

Effects of Isoflurane on the Baroreceptor Reflex

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The baroreceptor reflex has been found to be attenuated during anesthesia, but the effects of the relatively new anesthetic, isoflurane, on baroreflex function have not been examined thoroughly. This study was performed to determine the effects of isoflurane on each component of the baroreceptor reflex arc, including the receptors, afferent and efferent nerve pathways, central integratory centers, peripheral ganglia, and the heart. Baroreflex effects on heart rate initiated by systemic pressure changes were examined in conscious and anesthetized dogs (1.3% and 2.6% isoflurane). The effects on individual components of the reflex arc were determined by examining carotid sinus baroreceptor afferent activity, sympathetic efferent nerve activity, and heart rate response to direct sympathetic and parasympathetic efferent nerve stimulation in anesthetized dogs. Preganglionic and postganglionic nerve activities were recorded simultaneously during baroreflex activation to determine ganglionic effects of isoflurane. Baroreflex-induced changes in heart rate were not depressed significantly until 2.6% isoflurane if blood pressure changes due to anesthetic administration were prevented. Significant decreases in baseline sympathetic efferent nerve activity were found at 1.3% and 2.6% isoflurane, with depression of postganglionic activity significantly greater than preganglionic activity at 2.6% isoflurane, indicating a ganglionic effect of isoflurane. Cardiac chronotropic responses to direct stimulation of sympathetic and vagal fibers were attenuated significantly by isoflurane, with sympathetic stimulation showing the greater sensitivity to the anesthetic. Carotid baroreceptor afferent activity was increased by isoflurane, and this sensitization of the baroreceptors appeared to contribute to the decreased levels of sympathetic tone. Therefore, although isoflurane was found to alter the baroreceptor reflex through its effects at multiple sites of the baroreflex arc, significant depression of the cardiac chronotropic component of the reflex was seen only at 2.6% isoflurane. (Key words: Anesthetics, volatile: isoflurane. Blood pressure: baroreceptor reflexes. Heart: cardiovascular reflexes. Sympathetic nervous system: reflexes. Parasympathetic nervous system: reflexes. Nerve: ganglionic transmission.)

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WHILE MOST INHALATIONAL ANESTHETICS have been shown to depress cardiovascular reflex regulation,¹ the effects of isoflurane (I) have not been studied thoroughly. Isoflurane has been found to attenuate the changes in arterial blood pressure, heart rate, and efferent autonomic nerve activity produced by stimulation of aortic baroreceptor fibers in the aortic depressor nerve.² Clinical use of isoflurane has shown that blood pressure and total peripheral resistance decrease in a dose-related fashion, while heart rate increases to about 20% above awake values.³ Cardiac output is maintained by the tachycardia, which may be a reflex response to the accompanying arterial hypotension. Therefore, available evidence suggests that baroreceptor reflexes may be depressed but remain functional during isoflurane anesthesia, possibly to a greater extent than with other clinically useful anesthetics.

The present study was performed to determine the effects of isoflurane on the carotid sinus baroreceptor reflex, examining the possibility of multiple sites of action of isoflurane on baroreflex function. Individual levels of the baroreflex arc were investigated, including 1) the baroreceptors, through their afferent input; 2) the central nervous system, through preganglionic sympathetic efferent nerve activity (SENA); 3) ganglion transmission, through postganglionic SENA; and 4) the direct end organ responses of the heart, through direct stimulation of sympathetic and parasympathetic efferent cardiac nerves. Isoflurane was found to have effects on every component of the baroreceptor reflex arc, ultimately leading to attenuation of the reflex at the 2 MAC concentration.

Methods

EVALUATION OF THE BARORECEPTOR REFLEX IN CONSCIOUS AND ANESTHETIZED DOGS

The effect of isoflurane on the heart rate component of the carotid baroreceptor reflex was examined in eight unanesthetized dogs (17–22 kg) with exteriorized carotid artery loops produced by the technique of Meier and Long.⁴ A 20-gauge catheter was placed percutaneously into the exteriorized artery to obtain recordings of carotid artery blood pressure in the conscious animal. Resting carotid blood pressure was measured using a Statham transducer, monitored along with ECG on a Grass recorder, and recorded on a Vetter FM tape recorder. Reflex changes in heart rate were initiated in the conscious animals by decreasing or increasing blood pressure with sodium nitroprusside (100–300 mg/min) or phenyleph-

rine (10–50 mg/min), respectively, administered through a catheter in the cephalic vein. After each manipulation the animal was allowed to return to the control awake blood pressure.

The same dogs then were anesthetized with an inhalational technique, using 4% I and oxygen administered by mask and then intubated. The animals had been trained to breathe through specially constructed masks⁵ so that their responses to isoflurane would not be affected by any distress produced by the act of induction. The dogs then were exposed to both 1.3% and 2.6% I for 30 min in random order using a previously calibrated vaporizer with a Foregger anesthesia machine, Bird Mark 7 respirator, and a Mark 4 anesthesia assistant/controller. The whole blood levels of isoflurane corresponding to alveolar concentrations of 1.3% and 2.6% I were 0.76 ± 0.12 mg/ml and 1.45 ± 0.30 mg/ml, respectively, determined by the chromatographic technique of Lowe.⁶ Equilibrium at each anesthetic level was ensured by determining isoflurane concentrations at 5-min intervals throughout the 30-min exposure. Equilibrium was found to occur within 10–15 min following each change in anesthetic level. The reflex changes in heart rate were induced at both levels of isoflurane by decreasing and increasing blood pressure with nitroprusside and phenylephrine, while ECG and carotid blood pressure were recorded as previously described. Blood-gas analysis was done at frequent intervals using a Radiometer blood-gas analyzer. Ventilation was adjusted to maintain P_{aCO_2} at 30–40 mmHg and P_{aO_2} above 100 mmHg to minimize stimulation of chemoreceptors. $NaHCO_3$ was administered intravenously to maintain arterial pH between 7.3 and 7.4. The above experiment was repeated in two other series, with some modifications. In the first, blood pressure was maintained constant at the preanesthetic level with an infusion of phenylephrine. Alterations in blood pressure using phenylephrine and nitroprusside were imposed on this otherwise constant pressure. In the second study, thiopental (25 mg/kg) was administered for induction prior to isoflurane. Blood pressure was altered as explained above.

A PDP11/10 computer and HP 2647A Graphics Terminal were used to analyze changes in R-R interval *versus* blood pressure for the conscious and anesthetized dogs. Regression analysis of R-R interval *versus* blood pressure was performed, and the mean slopes of the regression lines were determined for each level of anesthesia under each protocol and compared using a two-way analysis of variance. Significant differences between slopes, set at $P < 0.05$, were tested using Duncan's Multiple Range test.

THIOPENTAL-O₂-ISOFLURANE ANESTHETIZED DOGS—CAROTID SINUS NERVE RECORDING

The direct effects of isoflurane on baroreceptors were examined by applying dynamic pressure stimuli to an

isolated perfused carotid sinus exposed to 1.3% and 2.6% I, while recording afferent activity from the carotid sinus nerve.⁷ Eight dogs were anesthetized and maintained on a thiopental infusion of $5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. This level of anesthesia has been found to produce a stable level of anesthesia in dogs, evidenced by constant patterns of respiratory activity and sympathetic efferent nerve activity.⁸ A femoral artery was cannulated for measurement of systemic blood pressure. The left carotid sinus was isolated and perfused by a system that localized isoflurane exposure to the isolated sinus.⁷ Standardized sine wave changes in sinus pressure produced by a servocontrolled roller pump then were used to stimulate the baroreceptors at 0%, 1.3%, and 2.6% I in random order. These levels corresponded to isoflurane levels in the perfusate of 0.0 mg/ml (0.0% I), 0.87 ± 0.21 mg/ml (1.3% I), and 1.91 ± 0.32 mg/ml (2.6% I). Anesthetic levels were maintained for 20 min prior to pressure changes to ensure equilibrium, which actually was complete within 10 min as determined by chromatographic analysis of perfusate samples withdrawn at 5-min intervals. The left carotid sinus nerve was isolated, sectioned, and placed under mineral oil. Baroreceptor afferent nerve activity from the sinus nerve was recorded from small few-fiber preparations using tungsten carbide electrodes connected via a high-gain preamplifier/filter amplifier system to a Vetter FM tape recorder. Perfusion pressure, arterial pressure, and carotid sinus nerve activity were recorded on a Grass recorder and FM tape recorder. Carotid sinus afferent nerve activity was recorded using sine wave pressure changes that altered sinus pressure from 75 to 175 mmHg. Carotid sinus nerve activity during the ascending portion of the pressure wave was used to quantitate the dynamic characteristics of the carotid baroreceptors. The nerve activity was analyzed up to the saturation pressure, at which point no further increases in nerve activity were produced, despite increases in the sinus pressure. The slope of this nerve activity-sinus pressure curve has been defined as an index of receptor sensitivity.⁷ Regression analysis was performed on the slopes determined by the least-squares method. The mean slopes for each level of isoflurane were compared statistically using a two-way analysis of variance with significance set at the $P < 0.05$ level.

THIOPENTAL-O₂-ISOFLURANE ANESTHETIZED DOGS—SYMPATHETIC EFFERENT NERVE ACTIVITY

The effects of isoflurane on the central nervous system component of the baroreceptor reflex were examined by recording the reflex changes in preganglionic sympathetic efferent nerve activity (SENA) in the T₃ white ramus, initiated by increases and decreases in systemic blood pressure.⁷ Baseline and reflex changes in preganglionic SENA in response to 50 mmHg increases and decreases in systemic blood pressure produced via a pressurized

reservoir system⁷ at 0%, 1.3%, and 2.6% I were studied in six dogs anesthetized and maintained on a thiopental infusion of $5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. Nerve activity was recorded from small multifiber preparations before and during 30-s pressure changes.

The effect of isoflurane on ganglionic transmission was studied by simultaneously recording the response of postganglionic SENA in the ventral ansa subclavian while recording the preganglionic SENA described above. The differences in responses of the preganglionic *versus* postganglionic SENA were attributed to the ganglionic effects of isoflurane. Both nerve activities and femoral blood pressure were recorded on the Vetter FM tape recorder and Grass polygraph.

Baseline preganglionic and postganglionic SENA were analyzed by processing averaged activity through a voltage-to-frequency converter and then counting spikes/unit time during each control period preceding a pressure change. Reflex changes in preganglionic and postganglionic SENA were examined by analyzing nerve activity during the last 10 s of each 30 s pressure change. The mean values for baseline levels and reflex changes in preganglionic and postganglionic SENA, expressed as a percentage of the control baseline levels at 0% I, were statistically compared for each level of anesthetic using a two-way analysis of variance and Duncan's Multiple Range Test. The respective values for preganglionic and postganglionic nerve activities at each level of isoflurane also were compared with each other using a two-way analysis of variance.

THIOPENTAL-O₂-ISOFLURANE ANESTHETIZED DOGS—DIRECT CARDIAC EFFERENT NERVE STIMULATION

The end-organ effects of isoflurane on the heart were determined by measuring the chronotropic response of the heart to direct sympathetic and parasympathetic efferent stimulation at 0%, 1.3%, and 2.6% I.⁷ Six mongrel dogs were anesthetized and maintained on a thiopental infusion of $5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. Femoral blood pressure and ECG were recorded on a Vetter FM tape recorder. The peripheral ends of the right ventral ansa subclavian (sympathetic) and right vagus (parasympathetic) alternately were stimulated with constant current supramaximal stimuli with frequencies of 0, 1, 2, 4, 8, 10, 15, and 20 Hz at 0%, 1.3%, and 2.6% I. The procedure above was repeated in six additional dogs in which the blood pressure was kept constant at the control level (0% I) by slow infusion of phenylephrine during administration of 1.3% and 2.6% I.

The largest decrease in heart rate obtained with vagal stimulation during 0% I was taken as the maximal response (−100%) for that procedure, and all other heart rate changes produced by vagal stimulation were normalized as percentages of that maximal response. Similar

quantitation was done for sympathetic stimulation, taking the maximal increase in heart rate (100%) at 0% as the maximal response. The mean values of the percentage changes in heart rate were plotted *versus* frequency for each level of isoflurane. Regression analysis was performed and slopes of the stimulation curves at each level of anesthetic were compared using a two-way analysis of variance and Duncan's Multiple Range Test. To determine whether differences in initial heart rates might have affected the magnitude of the evoked changes or the ability of the heart to respond, analysis of absolute heart rates was performed using multivariate nonlinear regression analysis. At each level of isoflurane, the heart rate response (Y) was described in terms of stimulation frequency (X) by fitting the nonlinear regression curve $Y = a \exp(-b \exp[-cx])$. In this model the initial heart rate ($a \exp[-b]$) progresses to the asymptotic value (a) as the stimulation frequency increases. The c value determines the speed of change in heart rate. Multivariate analysis of variance and multiple comparisons were applied to the a, b, and c values to test for isoflurane effects on the heart rate–stimulation frequency relationship for sympathetic and vagal stimulation.

Results

Analysis of the baroreflex changes in heart rate produced by changes in systemic blood pressure showed that baroreflexes were well preserved with isoflurane only at 1 MAC, but there was an attenuation of the heart-rate reflex at 2 MAC (fig. 1, table 1). All responses of the conscious dogs had significantly greater slopes than those from dogs anesthetized at 2.6% ($P < 0.01$). Only the tachycardic response to a decrease in blood pressure was depressed significantly at 1.3% I ($P < 0.05$), while the bradycardic response to an increase in pressure was not affected significantly. When blood pressure was maintained with slow infusion of phenylephrine during isoflurane administration, none of the pressor or depressor responses at 1 MAC were attenuated significantly (table 1). Again, the responses at 2 MAC were depressed significantly compared with the heart rate changes for conscious and 1.3% I animals. In the third study, utilizing thiopental induction, responses at each level of anesthetic were significantly less than for conscious dogs, except the pressor response at 0% I (table 1). Responses at 0% and 1.3% I were not significantly different from each other, but the reflex at 2.6% I was significantly less than both. All responses following thiopental plus isoflurane were less than the respective ones with isoflurane only, but only the depressor response at 1.3% I and the pressor response of 2.6% I were significantly different (table 1).

Analysis of carotid sinus nerve activity initiated by dynamic changes in sinus pressure showed a dose-dependent effect of isoflurane at the receptor level (fig. 2, table 2). Evaluation of sinus nerve activity during the ascending

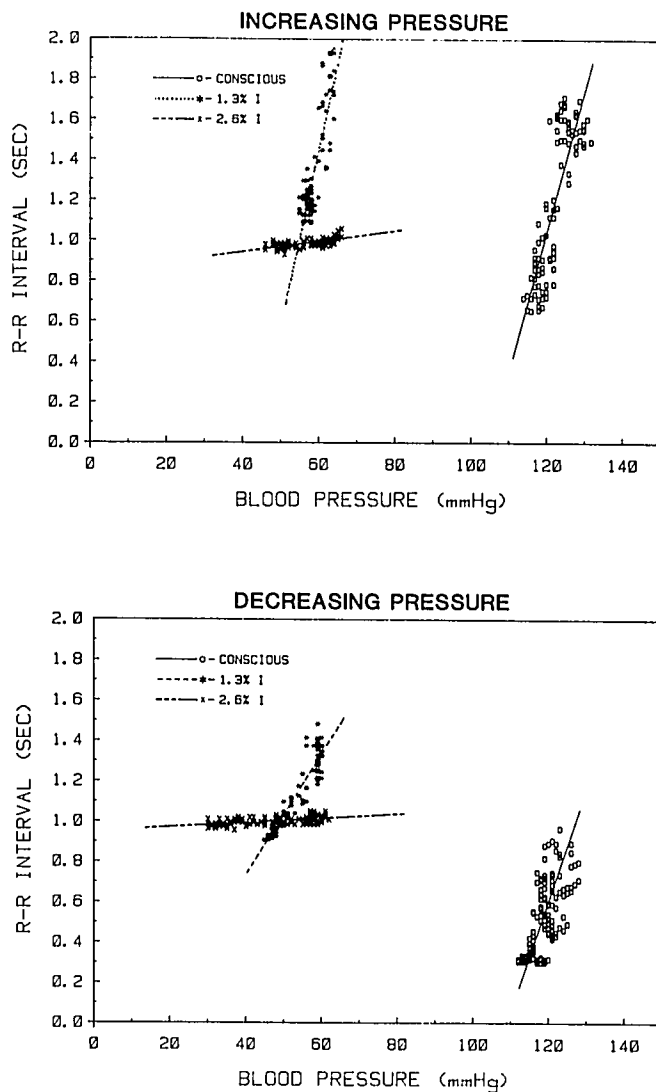


FIG. 1. Reflex changes produced in R-R interval (seconds) during increases and decreases in systemic blood pressure (mmHg) at 0.0%, 1.3%, and 2.6% isoflurane (I). The slopes of the responses show an attenuation of the reflexes at 2.6% I but no significant effect at 1.3% I. \circ = conscious animals, * = 1.3% I, \times = 2.6% I.

portion of the dynamic pressure changes showed a significantly greater slope at 1.3% I than at 0.0% I ($P < 0.01$). Nerve activity at 2.6% I was significantly greater than the activity at both 0.0% ($P < 0.01$) and 1.3% I ($P < 0.05$).

On the other hand, isoflurane was found to have a depressant effect on the central nervous system, seen by the lower baseline levels and reflex changes in preganglionic SENA produced by systemic pressure changes in the presence of varying isoflurane concentrations (table 3). Baseline levels of preganglionic SENA at 1.3% and

2.6% I were depressed significantly from 0% I ($P < 0.05$ and $P < 0.01$, respectively). Reflex changes in preganglionic SENA to increases and decreases in systemic pressure were depressed significantly at 2.6% compared with control ($P < 0.01$).

Simultaneous recordings of preganglionic and postganglionic sympathetic efferent activity indicated a ganglionic effect of isoflurane at the stellate ganglion ($P < 0.05$) (fig. 3, table 3). As with preganglionic SENA, baseline levels of postganglionic SENA were depressed significantly at 1.3% and 2.6% I ($P < 0.05$ and $P < 0.01$, respectively) as compared with 0% I. But unlike preganglionic SENA, baseline levels of postganglionic SENA at 2.6% I were also significantly less than at 1.3% I ($P < 0.05$). In addition, reflex changes in postganglionic SENA to increases in blood pressure at both 1.3% and 2.6% I were significantly less than at 0% I ($P < 0.05$, $P < 0.01$), while these responses for preganglionic SENA only were depressed significantly at 2.6% I.

Isoflurane blunted cardiac responses to direct efferent nerve stimulation. Efferent stimulation of the peripheral right vagus and ventral ansa subclavia produced decreases and increases (fig. 4) in heart rate, respectively. These changes in heart rate were depressed by increasing levels of isoflurane. When all responses were examined as percentages of the animals' maximal responses, the negative chronotropic effect to vagal stimulation at 1.3% I was found to be significantly less than that at 0% I ($P < 0.01$) (table 2). The response at 2.6% I was significantly less than at both 0.0% I and 1.3% I ($P < 0.01$). The positive chronotropic response to sympathetic stimulation at 1.3% I was also significantly less than that at 0% ($P < 0.05$) (table 2). Again, the response at 2.6% I was significantly depressed when compared with 0.0% and 1.3% I ($P < 0.01$). The responses in animals with blood pressure regulated at control levels were not significantly different from those with pressures that were allowed to change. The relationship of absolute heart rate to stimulation frequency of cardiac efferent fibers is shown in figure 5. Multivariate analysis applied to the three dimensional vectors of curvilinear regression coefficients of the data showed that control, 1.3%, and 2.6% isoflurane responses to sympathetic stimulation were significantly different ($P < 0.01$). Further statistical analysis revealed that the 1.3% and 2.6% isoflurane curves were both significantly different from the control regression curve ($P < 0.01$) and from each other ($P < 0.01$). Multivariate analysis applied to the regression coefficients of the control, 1.3%, and 2.6% isoflurane responses to vagal stimulation also showed that there was a significant difference among the curves ($P < 0.05$). In this case, each of the 1.3% and 2.6% isoflurane curves differed significantly from the control curve

TABLE 1. Effects of Isoflurane on the Heart Rate Component of the Baroreceptor Reflex

Isoflurane Concentration Plus Thiopental	Conscious Dogs	0.0% Isoflurane	1.3% Isoflurane	2.6% Isoflurane
Reflex changes in R-R interval <i>versus</i> mean blood pressure (slopes expressed as ms/mmHg)				
Increasing BP (n = 8)	66.8 ± 8.9		65.1 ± 9.4	6.3 ± 2.8*
Decreasing BP (n = 8)	35.5 ± 6.4		21.2 ± 3.8†	2.5 ± 0.8*
Reflex changes in R-R <i>versus</i> mean blood pressure (ms/mmHg) with baseline BP maintained with slow infusion of phenylephrine				
Increasing BP (n = 8)	81.3 ± 17.2		63.4 ± 17.5	2.6 ± 1.1*
Decreasing BP (n = 8)	26.7 ± 6.5		20.9 ± 7.1	3.7 ± 1.4*
Reflex changes in R-R interval <i>versus</i> mean blood pressure (ms/mmHg) with thiopental induction prior to isoflurane				
Increasing BP (n = 4)	59.4 ± 16.5	23.4 ± 12.8‡	15.7 ± 9.4‡§	1.8 ± 0.8¶
Decreasing BP (n = 4)	36.0 ± 5.1	22.9 ± 7.4	17.0 ± 5.4‡	1.3 ± 0.4§**

All values are the mean ± S.E.

* $P < 0.01$ *versus* conscious, 1.3% I.

† $P < 0.05$ *versus* conscious dogs.

‡ $P < 0.01$ *versus* conscious.

§ $P < 0.01$ *versus* respective value in presence of I only.

¶ $P < 0.01$ *versus* conscious; <0.05 *versus* 0%, 1.3% I.

** $P < 0.01$ *versus* conscious, 0% I; <0.05 *versus* 1.3% I.

($P < 0.05$), while the 1.3% and 2.6% isoflurane curves did not differ significantly from each other.

Discussion

Results from the present study suggest that isoflurane alone has only a small depressant effect on the intact baroreflex at the 1 MAC level if arterial pressure is main-

tained at the preanesthetic level. Under these conditions, the reflex changes in heart rate initiated by the baroreceptor reflex were not found to be significantly attenuated by isoflurane until the anesthetic was used at the 2 MAC level. If arterial pressure was allowed to decrease with isoflurane administration, the tachycardic responses to decreases in pressure were blunted significantly at 1 MAC, although the bradycardic responses to decreases

FIG. 2. Changes in carotid sinus nerve activity (spikes/100 ms) *versus* changes in carotid sinus pressure (mmHg) during the ascending limb of a sine wave pressure change in an isolated carotid sinus. The slopes of the responses at 0.0%, 1.3%, and 2.6% isoflurane (I) show a dose-dependent increase in baroreceptor activity with exposure to I. ○ = 0.0%, * = 1.3%, × = 2.6% I.

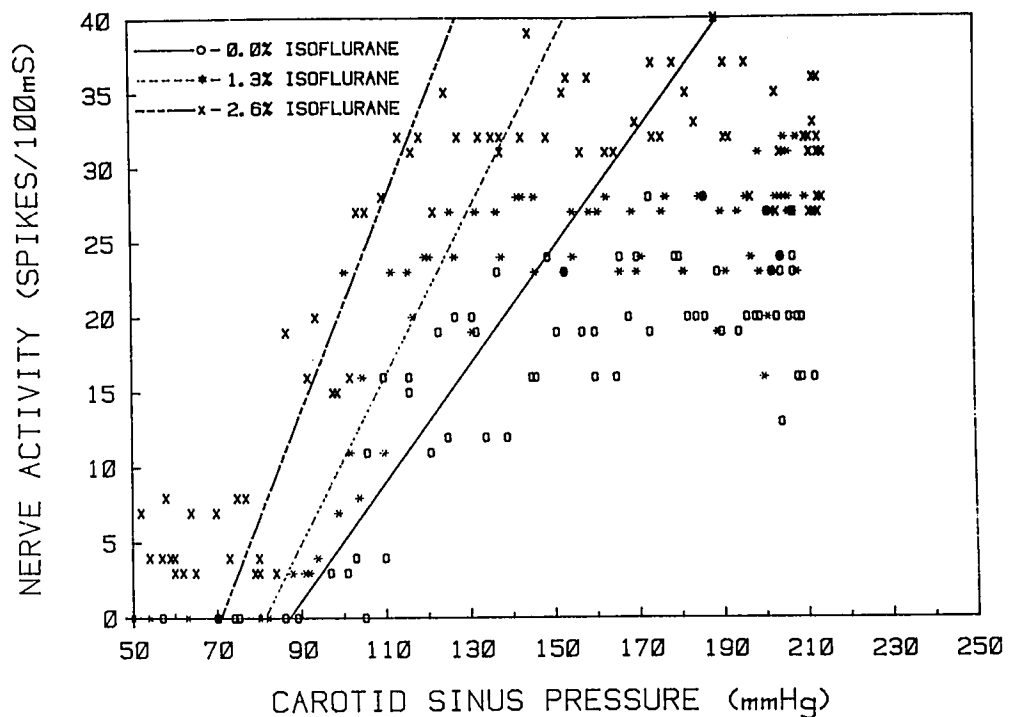


TABLE 2. Effects of Isoflurane on Various Components of the Baroreceptor Reflex

Isoflurane Concentration Plus Thiopental	0.0% Isoflurane	1.3% Isoflurane	2.5% Isoflurane
Carotid sinus nerve activity (NA) versus dynamic changes in carotid sinus pressure NA expressed as spikes · 100 mS ⁻¹ mmHg ⁻¹ (n = 6)			
Change in heart rate due to direct stimulation of cardiac efferent. Slopes expressed as: beats · min ⁻¹ Hz ⁻¹			
Vagal stimulation (n = 6)	6.16 ± 0.17	4.15 ± 0.63*	2.76 ± 0.72†
Sympathetic stimulation (n = 6)	10.50 ± 0.29	5.55 ± 0.97*	2.78 ± 0.28‡
Change in heart rate due to direct stimulation of cardiac efferent nerves with baseline BP maintained with slow infusion of phenylephrine. Slopes expressed as beats · min ⁻¹ Hz ⁻¹			
Vagal stimulation (n = 5)	6.13 ± 0.19	4.04 ± 0.97§	2.86 ± 0.62‡
Sympathetic stimulation (n = 5)	7.83 ± 0.78	5.55 ± 0.87*	3.54 ± 0.89†

Mean ± standard error.

* *P* < 0.01 versus 0% I.† *P* < 0.01 versus 0%, 1.3% I.‡ *P* < 0.01 versus 0% I, *P* < 0.05 versus 1.3% I.§ *P* < 0.05 versus 0% I.

in pressure were not different from control. These results suggest that unless arterial pressure is maintained during isoflurane administration, the decrease in blood pressure produced by the direct effects of the anesthetic on vascular smooth muscle³ can alter the magnitude of the reflex responses.

The administration of thiopental prior to isoflurane also altered the reflex responses to blood pressure changes. When thiopental induction was used in conjunction with isoflurane anesthesia, the reflexes at 0% and 1.3% I were less than in conscious animals but not different from each other. Isoflurane produced significant attenuation of the baroreceptor reflex at 2 MAC, at which point the heart rate response was found to be significantly less than in the conscious and 1 MAC animals. Thiopental

has been reported to equally depress both the pressor and depressor limbs of the baroreceptor reflex,^{9,10} but only the depressor limb of the reflex was depressed in the present study. The same results were found in an earlier study,⁷ although this differential response then was attributed to the effect of nitrous oxide, which accompanied the thiopental. The absence of nitrous oxide in the present study eliminates this possibility and suggests that a possible vagolytic effect of thiopental, similar to that of pentobarbital,¹¹ may be the cause of the preferential attenuation of the depressor response. The blunting of vagal activity necessarily would depress the reflex slowing of heart rate.

The site of isoflurane depression of the baroreceptor reflex could be at one or many components of the barore-

TABLE 3. Effects of Isoflurane on Baseline and Reflex Changes in Sympathetic Efferent Nerve Activity

Responses	0% Isoflurane	1.3% Isoflurane	2.6% Isoflurane
Baseline and reflex changes in sympathetic nerve activity in response to increases and decreases in systemic blood pressure. Expressed as % of baseline (control) level at 0.0% isoflurane (n = 6).			
Baseline levels of nerve activity			
Preganglionic activity	100	85.6 ± 4.79*	76.3 ± 6.51†
Postganglionic activity	100	82.1 ± 4.24*	67.0 ± 8.15‡
Reflex changes to decreases in blood pressure			
Preganglionic activity	6.27 ± 3.07	3.18 ± 1.65	1.49 ± 1.28*
Postganglionic activity	4.49 ± 0.69	2.95 ± 0.59	1.84 ± 1.06*
Reflex changes to increases in blood pressure			
Preganglionic activity	13.46 ± 6.42	4.92 ± 1.52	1.25 ± 0.46*
Postganglionic activity	11.92 ± 2.08	4.91 ± 2.01†	0.75 ± 0.44‡

Mean ± standard error.

* *P* < 0.05 versus control.† *P* < 0.01 versus control.‡ *P* < 0.05 versus preganglionic value at 2.6% I.

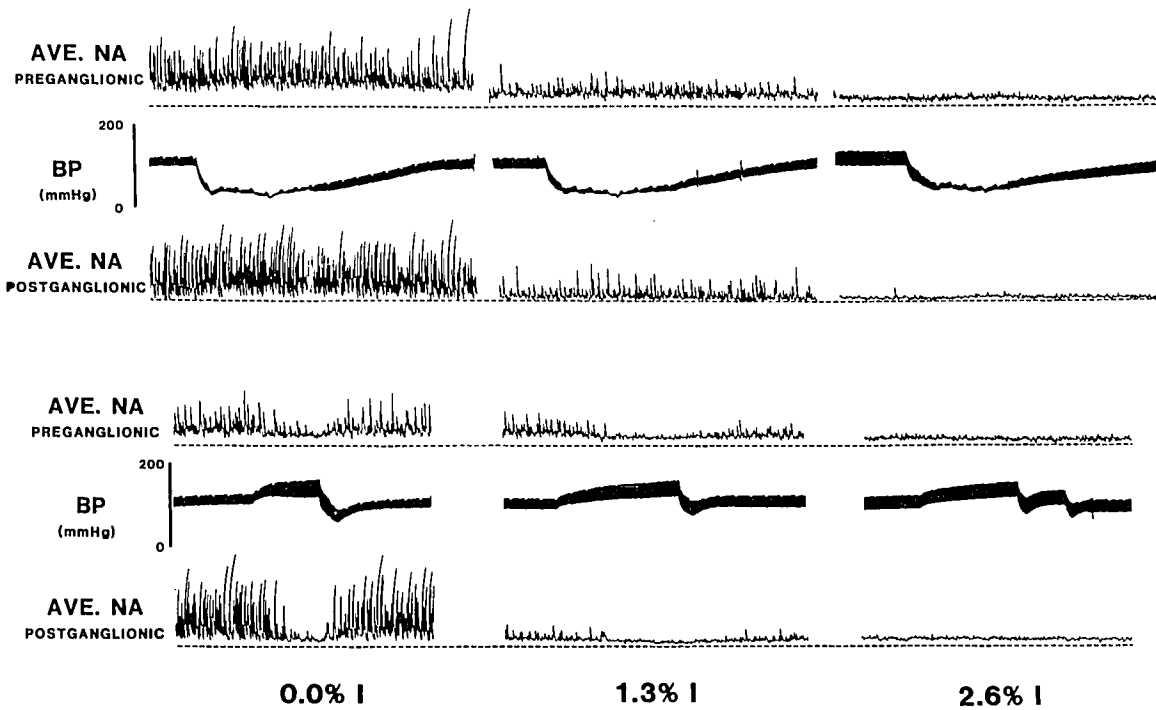


FIG. 3. The response of sympathetic preganglionic and postganglionic nerve activities (AVE NA) at 0.0%, 1.3%, and 2.6% isoflurane (I). Baseline levels of nerve activity were significantly less at each increasing level of I, and reflex changes in nerve activity at 2.6% I were significantly attenuated compared with those at 0.0% I.

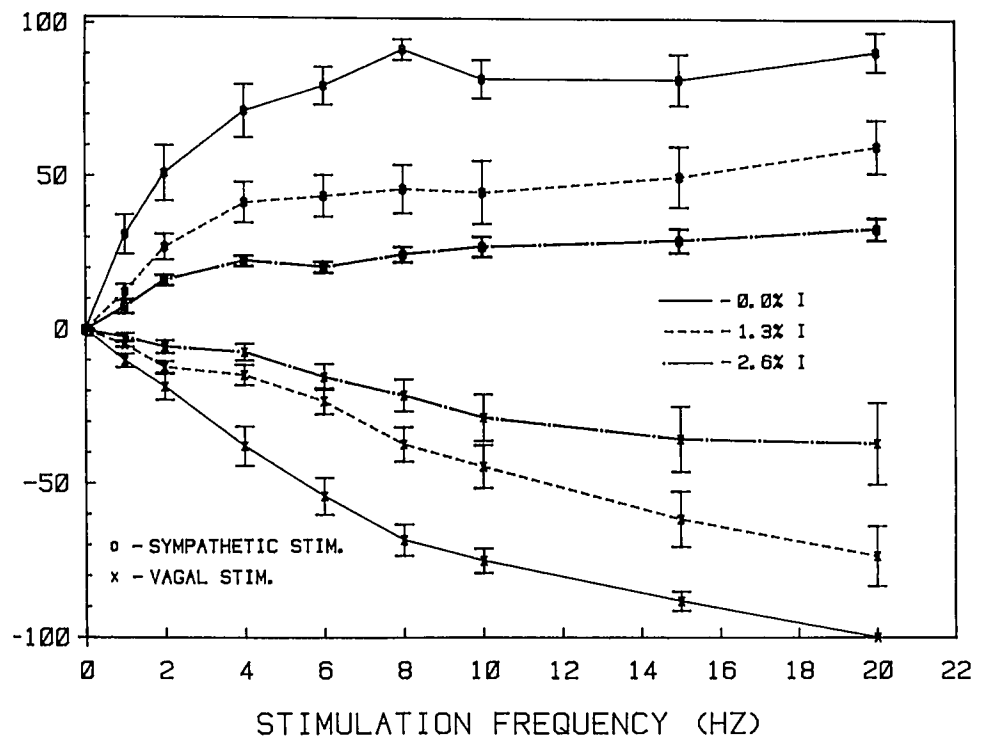


FIG. 4. Chronotropic response of the heart to vagal and sympathetic efferent stimulation at 0.0%, 1.3%, and 2.6% isoflurane (I). Responses, normalized to the maximal responses at 0.0% I, show a dose-dependent attenuation of the chronotropic responses. All values mean \pm SEM. — = 0.0% I, --- = 1.3% I, - · - = 2.6% I.

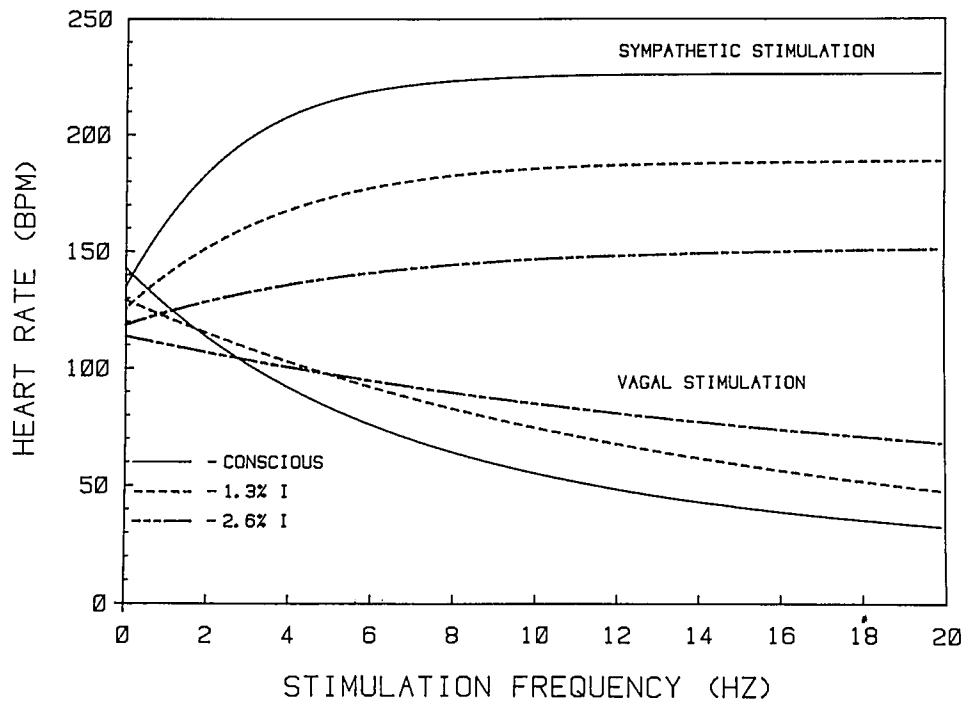


FIG. 5. Chronotropic response of the heart to sympathetic and parasympathetic (vagal) stimulation at 0.0%, 1.3%, and 2.6% isoflurane (I). The curves, the results of asymptotic nonlinear regression, indicate significantly slower rates of change of heart rate for both types of stimulations in the presence of isoflurane.

flex arc. The present study, which examined all levels of the baroreflex arc, determined that the sites of action of isoflurane included the baroreceptors, the afferent and efferent nerve pathways, the central nervous system, the peripheral ganglia, and the heart.

Isoflurane produced dose-dependent sensitization of the baroreceptors, an effect similar to that seen with other inhalational anesthetics.^{7,8,12,13} The sinus perfusion was isolated totally from the rest of the animal, and, therefore, the effects of isoflurane must have been due to its local actions at the sinus and not to any central effects. The sensitization could have been due to a direct action of isoflurane on the receptors or to an indirect effect of a change in the wall tension of the sinus, thereby altering the stimulus-response characteristics of the baroreceptors. In a study examining the effects of halothane on the carotid baroreceptors, the sensitization that occurred was found to be due to both possible mechanisms.⁸ Isoflurane also may exert this dual effect to alter sensitivity. The sensitization does not appear to correlate with the observed attenuation of the baroreflex during the use of isoflurane but may partially explain depression of the baseline sympathetic efferent nerve activity. This decrease in sympathetic tone, produced by increased baroreceptor afferent activity, may play a role in reflex attenuation accompanying isoflurane administration, blunting the functional responses of sympathetic efferent activity.

Isoflurane was found to significantly depress the central nervous system component of the baroreceptor reflex at

1 and 2 MAC, seen as a significant attenuation of baseline levels of preganglionic sympathetic efferent activity recorded in this study at both levels of isoflurane. The attenuated reflex changes in preganglionic sympathetic efferent activity with 2 MAC I may be due to both central nervous system depression as well as lowered sympathetic tone resulting from baroreceptor sensitization. Depression of central nervous system centers that regulate cardiovascular reflex regulation has been reported for halothane,^{9,14} but little work has investigated the effects of isoflurane. One study,² examining the effects of aortic nerve stimulation, found that the aortic baroreflex remained intact but blunted during isoflurane anesthesia. The study found that isoflurane preferentially depressed parasympathetic more than sympathetic efferent nerve activity. The present investigation did not measure directly vagal activity, but, as stated, found a significant depression of sympathetic efferent nerve activity. The results of the whole animal portion of this reflex study found that when arterial pressure was maintained during isoflurane administration, the alterations of the reflex responses to both increases and decreases in blood pressure were similar at all levels of isoflurane. This would suggest that both autonomic divisions were depressed similarly.

Differential depression of preganglionic *versus* postganglionic fibers with isoflurane provided evidence for a ganglionic effect of isoflurane at 2 MAC. The significantly greater depression of baseline and reflex changes

in postganglionic *versus* preganglionic activity indicates that isoflurane blunted a component of ganglionic transmission, although the site of this effect is not known. A recent study¹⁵ examining the effects of halothane on sympathetic ganglionic transmission indicates that this anesthetic depresses ganglionic transmission through a decrease in transmitter release or through a postjunctional receptor effect. Halothane has been shown to depress ganglionic transmission that involves either nicotinic or muscarinic receptors,¹⁶ and both halothane and isoflurane have been shown to produce varying degrees of neuromuscular blockade.³

The study of the chronotropic responses of the heart showed a significant reduction in response of the heart to direct sympathetic and parasympathetic efferent stimulation at both 1 and 2 MAC isoflurane, when expressed as a percentage of the maximum heart rate change at 0% isoflurane. The attenuation in chronotropic response seen in this study with isoflurane may be due to a direct effect on cardiac cells or to an effect on autonomic neuroeffector transmission. Isoflurane has been shown to reduce the inward calcium current during phase 4 depolarization of the sinus node action potential.¹⁷ This effect was reversed by addition of norepinephrine or pacing, which suggests that cells do not lose their ability to respond to stimulation.

Assuming that autonomic neuroeffector transmission has some similar mechanisms to those for autonomic ganglionic transmission, the attenuation of the cardiac chronotropic responses also may be due to decreased release of neurotransmitter. These modes of transmission are known to involve calcium-mediated transmitter release, and inhalational anesthetics are known to alter calcium flux across myocardial¹⁸ and smooth muscle cells.¹⁹ This possible mechanism for the blunting of chronotropic responses of the heart may explain the blunted responses to both sympathetic and parasympathetic stimulation. An atropinelike or a beta-stimulating effect of isoflurane³ would not explain the attenuated responses to sympathetic stimulation. Furthermore, these proposed mechanisms have not been documented rigorously in the literature. Thus, calcium-mediated responses such as synaptic transmission, neuromuscular transmission, or cardiac cell action potentials all appear to be depressed by both halothane and isoflurane.

Analysis of heart rate changes produced by direct efferent stimulation expressed as percentage of maximum or as absolute values revealed similar results, indicating that the differences in initial heart rates at different isoflurane levels did not affect the final responses. The greater attenuation of sympathetically stimulated changes shown by the multivariate analysis correlated with the greater depression of the intact pressor reflex seen when

systemic pressure was not maintained at preanesthetic levels. This suggests that sympathetic mediated responses may be more sensitive to the depressant effect of isoflurane.

In summary, isoflurane was found to have an anesthetic action at multiple levels of the baroreceptor reflex, from the carotid sinus baroreceptors to the heart. Isoflurane was not found to depress the baroreflex-induced heart rate changes until 2 MAC, yet many individual components of the reflex arc were found to be depressed significantly at 1 MAC. Two possibilities may explain this result. First, the baroreceptors were sensitized by isoflurane at both 1 and 2 MAC, and this increased sensitivity may have overcome the local effect of isoflurane at the other sites. There is some evidence for this theory, for reflex changes in preganglionic efferent nerve activity were not blunted at 1 MAC, although baseline levels of activity were significantly less. These results suggest that the system was still capable of responding, although it was set at a lower point. Secondly, the effects of isoflurane on most individual components of the baroreflex arc were studied in the presence of thiopental. When this agent was present during determination of the reflex response in the intact animal, the heart rate changes also were blunted significantly at 1 MAC, in contrast to the effect of isoflurane at this level seen in the absence of thiopental. Thus, some of the attenuation seen in the responses of each component of the reflex arc actually may have been due to both thiopental and isoflurane at 1 MAC I, while additional effects of isoflurane only were seen at 2 MAC I.

The results obtained with isoflurane contrast with those from a previous study, which examined the effects of halothane with thiopental induction on the baroreceptor reflex.⁷ In that study, halothane plus thiopental produced the greatest attenuation of the reflex change in heart rate at 1 MAC, with no further depression at 2 MAC. Therefore, at comparable 1 MAC doses, the present study found isoflurane to be less depressant than halothane on baroreflex-induced changes in heart rate. There are several possible clinical implications of these findings. First, it might be interpreted that improved baroreflex function is advantageous in the presence of some circulatory insults such as acute hypovolemia. Secondly, it is possible that clinical circumstances might favor depressed baroreflex responsiveness. For example, blunting of reflex tachycardia in patients with coronary artery disease and myocardial ischemia usually is considered to be advantageous in the clinical management of such patients, for it reduces the effects of tachycardia on myocardial oxygen requirements. It is hoped that the new and detailed information on the effect of anesthetics on reflex regulation of the

cardiovascular system will provide insight into anesthetic choice under different clinical situations.

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