ± 16% of baseline about 25 minutes after injection (P = .063), while ScNA recovered to 101% ± 13% of baseline about 30 minutes after injection (P = .952) (Figure 2A). HR showed parallel reduction to 78% ± 10% of baseline about 2 minutes after injection (P = .008). BP decreased significantly about 4 minutes after injection to 90% ± 7% of baseline (P = .028) (Figure 2E). After morphine injection, SGNA reduced to 76% ± 17% (P = .046) 5 minutes after injection, then partially recovered to 85% ± 15% (P = .100) 30 minutes after injection. ScNA reduced to 79% ± 6% (P = .001) 10 minutes after injection, then partially recovered to 83% ± 10% (P = .036) 30 minutes after injection (Figure 3B). SGNA and ScNA after hydromorphone injection continued to decline, reaching 66% ± 16% (P = .013) and 71% ± 14% (P = .016) of baseline at 30 minutes after injection (Figure 3C). Midazolam had no significant effects on SGNA or ScNA. At 30 minutes after injection, SGNA was 104% ± 15% (P = .565) of baseline, while ScNA was 98% ± 9% (P = .939) of baseline (Figure 3D). HR and BP changes paralleled the changes of SGNA and ScNA (Figures 3E–3H). Dexmedetomidine had the greatest effects on the maximal reduction of SGNA (by 40.4% ± 5.4%; P < .001), ScNA (by 55.7% ± 7.8%; P < .001), HR (by 49.8% ± 5.6%; P < .001), and mBP (by 69.5% ± 7.3%; P = .045) among all drugs studied. Repeated measures ANOVA was also performed individually to compare overall differences among different time points. F and P values are shown in each panel.

**Effect of anesthetic/sedative agents on sympathetic nerve activity in humans**

The demographics and clinical characteristics of all 12 patients were listed in Table 1. Figure 4 shows the effect of propofol on sympathetic nerve activities in a patient who underwent cardioversion. Figure 4A shows three 30-second tracings of chest SKNA, arm SKNA, ECG, and HR before propofol injection, 1 minute after propofol injection, and after cardioversion. SKNA was suppressed after administration of propofol but briefly increased by cardioversion in this and all patients studied. ECG shows AF before and after propofol injection, which turns to sinus rhythm after cardioversion. Figure 4B shows aSKNA and HR over an 18-minute period. The black dotted lines show the timing of propofol injection (50 mg each time). Transient elevation of SKNA (blue arrows), probably because of pain on propofol injection, was followed by SKNA suppression. Cardioversion (red dotted
lines) were followed by large transient SKNA elevation (red arrows). Propofol suppressed SKNA for at least 10 minutes. Average chest SKNA at different time point of all 11 patients is shown in Figure 5A. There were large differences of baseline SKNA as well as the responses to propofol. All patients converted to sinus rhythm except for one (no. 1) who had a high baseline SKNA that was only briefly suppressed by propofol. Of the 11 patients recorded, bolus propofol administration significantly reduced aSKNA from $1.11 \pm 0.25 \mu V$ to $0.89 \pm 0.36 \mu V$ 5 minutes after injection ($P < .05$) and $0.77 \pm 0.14 \mu V$ 10 minutes after injection ($P < .01$) (Figure 5B).

One patient (male; age 62 years) received methohexital (100 mg total) before cardioversion. Figure 6 shows the effect of methohexital on SKNA and HR in this patient. Figure 6A shows that methohexital decreased SKNA. Cardioversion shock transiently increased SKNA. ECG shows AF before and after methohexital injection, which turns to sinus rhythm after cardioversion. Figure 6B shows a 33-minute continuous recording of aSKNA and HR. Methohexital injections (50 and 30 mg each) are shown by the black lines. Figure 6C shows the mean values of SKNA and HR in different time segments in this patient. Methohexital decreased chest aSKNA from $1.59 \pm 0.45 \mu V$ to $1.22 \pm 0.58 \mu V$ ($P < .001$) and arm aSKNA from $0.76 \pm 0.43 \mu V$ to $0.55 \pm 0.07 \mu V$ ($P = .001$). The effects lasted for at least 10 minutes after the cardioversion shock.

**Discussion**

We observed in normal ambulatory dogs and humans the effects of widely used anesthetic/sedative agents on SNA. Dexmedetomidine and opioids (morphine and hydromorphone) significantly suppress SNA in dogs. Among these agents, dexmedetomidine seems to have the most profound effects. Propofol and methohexital significantly suppress SKNA in humans, but the duration of SKNA suppression varies among different patients. These findings indicate that anesthetic/sedative agents commonly used in electrophysiological laboratories have variable effects on SNA.

**Direct SNA recordings in animal models**

Monitoring sympathetic tone using commercially available devices relies on measures such as BP and HR, which may provide conflicting information on sympathetic tone during anesthesia. It is highly desirable to develop methods to directly measure SNA during surgical operations or electrophysiological procedures. We reported that in canine models,
SNA recorded from the thoracic skin closely correlates with SGNA in ambulatory dogs. We also showed that SNA recorded with standard ECG patch electrodes (SKNA) can be used to measure sympathetic tone in humans. However, no data to compare the simultaneous responses of SGNA and ScNA to anesthetic/sedative agents are available. The results of the present study documented that SGNA and ScNA responded similarly to drug administration, supporting the use of skin SNA to estimate cardiac sympathetic tone during anesthesia and sedation.

**Effects of dexmedetomidine**

Dexmedetomidine, a specific and selective α2-adrenoceptor agonist, reduces SNA to multiple tissues and vascular beds. Our results confirmed that dexmedetomidine suppresses SNA, HR, and BP in ambulatory dogs. These results are consistent with previous microneurography studies in humans. In that study, the investigators used microneurography techniques to show that cocaine increased whereas dexmedetomidine decreased skin SNA, BP, and HR. The same group also showed that opposite to what was observed in skin SNA responses, muscle SNA was suppressed by elevated BP during cocaine administration. The discrepancies between skin and muscle SNA have also been reported in a study of white coat hypertension. In the present study, we found that SKNA and SGNA in ambulatory dogs were well correlated and responded similarly to anesthetic agents. Because skin sympathetic nerves originate primarily from the ipsilateral SG, these data suggest that skin SNA may serve as a useful tool for monitoring cardiac sympathetic tone during anesthesia and sedation. This information may be helpful in guiding anesthesia/sedation during electrophysiological procedures.

**Effects of opioids and midazolam on SNA in dogs**

Opioid receptors are ubiquitously present in the heart, vasculature, and ganglia. In previous studies in dogs, opioid agents decreased HR, BP, and norepinephrine and epinephrine plasma concentrations due to decreased sympathetic outflow measured by renal SNA. However, morphine and fentanyl also cause unspecific histamine release–related vasodilation that reduces BP. Therefore, reduction of BP after drug administration does not necessarily indicate a reduction of SNA. In fact, microneurography studies showed no acute

![Figure 3](https://example.com/figure3.png)

**Table 1**  Patient characteristics

<table>
<thead>
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<th>Propofol (n = 11)</th>
<th>Methohexital (n = 1)</th>
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<tr>
<td>Age (y)</td>
<td>68.5 ± 9.3</td>
<td>62.0</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>9/2</td>
<td>1/0</td>
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<tr>
<td>Body weight (kg)</td>
<td>100.1 ± 27.6</td>
<td>153.5</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>31.5 ± 6.8</td>
<td>44.5</td>
</tr>
<tr>
<td>Dosage (mg/kg)</td>
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<td>0.65</td>
</tr>
<tr>
<td>Persistent atrial fibrillation</td>
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<td>0</td>
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<tr>
<td>Paroxysmal atrial fibrillation</td>
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<td>1</td>
</tr>
<tr>
<td>Atrial flutter</td>
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<td>0</td>
</tr>
<tr>
<td>Restore to sinus rhythm</td>
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<tr>
<td>Previous ablation</td>
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</tr>
<tr>
<td>Sleep apnea</td>
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</tbody>
</table>

Propofol values are given as mean ± SD or n. ICD = implantable cardioverter-defibrillator.
effects of fentanyl (a potent synthetic opioid) on muscle SNA in humans. Chronic mu-opioid receptor stimulation markedly decreases muscle SNA and its response to hypotension; however, those studies did not measure skin SNA.

We were not able to find reports of microneurography studies on midazolam in the literature. However, anxiolytic therapy with alprazolam (a benzodiazepine) increases muscle SNA and HR, not only in patients with panic disorder but also in healthy controls. In the present study, we observed that midazolam had no significant effects on sympathetic tone but slightly decreased BP about 10 minutes after intravenous injection. The mechanism of reduction in BP after midazolam may be explained by decreased systemic vascular resistance and myocardial contractility.

Figure 4  Effects of propofol on sympathetic nerve activity in a patient undergoing cardioversion. A: The 30-second tracings of chest SKNA, arm SKNA, ECG, and HR before propofol injection, 1 minute after propofol injection and after cardioversion. Propofol decreased SKNA on both chest and arm leads. ECG shows atrial fibrillation (AF) before and after propofol injection, which turns to sinus rhythm after cardioversion (red arrow). Note that there was transient elevation of chest and arm SKNA immediately after cardioversion. B: An 18-minute continuous recording of aSKNA and HR. SKNA increased shortly (blue arrows) after each dose of propofol injection (50 mg at the black dotted lines) because of injection pain. SKNA then progressively decreased. Cardioversion shocks (red line segments) induced large SKNA bursts (red arrows) followed by continued quiescence of SKNA. Propofol suppressed SKNA for at least 10 minutes. SKNA = skin sympathetic nerve activity; other abbreviations as in Figure 1.

Figure 5  Effects of propofol and cardioversion (CV) on average skin sympathetic nerve activity (aSKNA) in all 11 patients. A: Chest aSKNA for each patient. In patient 1, sinus rhythm was not restored after CV; this patient manifested the highest SKNA among all patients. Whether the high SKNA contributed to CV failure remains unknown. B: Average level of SKNA in the patients. *P < .05; **P < .01 vs baseline.
**Effects of propofol and methohexital on human SKNA**

Propofol has significant ion channel effects and has been reported to be both antiarrhythmic and proarrhythmic.\(^\text{27}\) However, its use is associated with a low incidence of ventricular arrhythmias.\(^\text{28}\) Propofol inhibits muscle SNA, HR, and BP and decreases baroreflex sensitivity.\(^\text{26}\) When used to control the pressor response during surgery, the vasodilating effect of propofol overrides the neural vasoconstriction induced by surgery, and a further inhibition of the cardiac baroreflex is observed. We were not able to find reports on the effects of propofol on skin SNA in the literature. The results of our study indicate that propofol is a potent inhibitor of SKNA, although the duration and magnitudes of inhibition varied among patients. There is a heterogeneity in the patient cohort. Structural heart diseases may be associated with higher basal levels of SNA, resulting in more resistance to propofol suppression. Among susceptible patients, the SNA suppression effects might prevent arrhythmia induction during electrophysiological studies. Methohexital is also a muscle SNA inhibitor.\(^\text{30}\) Only 1 patient in our study received methohexital. In this patient, significant reductions of SKNA and HR occurred, and the effects lasted more than 10 minutes.

**Antiarrhythmic effects of anesthesia agents**

Anesthesia has been used for temporary arrhythmia control. Thoracic epidural anesthesia can be effective for cardiac arrhythmia control and is useful for short-term management of ventricular tachycardia storm.\(^\text{31}\) Selective mu-opioid receptor agonists, such as fentanyl and morphine, increase the ventricular fibrillation threshold in dogs with coronary artery occlusion.\(^\text{32}\) A meta-analysis including 1295 patients in 9 studies concluded that dexmedetomidine is associated with a lower incidence of ventricular arrhythmia after elective cardiac surgery.\(^\text{33}\) Methohexital minimizes the possibility of potentially life-threatening cardiac arrhythmias during electroconvulsive therapy compared with thiaylal or thiopental.\(^\text{34}\) In contrast, midazolam, which does not suppress SKNA, does not alter the inducibility of reentrant tachycardia nor has it been shown to affect the sinoatrial node, refractory periods of atrioventricular conduction, or accessory pathways.\(^\text{35}\) We propose that the SNA suppression effects might play a role in the mechanism by which anesthetic/sedative agents suppress cardiac arrhythmias.

**Implications to clinical and translational research**

The existing techniques of studying SNA in humans have certain limitations. HR variability analyses do not have enough temporal resolution to study the SNA and BP on a beat-to-beat basis. Microneurography recordings have sufficient temporal resolution to document an association between SNA and BP. However, because of the difficulties in maintaining sustained impalement, it is impractical to use microneurography techniques for continuous SNA monitoring during electrophysiological studies or surgery. We propose that neuECG recordings can provide useful information by simultaneously measuring ECG and SKNA during...
anesthesia and sedation. These real-time data might be useful in guiding anesthesia during electrophysiological procedures.

Study limitations
This study is limited by the single dose of each agent used and the lack of information about the relative level of sedation achieved by each of those agents. Therefore, the effects of these agents on SNA after long-term administration remain unknown. In addition, no nociceptive stimulus was performed to determine whether SNA suppression could be reversed in the presence of pain. We did not measure parasympathetic nerve activity during the study. Therefore, the effects of these agents on parasympathetic activity remain unknown.

Conclusion
We found that dexmedetomidine, morphine, and hydromorphone suppressed, whereas midazolam had no significant effects on, SGNA and skin SNA in dogs. Propofol and methohexital suppressed SKNA in humans. neuECG recordings might be a useful tool in monitoring SNA during anesthesia and sedation.

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References
diatric Anaesthesia 2017;27:45–51.
physiol 2015;26:70–78.