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Sympathetic Efferent Nerve Activity in Conscious and Isoflurane-anesthetized Dogs

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The hypotension accompanying isoflurane suggests that the anesthetic produces an attenuation of sympathetic tone. Previous studies examining the effects of isoflurane on sympathetic efferent nerve activity have required concomitant use of a basal anesthetic or decerebration, both of which independently alter sympathetic activity. This study was performed to examine the effects of isoflurane on sympathetic efferent nerve activity in the absence of basal anesthetic or decerebration. Five mongrel dogs were anesthetized with 4% isoflurane by mask. Platinum electrodes chronically were implanted around a renal nerve adjacent to the renal artery in order to measure renal sympathetic efferent nerve activity in the conscious and anesthetized animal. After 5–24 h for recovery, renal nerve activity and arterial pressure (via an implanted femoral artery cannula) were measured in the conscious, resting animal (control); during induction (4% isoflurane) and intubation; in the anesthetized animal (1.5% and 2.5% isoflurane); and during recovery and extubation.

Isoflurane produced a significant dose-dependent depression of arterial blood pressure but did not significantly change heart rate from control. Renal sympathetic efferent nerve activity at 1.5% isoflurane was not significantly different from that in conscious animals, but nerve activity at 2.5% isoflurane was depressed significantly from both control and 1.5% isoflurane. Both intubation and extubation were accompanied by an increase in sympathetic nerve activity. Isoflurane appeared to directly depress sympathetic activity at both levels of anesthesia, but the direct depression of activity at 1.5% isoflurane seemed to be countered by reflex increases in sympathetic tone due to the hypotension accompanying the anesthesia. At 2.5% isoflurane, the central depression of reflex activity by isoflurane combined with direct depression of sympathetic efferent activity resulted in the attenuation of renal nerve activity. (Key words: Anesthetics, volatile: isoflurane. Nerve: activity, recording. Reflexes: baroreceptor. Sympathetic nervous system: reflexes.)

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ISOFLURANE ANESTHESIA has been found to produce hypotension and vasodilation,[1–3] yet maintain cardiac output possibly by an accompanying tachycardia.[1–3] The tachycardia suggests an increase in sympathetic activity, but the hypotension and vasodilation argue against this possibility. Alternative possibilities are that direct vasodilator effects[1,4] at some levels of isoflurane anesthesia are dominant over reflexly induced increases in sympathetic nerve activity or that there is a relatively greater decrease in parasympathetic *versus* sympathetic nerve activity.[5] Previous studies using a variety of preparations have shown sympathetic efferent nerve activity (SENA) to be decreased by inhalational anesthetics, including halothane[6,7] and enflurane,[8] while agents such as nitrous oxide,[9] cyclopropane,[10] and diethyl ether[10] produce increases in preganglionic SENA. The effects of isoflurane on SENA have not been studied as extensively. The studies that have been done have required a basal anesthetic in addition to isoflurane to permit nerve recordings. Skovsted *et al.*,[5] in cats anesthetized with nitrous oxide and paralyzed with decamethonium, found SENA to be moderately decreased at 1% inspired isoflurane with a greater decrease to 39% of control at 1.8% isoflurane. Similar results were found in decerebrate cats. Seagard *et al.*[11] found that both preganglionic and postganglionic SENA were decreased at both 1.3% and 2.6% inspired isoflurane in the presence of a basal thiopental anesthesia, with greater attenuation seen in the postganglionic activity. Both the above studies found that the SENA response to baroreceptor input was not blunted significantly except at deeper levels of anesthesia. Complicating factors in the previous studies were the presence of either a basal anesthetic in addition to isoflurane or decerebration, both of which could alter responses to the anesthetic alone.

This study was performed to determine the effects of isoflurane on SENA in the absence of basal anesthetics. Nerve recordings of renal SENA obtained from chronically implanted electrodes were obtained from conscious dogs and compared with recorded levels of renal SENA at 1.5% and 2.5% inspired isoflurane in the same animals induced and maintained on isoflurane anesthesia only. In addition, SENA was recorded during induction, intubation, recovery, and extubation to examine the re-

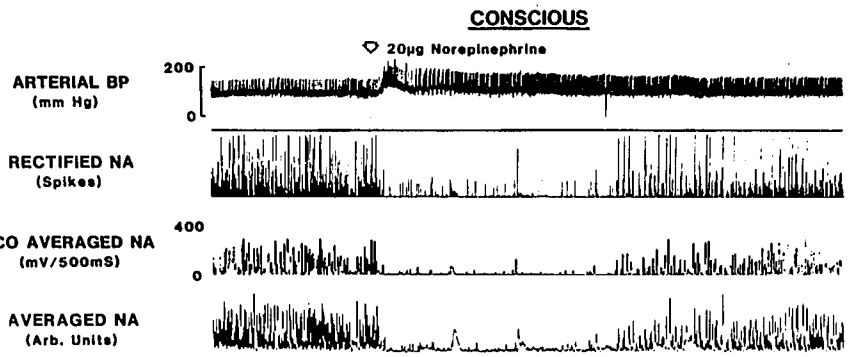

FIG. 1. Response of renal sympathetic efferent nerve activity (SENA) to an acute elevation of arterial blood pressure (BP) produced by a bolus injection of 20 µg norepinephrine. Nerve activity is presented as raw rectified activity (Rectified NA), voltage to frequency converted averaged activity (VCO Averaged NA), and leaky integrator averaged activity (Averaged NA). The characteristic baroreflex-induced attenuation of nerve activity was used to verify that the activity under investigation was sympathetic and efferent in nature.

sponse of the sympathetic nervous system to these procedures during and after isoflurane anesthesia.

Methods

Five mongrel dogs (>17 kg) were induced with 4% isoflurane by mask as described previously,[11] intubated, and maintained on 1.5% to 2.5% isoflurane in oxygen. To permit recording of arterial blood pressure, a cannula was implanted in the aorta via a femoral artery. Blood pressure, obtained via a Statham® P23id pressure transducer, was displayed on a Grass® Model 7 polygraph and recorded on a Tandberg® FM tape recorder. Techniques described previously were utilized for nerve recording.** In summary, the left renal artery and adjacent nerves were exposed through a flank incision and one renal nerve carefully was isolated from surrounding tissue. Two fine platinum wire electrodes attached to flexible electrode leads were coiled around the nerve. A ground wire was implanted into nearby connective tissue. The entire nerve–electrode preparation was anchored to prevent movement and then embedded in silicone to isolate the preparation from the surrounding tissue and fluids. Nerve activity was monitored throughout the procedure to ensure that the nerve was viable. Nerve activity was recorded using a Grass® 7HIP high impedance probe connected to a Grass® 7P511J amplifier. Activity was recorded on the Tandberg® tape recorder and directed into a moving time averager, whose output was displayed on the Grass® polygraph. The electrode leads and femoral cannula were exteriorized in the midcervical region via a subcutaneous tunnel, the incisions were closed, and the animal allowed to awaken. At least 5 h were allowed for recovery prior to any experiments. Nerve recordings were obtained from animals over a range of 5–24 h following surgery. In two dogs, activity recorded at both 5 and 24 h was compared, and no significant differences were found beween the data recorded at these two periods.

** Osborn JL: Baroreflex influences on renal sympathetic nerve activity in conscious and anesthetized dogs, unpublished data.

Prior to testing the effects of isoflurane on SENA, a pressor test was performed to confirm that the nerve activity under investigation was in fact sympathetic and efferent in nature. Acute elevation of arterial pressure, produced by an infusion of 20 µg norepinephrine iv, was initiated to reflexly evoke baroreceptor inhibition of SENA (fig. 1). If the nerve activity being recorded was determined to be sympathetic efferent activity, by exhibiting a reflex decrease corresponding to the elevation in arterial pressure, the nerve was retained and used for determination of the effects of isoflurane on SENA. The experimental protocol was as follows.

Control renal SENA and arterial blood pressure were obtained from a conscious, resting animal. The dog then was induced with 4% isoflurane via a mask, intubated, and placed on 1.5% or 2.5% isoflurane in oxygen, chosen in random order, using a previously calibrated vaporizer, Foregger® anesthesia machine and a Monaghan® 300 D/M ventilator. Nerve activity was recorded continuously during the induction and intubation. Blood gases and *p*H were determined at frequent intervals and kept within normal limits by adjustment of ventilation or infusion of sodium bicarbonate. The dog then was maintained at the appropriate level of isoflurane for 20 min. Previous studies had found that blood concentrations of isoflurane equilibrated within 15 min to a change in inspired isoflurane.[11] To verify this finding for this experiment, blood samples from two dogs were obtained after 20 min at each level of isoflurane, and the levels of the anesthetic were determined by the chromatographic technique of Lowe.[12] The levels of isoflurane corresponding to 1.5 and 2.5% isoflurane were 0.6 and 1.62 mM, respectively. Following each 20-min isoflurane exposure, nerve activity and arterial pressure were recorded for 2 min. The isoflurane then was changed to the remaining level, and the 20-min exposure was repeated. When nerve activity had been obtained at both levels of isoflurane, the anesthetic was eliminated and the animal was allowed to recover. Nerve activity and blood pressure were recorded continuously during recovery and extubation.

TABLE 1. Arterial Blood Pressure, Heart Rate, and SENA from Conscious and Anesthetized Dogs (n = 5)

	Conscious Dogs	1.5% Isoflurane	2.5% Isoflurane
Mean arterial blood pressure (mmHg)	103 ± 3	80 ± 6*	63 ± 3†
Heart rate (beats/min)	96 ± 14	85 ± 13	103 ± 3
VCO averaged SENA per cent control (mV/500 ms)	100	96 ± 17	64 ± 7‡
AVE SENA per cent control (Arb. Units)	100	99 ± 3	64 ± 5‡

Mean ± standard error.
* $P < 0.01$ *versus* conscious.
† $P < 0.01$ *versus* conscious, 1.5% isoflurane.
‡ $P < 0.05$ *versus* conscious, 1.5% isoflurane.

Nerve activity and blood pressure were analyzed using a PDP 11/10 computer and a Hewlett Packard® 2647F Intelligent Graphics Terminal and 9872A Plotter. Thirty seconds of SENA and BP were analyzed at control, 1.5% and 2.5% isoflurane for each dog. In addition, nerve activity prior to, during, and following intubation and extubation was analyzed. Nerve activity was analyzed utilizing two methods that respond linearly to amplitude, frequency, and duration changes in multifiber nerve preparations. Averaged nerve activity (AVE) was obtained by passing full wave rectified spikes through a threshold to eliminate background noise. The resulting signal was processed by a leaky integrator with a time constant of 140 or 280 ms. A second method processed the rectified signal minus noise through a voltage-to-frequency converter (VCO), whose instantaneous frequency output was proportional to the voltage input. The VCO output was counted by a digital timer with an analog output. Both methods provided signals proportional to the total voltage (nerve activity input). Leaky integration has been found to be an easy method for on-line analysis of nerve activity. However, for quantification of precise phase relationships between nerve activity and other physiologic parameters such as ECG and blood pressure, the VCO has been found to have a shorter response time, with a fixed phase shift equal to one sampling period. To determine if one method was preferable over the other for analysis of chronically recorded activity, both methods were utilized in the present study. The output of the methods of analysis were sampled at 100-ms intervals by the PDP 11/10s A/D converter for storage and further processing. Nerve activity from conscious and anesthetized animals using both methods were compared with each other using a two-way analysis of variance and Duncan's Multiple Range Test.

Results

Isoflurane administration produced a dose-dependent hypotension (table 1), reducing mean arterial blood pressure from 103 ± 3 mmHg in conscious animals (control) to 80 ± 6 mmHg at 1.5% isoflurane and 63 ± 3 mmHg at 2.5% isoflurane. Mean arterial pressure at each level of isoflurane was significantly less than control ($P < 0.01$), and pressure at 2.5% isoflurane was significantly less than at 1.5% isoflurane ($P < 0.01$). No significant changes in heart rate accompanied isoflurane anesthesia (table 1).

Analysis of nerve activity using both methods provided similar results. Responses to isoflurane were similar in all animals. Renal SENA was not altered significantly at 1.5% isoflurane but was significantly less at 2.5% isoflurane than it was at control (conscious dogs, $P < 0.05$) and at 1.5% isoflurane ($P < 0.05$) (table 1, fig. 2). Intubation and extubation both were accompanied by a burst of renal SENA and a sudden change in mean arterial blood pressure (fig. 3). The burst of SENA appeared to correlate with either a sudden increase in arterial pressure (intubation, fig. 3) or a tachycardia (extubation, figs. 3 and 4) or both. If the hypertension was great enough, some animals actually responded with a reflex-induced bradycardia (intubation, fig. 3). In three of the five animals, there was an observable increase in SENA during induction that could be correlated to a period of excitement (fig. 3). In four of the five animals, there was a period of heightened SENA during recovery prior to extubation (fig. 4). This increased activity usually was lost following extubation.

Discussion

The level of renal SENA recorded in this study appeared to be dependent on both the direct depressant effects of isoflurane on the central nervous system and on the hypotensive action of isoflurane, which lowered arterial pressure. The hypotension accompanying isoflurane administration decreased afferent baroreceptor input, resulting in less central inhibition of SENA. At 1.5% isoflurane, this decrease in central inhibition was sufficient to overcome any direct depressant effects of isoflurane. Therefore, renal SENA at this level of isoflurane was not significantly different from the conscious animal. At 2.5% isoflurane, the depressant central effects of isoflurane were large enough to result in a significant decrease in sympathetic tone, in spite a profound hypotension. The reported sensitizing effect of isoflurane on carotid sinus baroreceptors[11] may have potentiated the decrease in sympathetic tone.

These results were obtained without the presence of any basal anesthesia or altered basal sympathetic tone due to decerebration and therefore represent the action of isoflurane only on control of SENA. The ability to reflexly

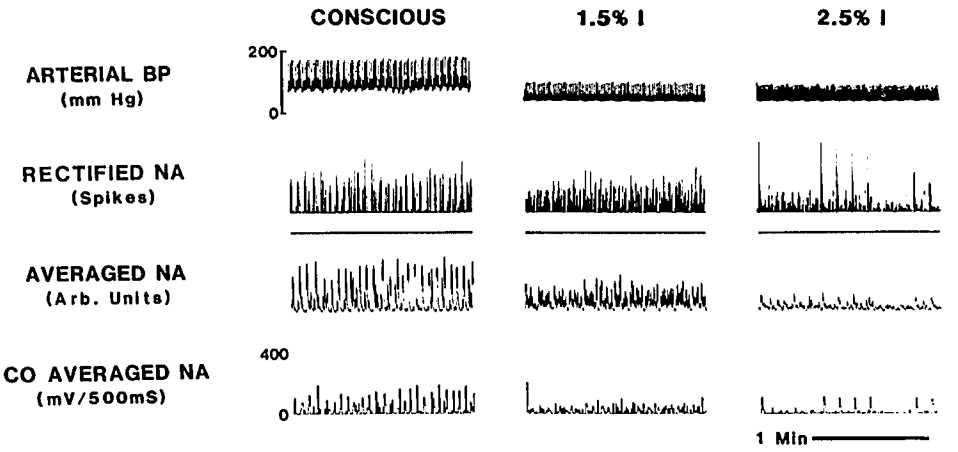

FIG. 2. Baseline renal sympathetic efferent nerve activity (NA) and arterial blood pressure (BP) recorded in the conscious resting dog (conscious) and in the same animal anesthetized at 1.5% and 2.5% inspired isoflurane. All levels of isoflurane were maintained for 20 min prior to recording. Nerve activity was depressed at only 2.5% isoflurane, while blood pressure showed a dose-dependent decrease at both 1.5% and 2.5% isoflurane. The pattern of nerve activity changed as the corresponding heart rate and pulse pressure changed during isoflurane administration.

maintain sympathetic tone during isoflurane anesthesia may be the reason baroreflex activity at 1 MAC isoflurane has not been found to be depressed significantly.[5,11] Any depression of reflex activity at this level would argue for a peripheral effect of isoflurane, possibly at the level of the sympathetic ganglia or end-organ.

The length of time between surgery and recording of SENA ranged from 5–24 hr. No difference in baseline SENA, response of SENA to anesthesia, or baroreflex-induced changes in SENA[13] were seen in these animals when tested at 5 h *versus* 24 h following surgery. Although the effects of surgery were more acute at 5 h, the animals did not exhibit any exaggerated sympathetic tone or appear to be in pain. Blood concentrations of anesthetic were 0 mM at the time control responses were obtained, and therefore the isoflurane used during the initial surgery was not present to alter SENA.

The large bursts of renal SENA during intubation and extubation correlate well with the responses of hypertension and tachycardia seen clinically during these maneuvers.[14] The cardiovascular responses associated with intubation and extubation may be the result of a sudden generalized increase in sympathetic tone produced by stimulation of laryngeal or tracheal receptors[15] by movement of the endotracheal tube.

The technique of chronic nerve recording utilized in this study has permitted the acquisition of data under more "physiologic" conditions than previous studies. In a previous study,[11] with a thiopental infusion utilized as a basal anesthetic, baseline levels of both preganglionic and postganglionic sympathetic efferent nerve activity were found to be significantly depressed from control (0% isoflurane with thiopental) at both 1.3% and 2.6% isoflurane. Based on the present study, the attenuation of SENA found at 1.3% isoflurane may have been due to the effects of thiopental. The attenuation of SENA at

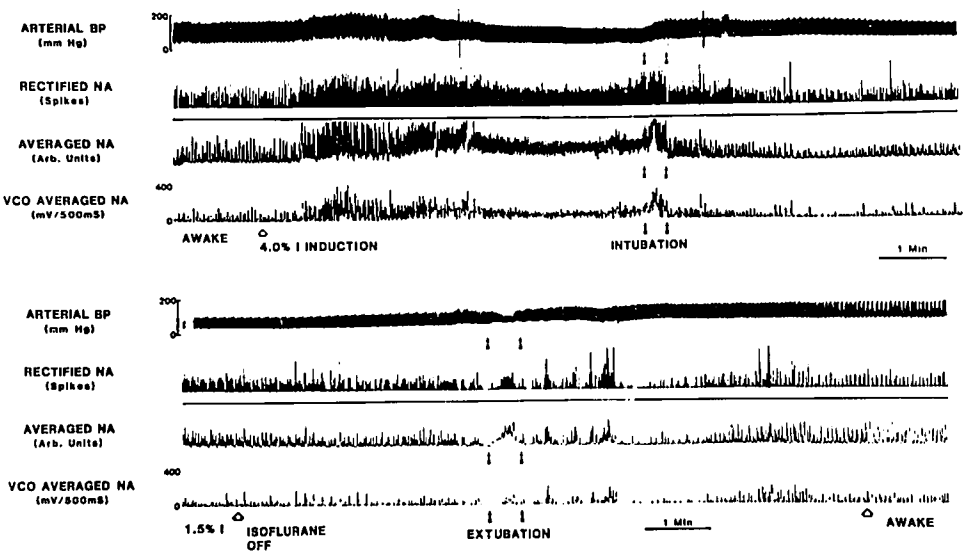

FIG. 3. Response of renal sympathetic efferent nerve activity (NA) to induction (4.0% induction, at arrows), intubation (at arrows), recovery (isoflurane off, at arrows), and extubation (at arrows). Isoflurane had been maintained at 1.5% for 20 min prior to recovery. Note the increase in SENA during induction, possibly corresponding to a period of excitement during anesthesia. Both intubation and extubation were accompanied by bursts of renal nerve activity, responses seen in all dogs studied. The reflex increase in renal SENA produced a hypertensive response during intubation and a tachycardic response (note decrease in pulse interval on blood pressure tracing) during extubation.

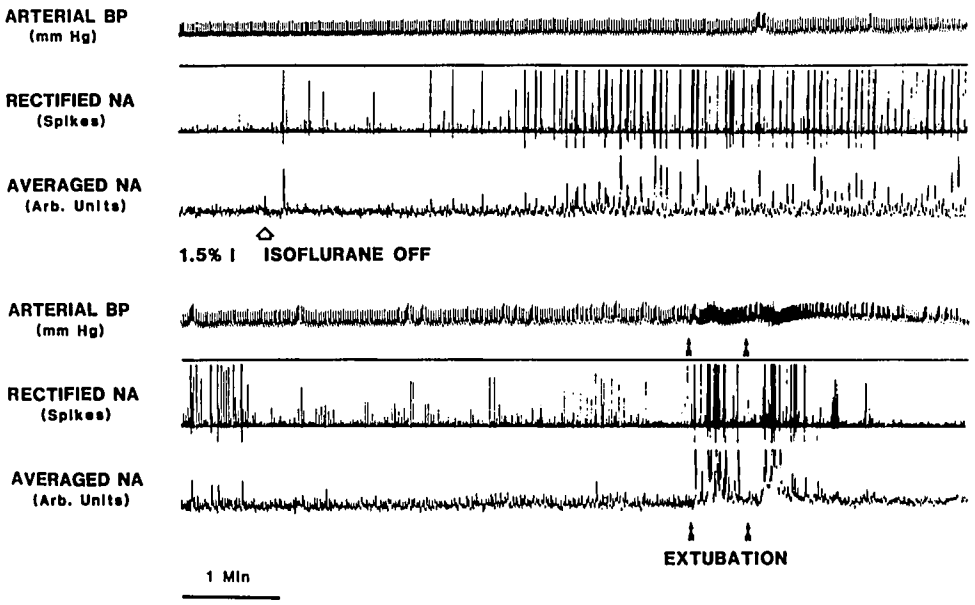

FIG. 4. Continuous recording of the response of renal sympathetic efferent nerve activity (NA) to recovery and extubation following a 20-min exposure to 1.5% isoflurane. The increase in nerve activity during recovery, possibly corresponding to a period of excitement, was seen in four of the five animals studied. Note the increase in heart rate (decrease in pulse interval on the blood pressure tracing) during extubation, associated with the burst of renal SENA.

2.3% isoflurane would have been the result of effects of both isoflurane and thiopental. The absence of basal anesthesia in the present study unmasked the actual effects of isoflurane on ongoing sympathetic tone. In addition, this study has documented a burst of sympathetic activity during intubation and extubation and increased sympathetic activity during the "excitement" phase of anesthesia. The technique of chronic nerve recording has permitted the acquisition of new information on the control of SENA during isoflurane anesthesia and during intubation/extubation.

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