Local versus Central Effect of Halothane on Carotid Sinus Baroreceptor Function

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Depressive effect of halothane on carotid sinus baroreceptor function may be due to direct local action, action in the CNS, or both. Pairs of dogs were anesthetized with pentobarbital and ventilated with oxygen. The carotid sinus of the recipient dog was isolated and perfused with blood from the common carotid artery of the donor dog. Blood from the recipient sinus was returned through its external carotid to the donor common carotid. Thus, both carotid sinuses of the donor and the contralateral carotid sinus of the recipient dog received uninterrupted circulation. Carotid sinus nerve action potentials and lingual artery pressure of the isolated recipient sinuses were recorded before and during steady state end-tidal halothane concentrations of 0, 0.5, 1.0, 1.5, 2.0, and 2.5% in oxygen, given randomly first to the donor dog (to evaluate direct local effect) and then to the recipient dog (to determine central effect). The dog not given halothane received pentobarbital. Plots of normalized nerve activity versus halothane concentrations showed approximately zero slope when the donor was given halothane but showed significant decrease in nerve activity when the recipient was given halothane. Halothane appears to have no direct local effect but causes depression of baroreceptor nerve activity, possibly via CNS inhibition of sympathetic efferents to the carotid sinus. (Key words: Anesthetics, volatile; halothane. Blood pressure regulation. Receptors: baroreceptors. Reflexes: baroreflexes.)

Previous studies of the effects of halothane on baroreceptor reflexes in both humans and animals have produced conflicting results. Several studies using the slope of blood pressure–heart rate interval relationship in humans or pressure–nerve activity relationship in the isolated carotid sinus preparation in animals have shown that halothane anesthesia depresses the baroreceptor reflex, a finding that has not been confirmed by others. Studies on the effect of halothane on the response of the afferent and efferent limbs of the baroreceptor reflex also have produced divergent results. For example, Biscoe and Miller have shown that in the completely isolated carotid sinuses of cats, rabbits, and dogs, 1–3% halothane enhanced action potentials recorded from single fibers of cut carotid sinus nerve throughout a wide range of applied pressures. They suggested that halothane hypotension and bradycardia may be due to sensitization of the carotid sinus and aortic arch baroreceptors. In contrast, Aars and Hauge have shown that in rabbits the same dose of halothane had no detectable effect on the action potentials recorded from the intact, whole aortic baroreceptor nerve. In addition, Skovstov and associates have reported that in cats 1.5 to 2% halothane produced only a slight depression of the action potentials of the cervical sympathetics and did not depress the barostatic reflex. More recently, Seagard and coworkers have shown that 1.5% halothane increased the slope of a linear equation fitted to the sigmoidal pressure–nerve activity relationship in the isolated canine carotid sinus. This apparent sensitization of baroreceptors was attributed to decreased sympathetic tone, thereby blunting the reflex changes in the baroreceptor nerve activity.

Price and co-workers were first to propose that halothane depresses the vasomotor center, thereby reducing arteriolar resistance and venous return, which causes hypotension and bradycardia. However, Wang and coworkers and Epstein and associates have reported that the hypotensive effect of halothane is mediated through its peripheral rather than its central action. These studies do not resolve the question of whether halothane depresses the vasomotor center. The results of previous studies reviewed above suggest that the depressant effect of halothane may be due to 1) its local direct action on the carotid sinus wall and receptor elements (local effect); or 2) its central action on the vasomotor center to modify baroreceptor function via the cervical sympathetic feedback efferents to the carotid sinus wall and via the non-sympathetic efferent fibers carried in the carotid sinus nerve possibly acting on the receptor element (central effect). Despite these possibilities, we are unaware of any quantitative study that has separated the central and peripheral effects of halothane on the barorectic reflex in an intact animal preparation. The present study was designed to partition the local and central effects of halothane on carotid sinus baroreceptor function in an intact carotid sinus nerve preparation that minimally compromised the physiologic integrity of the baroreceptor reflex feedback loop.

Using a modified cross-circulation technique, we quantitated the action potentials recorded from the intact carotid sinus baroreceptor nerve of a recipient dog that was perfused with the blood of a donor dog. This experimental protocol allowed us to determine the local and central effects of halothane on the intact carotid sinus baroreceptor function by giving the anesthetic to the donor or recipient dog, respectively.

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Materials and Methods

Surgical Preparation

Twenty conditioned mongrel dogs, ranging in weight from 20 to 25 kg, were sex and weight matched and used in pairs as follows. Both dogs initially were anesthetized with sodium pentobarbital (30 mg/kg, iv); they were intubated and ventilated with 100% oxygen to minimize chemoreceptor activation and to maintain arterial \( P_{CO_2} \) at about 38–42 mmHg. In each dog, a polyethylene catheter attached via a stopcock to a glass syringe was placed deep in the trachea through the endotracheal tube. This catheter was used throughout the experiment to sample the expired gas for determination of the end-tidal halothane concentration. In each dog, the left femoral vein was cannulated with a 16-gauge catheter for the administration of anesthetic and iv solution; the right femoral artery was cannulated with a 14-gauge catheter for the measurement of arterial pressure via a calibrated Statham P50 miniature pressure transducer coupled with a Statham model SP 1400 pressure-monitoring system (Statham Instruments Divisions, Gould, Inc., Oxnard, California).

Either the right or left carotid sinus area of one dog (recipient) was exposed by cautery and careful blunt dissection. Using an operating microscope, the baroreceptor branch of the carotid sinus nerve was located and identified by monitoring auditory the phasic relation of the spike frequency to pressure pulse. Except for being placed on the electrode, the nerve was not subjected to any additional handling and the nerve sheath was left intact. Furthermore, care was taken not to disturb the sympathetic innervation to the carotid sinus.14

Following identification, the nerve was left undisturbed while the recipient carotid sinus functionally was isolated from its circulation as follows. The occipital, the ascending pharyngeal, and all collateral arteries except the common, lingual, internal, and external carotid arteries were ligated. The lingual artery then was cannulated with a 20-gauge catheter for measurement of the intrasinus pressure via another calibrated P50 Statham miniature pressure transducer. The common carotid artery of the donor dog then was exposed by cautery and careful blunt dissection, and the bleeding vessels were ligated. The donor dog initially was heparinized (300 U/kg) by intravenous injection of sodium heparin, then repeated doses of heparin (150 U/kg) were given every hour to the donor dog to prevent formation of blood clots during the cross-circulation. As depicted schematically in figure 1, the donor dog was placed beside the recipient dog and the cross-circulation was established as follows. The isolated carotid sinus of the recipient dog was perfused by routing the blood from the carotid artery of the donor dog to the common carotid artery of the isolated recipient sinus via a large bore, short, rigid catheter. This catheter system caused minimal dampening of the arterial pulse. The blood from the isolated carotid sinus was returned via the external carotid artery to the donor dog via another rigid catheter. In this manner, both carotid sinuses of the donor dog and the contralateral carotid sinus of the recipient dog received uninterrupted normal circulation.

To counteract the effect of halothane on the donor dog’s blood pressure and hence the recipient dog’s carotid sinus perfusion pressure, the body of the donor dog was raised so as to maintain the same level of pre-cross-circulation intrasinus pulsatile pressure.

Data Acquisition

The experimental design consisted of simultaneously recording the intrasinus pressure and baroreceptor nerve action potentials from whole intact nerve before and after establishing cross-circulation. Following this, halothane was given at random to the donor dog (to evaluate direct local effect) and to the recipient dog (to determine central effect). End-tidal concentrations of halothane were established in steps of 0.0, 0.5, 1.0, 1.5, 2.0, 2.5% in oxygen and maintained for 30 min before making measurements. A semiclosed anesthesia circuit with a \( CO_2 \) absorption system and Vernitrol® (Ohio Medical Products, Madison, Wisconsin) vaporizer was used to administer the halothane vapor in oxygen mixtures. End-tidal halothane concentration was determined by a model 8000 gas chromatograph (Basic Gas Chromatograph,® Carle Instruments, Inc., Anaheim, California). End-tidal gas samples from the dog not receiving halothane also were analyzed to assure complete circulatory isolation and recovery from the previously administered halothane. Halothane was administered at random, and the dog not given halothane received pentobarbital anesthesia at a rate of 2 mg·kg\(^{-1}\)·h\(^{-1}\) via a model 341A syringe pump (Orion Research, Inc., Cambridge, Massachusetts). Although basal pentobarbital anesthesia used in this study may have a CNS effect, such an effect would be present in both donor and recipient dog and hence would be cancelled out insofar as the carotid sinus function is concerned. Arterial blood for \( pH, P_{CO_2} \), and \( P_O_2 \) determination was drawn every 45 min. Body temperature of both dogs was kept at 36 ± 1 °C with the aid of warming blankets.

The carotid sinus baroreceptor nerve action potentials were recorded by placing the intact nerve across a pair of platinum electrodes spaced 2 mm apart. The nerve signal was amplified successively by a Grass® Model P15 AG preamplifier with passband of 100–3,000 Hz, and a Tektronix® FM 122 differential amplifier with passband of 80–10,000 Hz. The second amplifier provided a suitable input voltage level for recording the nerve action potentials on a Sanborn® Model 3907A FM analog tape recorder (Hewlett-Packard, Palo Alto, California) at a

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speed of 15 in/s for subsequent computer analysis. The recipient dog’s carotid sinus nerve action potentials, intrasinus, and systemic arterial pressure, as well as the donor dog’s systemic arterial pressure were recorded for 2 min at the end of each exposure to different halothane concentrations. The nerve and pressure data thus obtained were analyzed as described below.

At the end of a given experiment, halothane was discontinued, and 30–40 min were allowed for recovery from halothane. At this time, end-tidal gas analyses were performed, and when halothane concentrations were near zero, another carotid sinus nerve action potential was recorded to determine if the nerve activity had returned to baseline level.

**Data Analysis**

*Quantitation of Whole Baroreceptor Nerve Signal:* The action potentials recorded from the carotid sinus nerve in this study represent activity in the whole, intact baroreceptor nerve. They exhibit a distinct modulation of both frequency and amplitude of spikes during the pressure forcing generated from each cardiac cycle of the donor dog. The demodulation of the action potential provides a measure of the integrated electrical activity in the whole nerve and represents the sum of activity of all those units firing synchronously with each pressure pulse. The recorded action potentials were demodulated by a previously described technique. The whole baroreceptor nerve signals, thus demodulated, and the forcing intrasinus pressures generated by the donor dog, were digitized as follows.

**Analog-to-digital Conversion:** The demodulated nerve signal and the intrasinus pressure of the recipient dog simultaneously were digitized by the analog-to-digital (A/D) conversion unit of a PDP-12A Digital Computer (Digital Equipment Corp., Maynard, Massachusetts). The femoral arterial pressures of both recipient and donor dogs also were digitized. The computer was programmed to sample 2048 pairs of pressure and nerve data points at a sampling rate determined by the frequency of the intrasinus pressure forcing generated from the cardiac cycle of the donor dog. This variable sampling rate made it possible to digitize the same number of cycles of pressure and nerve data, regardless of the frequency of the pressure forcing. Since the data were obtained in the steady state.
condition, the variable sampling rate eliminated the presence of any time trends in the digitized data and yielded an accurate representation of the data consistent with the principal of stationarity that was incorporated in the A/D conversion program.\textsuperscript{15,16}

Data Reduction: To reduce variability, the digitized data were averaged as follows. Several consecutive sections of the pressure and nerve data were digitized, yielding a minimum of 50 cycles each. Using these data, an “average” digitized pressure and nerve cycle was obtained by averaging the corresponding points in each cycle. This averaging technique improved the signal-to-noise ratio of the data by a factor of \( \sqrt{N} \) or 7, where \( N \) is the number of cycles used to obtain the “average” cycle.\textsuperscript{16}

To eliminate within-dog and between-dog variations, the pressure and nerve data were treated as follows. For each dog, the computed nerve activity and pressure values were plotted as a function of different end-tidal halothane concentrations. Since these plots yielded a similar pattern of relationship for all experiments, indicating that the dogs belong to the same population, the data for each dog first were normalized and then combined to obtain a pooled relationship. The nerve data were normalized as follows. For each halothane series experiment in each dog, the digitized nerve data were normalized by expressing each value as a percentage of mean of the control values (zero end-tidal halothane concentration). These values then were averaged for each halothane group for all experiments to obtain mean ± SD for the nerve response for a given end-tidal halothane concentration at the mean intrasinus pressure. The latter, of course, was kept constant in each experiment by gravitational adjustment of the lower extremities of the donor dog and with fluid infusion during the administration of different end-tidal halothane concentrations. These normalized and pooled data then were fitted to an appropriate equation using least-squares technique. The plotted and statistically fitted data thus obtained were used to construct the following four relationships for both donor and recipient dogs. These relationships were as follows: 1) normalized nerve action potentials versus halothane concentrations; 2) carotid sinus pressure versus halothane concentrations; 3) recipient systemic arterial pressure versus halothane concentrations; and 4) donor systemic arterial pressure versus halothane concentrations.

Results

The purpose of this study was to partition the local and central effects of halothane on carotid sinus baroreceptor function while keeping the intrasinus pressure constant. To facilitate presentation, the hemodynamic and baroreceptor function data were compared between the donor and the recipient dogs when either donor or recipient dog was receiving halothane.

Effect of Halothane on Femoral Pressure When Donor Dog Was Given Halothane

Figure 2 compares the least-squares plots of the normalized femoral arterial pressure as a function of percent end-tidal halothane concentrations for donor (triangles) and recipient (circles) dogs when donor dog was given halothane. Although the differences in the arterial blood pressures of different dogs were not significant, the pressure data shown in figures 2, 3, and 4 were normalized to eliminate between-dog variations. The normalization procedure consisted of dividing each pressure value by the mean pressure during the 5-min control period. Similar to the nerve data, the normalized pressure data were expressed as a percentage of control. The units are in per cent. As shown, there was a significant \( P < 0.01 \) and dose-dependent reduction in donor dog’s systemic arterial pressure. In contrast, there was little or no change in recipient blood pressure with increasing halothane concentrations.

Effect of Halothane on Femoral Pressure When Recipient Dog Was Given Halothane

Figure 3 compares the least-squares plots of the normalized femoral arterial pressure as a function of percent end-tidal halothane concentrations for donor (triangles) and recipient (circles) dogs when recipient was given halothane. As shown, there was a significant \( P < 0.01 \) and dose-dependent reduction in recipient dog’s systemic ar-
terial pressure. In contrast, there was little or no change in donor dog's blood pressure with increasing halothane concentrations.

**Effect of Halothane on Recipient Intrasinus Pressure When Recipient or Donor Dog Was Given Halothane**

Figure 4 compares the least-squares plots of the normalized lingual artery (intrasinus) pressure as a function of end-tidal halothane concentrations for donor (triangles) and recipient (circles) dogs when donor or recipient dog was given halothane. As shown, the intrasinus pressure was maintained constant as halothane concentration was altered. We observed no statistical difference between the slope of the two regression lines. Since halothane causes a dose-dependent reduction in systemic blood pressure, it was necessary to maintain intrasinus pressure constant so as to study the local and central effects of halothane on the carotid sinus function during the course of this study. The depressant effect of halothane on the blood pressure when the donor was given halothane was compensated for by intravenous fluid infusion and gravitational adjustment of the lower half of the body of the donor dog so as to assure a constant intrasinus pressure. The data presented in figure 4 demonstrate the adequacy and sufficiency of our technique in maintaining intrasinus pressure relatively constant as halothane concentration was altered.

**Effect of Halothane on Recipient's Carotid Sinus Nerve Action Potentials When Recipient or Donor Dog Was Given Halothane**

Figure 5 compares the least-squares plots of the normalized total nerve activity as a function of percentage end-tidal halothane concentrations for donor (triangles) and recipient (circles) dogs when donor or recipient dog was given halothane. To illustrate the depressant effects of halothane on baroreceptor nerve activity when the recipient dog was given halothane relative to the response obtained when the donor dog was given halothane, the recipient data were plotted by eliminating the nerve activity data corresponding to 0% end-tidal halothane concentration. As shown, there was little or no change in the recipient's carotid sinus nerve action potentials when the donor dog was given halothane. In contrast, halothane given to the recipient dog resulted in a 40% reduction in the baroreceptor nerve activity. The y-intercept of this regression line is also significantly different from that describing the response when the donor dog was given halothane. This finding suggests the possibility of CNS-mediated inhibition of the baroreceptor function by the two separate pathways described above. Inhibition of the nonsympathetic efferent fibers in the carotid sinus nerve (which normally inhibit baroreceptor function) at halothane concentrations exceeding 1.5% may account for the enhanced nerve activity seen in this study (fig. 6). The recipient data plotted in figure 5 appeared to be clustered in two regions, depending on halothane concentration: a low halothane dose-response (0.00 to 1.25%) region and a high halothane dose-response (1.25 to 2.5%)
halothane appears to have a biphasic effect on baroreceptor function, a finding similar to a previous observation in renal hypertension.\textsuperscript{17}

**Discussion**

Halothane effects on blood pressure and heart rate have been related largely to its effect on the myocardium and peripheral vascular system. Halothane effects tend to be ubiquitous and the results of actions at multiple sites. One of the observed effects of halothane is its depression of the baroreceptor mechanism whose pressure receptors mainly are found in the carotid sinus, the aortic arch, the atria, and the lungs.

The purpose of this study was to determine if halothane anesthesia depresses the barostatic reflex and, if so, to partition this depressive effect between the peripheral receptors, namely, the carotid sinus baroreceptors, and the central vasomotor center. We used a modified cross-circulation technique that preserved the physiologic integrity of the baroreceptor feedback loop and sympathetic innervation to the carotid sinus. Additionally, this preparation allowed us to maintain blood temperature, $P_{CO_2}$, and pH within normal limits, factors that are known to influence baroreceptor function. Also, both dogs were ventilated with 100% oxygen to minimize chemoreceptor stimulation. Based on previous studies that used the isolated carotid sinus and Ringer superfused preparation,\textsuperscript{4} we were anticipating that the direct smooth muscle relaxant effect of halothane could alter carotid sinus wall tension or its direct effect on receptor elements might lead to an increase or a decrease in carotid sinus baroreceptor nerve action potentials. Contrary to our expectations, we found that inspired halothane ranging in concentrations from 0.5 to 2.5% given to the donor dog (to evaluate the direct local effect), while intrasinus pressure was kept constant, had no statistically detectable effect on the carotid sinus baroreceptor response as defined by pressure–nerve activity relationship. This suggested that halothane does not act locally to alter the carotid sinus baroreceptor function. In contrast, the same doses of halothane given to the recipient dog (to evaluate the central effect) resulted in a progressive and statistically significant ($P < 0.05$) decrease in the baroreceptor response. This finding suggests the possibility of a CNS-mediated inhibition of the baroreceptor response. In addition, we found that this central inhibition of halothane produced a biphasic effect on the pressure–nerve activity relationship. Thus, inspired halothane concentrations below 1.25% caused a dose-dependent depression of the pressure–nerve activity relationship, whereas an increase in the inspired halothane concentration beyond 1.25% tended to increase baroreceptor response toward the baseline values. We have observed a similar halothane dose–dependent biphasic effect on the pressure–nerve activity relationship in the
carotid sinus of one-kidney one clip Goldblatt hypertensive dogs.17

The observed biphasic response may be explained as follows. At low inspired concentrations (0.5 to 1.25%), halothane given to the recipient dog depresses the vasomotor center, thereby reducing sympathetic efferent activity to the carotid sinus. Since stimulation of sympathetic efferents to the carotid sinus has been shown to potentiate the baroreceptor response,18,19 halothane inhibition of central sympathetics would lead to reduction of nerve action potentials. However, as the halothane concentration is increased above 1.25% the progressive systemic hypotension increases sympathetic activity by the contralateral carotid sinus, while the intrasinus pressure of the isolated carotid sinus is kept constant. This increase in sympathetic activity at high inspired halothane concentrations might explain the observed increase in carotid sinus nerve activity. This is consistent with the observations of Millar and co-workers,20 who found an increase in postganglionic sympathetic activity in cats with halothane concentration in excess of 2%.

Another possible explanation for the observed biphasic effect is that halothane may influence the activity of a nonsympathetic pathway that directly could inhibit baroreceptor function. The existence of such a pathway has been proposed by two recent studies. Majcherzyk and co-workers21 have shown that the carotid sinus nerve in cats contains efferent fibers that inhibit chemoreceptor function. In a recent study, Koushanpour and Behnia22 proposed how the CNS might modulate the baroreceptor process to account for diminished receptor sensitivity and baroreceptor resetting in dogs in the face of high intrasinus pressure and normal wall distensibility. This proposal was based on the observation that the pressure–nerve activity relationship for both intact and cut (the baroreceptor nerve was cut at its junction with the glossopharyngeal nerve) carotid sinus nerve were sigmoidal, but the relationship for the cut nerve was shifted toward the nerve-activity axis at intrasinus pressure forcing exceeding 100 mmHg. This finding that cutting the nerve increased baroreceptor nerve output suggested the possibility that the carotid sinus nerve contains efferent fibers that are inhibitory to the baroreceptors and that their effect is more evident at hypertensive pressures. Therefore, it is conceivable that halothane at concentrations above 1.25% preferentially may excite this inhibitory efferent pathway, thereby diminishing baroreceptor inhibition of sympathetic efferents to the carotid sinus, causing a net increase in baroreceptor nerve action potentials.

Using an isolated perfused canine head preparation, Price and co-workers23 found that administration of 1% halothane to the cephalic circulation resulted in the loss of corneal reflex, hypotension, bradycardia, diminished cardiac contractile force, and a reduction in the hemo-
dynamic response to carotid sinus occlusion. Evidence of central sympathetic depression was also obtained by Price and co-workers4 by direct intramedullary injection of halothane. They attributed these changes to central inhibition of efferent sympathetic nervous activity and, hence depressed barostatic reflex by halothane. In contrast, Wang and co-workers13 and Epstein and associates,8 using similar preparations as Price and co-workers,3 found that administration of 0.5 to 3% halothane to the cephalic circulation caused little or no reduction in vasomotor responses. However, when halothane was given to the recipient's body only, marked reduction of vasomotor responses was observed. They suggested that halothane causes no significant centrally mediated depression of the cardiovascular function. Because these investigators did not directly quantitate baroreceptor function, their findings, though contradicting each other, cannot be compared directly with the results obtained in the present study.

A number of studies have examined the effect of halothane on the barostatic reflex in humans, as well as the carotid sinus and aortic arch baroreceptors in several animal models. Using the slope of the relationship between R-R interval and mean arterial blood pressure as an index of sensitivity of baroreflex function in humans, Duke and co-workers24 found that 0.7% halothane significantly depressed and 1.1% completely abolished the baroreflex function. Bristow and associates1 have shown that halothane and nitrous oxide anesthesia results in a marked reflex resetting, producing a combination of bradycardia and hypotension. The possible site for this effect was attributed to the baroreceptors and afferent pathway, integrating centers in the central nervous system and efferent sympathetic or vagal pathways.

In a recent study, Seagard and colleagues25 reported that the slope of the sigmoidal relationship of the carotid sinus nerve activity to intrasinus pressure, as defined by a first-order equation, significantly was increased with 1.5% inspired halothane as compared with the slopes found at 0 and 0.75% inspired halothane concentrations. They concluded that halothane at high concentration sensitizes the receptor, thereby blunting the reflex changes in nerve activity via decreased sympathetic tone. In the present study, we found that halothane in inspired concentration of 1.25–2.5% administered to the central nervous system (given to the recipient dog) caused an increase in nerve action potentials but had no direct local effect on baroreceptor function. This difference between our findings and those reported by Seagard and co-workers22,23 could be attributed to the differences in the experimental techniques and statistical analysis of data used in the two studies.

In conclusion, we feel that the present study represents a first attempt to partition quantitatively the local and
central effects of halothane on baroreceptor reflex. It appears that halothane modification of the baroreflex is mediated primarily through its action on the vasomotor center possibly via a nonsympathetic inhibitory efferent pathway to the carotid sinus. In addition, halothane could affect all components of the baroreceptor feedback loop, leading to the overall reflex changes observed in this study.

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References