

Effect of Halothane on Cardiac Acceleration Response to Somatic Nerve Stimulation in Dogs

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In six dogs, the authors investigated the effect of halothane on cardiac acceleration response to the electrical stimulation of a cutaneous nerve. It was found that increasing the concentration of halothane was associated with a proportional depression of the cardiac acceleration response to somatic nerve stimulation ($y = 99.8 - 44.3x$; $y = \Delta HR$, $x =$ halothane end-tidal concentration). Relationship of the response to end-tidal anesthetic concentration was characterized by a strong correlation ($r = -0.93$, $P < 0.0001$). Complete abolition of the increase in heart rate in response to somatic nerve stimulation was observed at a halothane end-tidal concentration of 2.2 vol% (extrapolation). It is suggested that suppression of heart rate increase to noxious stimulation may be used as a graded index of the depth of anesthesia for halothane. (Key words: Anesthesia: depth. Anesthetics, volatile: halothane. Heart: rate response. Potency, anesthetic: MAC.)

IN RAT EXPERIMENTS, the anesthetic-induced abolition of heart rate increase to noxious stimulation (HR ED₅₀), in contrast to the loss of righting reflex (RR ED₅₀), has a constant ratio to MAC.¹ It also was suggested that heart rate response to noxious stimulation may be used as an alternative index for the measurement of anesthetic potency.^{1,2} This suggestion was related to the cardiac acceleration response used as a quantal (all-or-none) index of anesthesia (presence or absence of the complete blockade of the cardiac acceleration response) analogous to the blockade of movement response. However, the cardiac acceleration response in contrast to the movement response has the nature of a graded type of response. Therefore, measuring the depth of anesthesia by the degree of suppression of the cardiac acceleration response might be possible. In other words, it may be used as a graded index of anesthesia. The use of the suppression of cardiac acceleration to noxious stimulation as a graded index of the depth of anesthesia may be acceptable only on the condition that a gradual increase in anesthetic concentration causes a proportional depression of this index. The aim of the present study was to investigate to what extent the effect of halothane on the cardiac acceleration, caused by noxious stimulation, correlates with the agent's end-tidal concentration.

Methods

Experiments were performed on six mongrel dogs weighing between 15 and 30 kg. Anesthesia was induced with methohexital (8 mg/kg, iv), and myorelaxation was provided with pancuronium (initial bolus dose of 80 $\mu\text{g}/\text{kg}$, iv, followed by a continuous infusion of 20 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$). After endotracheal intubation with a cuffed tube, animals were ventilated with a 613 Harvard® ventilator. The ventilatory rate was adjusted to maintain PaCO₂ at 35 to 45 mmHg. Anesthesia was maintained with halothane (1.5 vol% in oxygen), delivered by a calibrated Dräger® vaporizer. End-tidal gas was sampled by suction through a nylon catheter inserted into and down the endotracheal tube. Halothane end-tidal concentrations were determined with a calibrated (MGA 1100 Perkin-Elmer Mass Spectrometer® and containers with reference concentrations of halothane) Beckman® LB-2 infrared spectrometer. Intravenous fluid (lactated Ringer's solution) was given continuously (5 ml · kg⁻¹ · h⁻¹) during each experiment. Body temperature was controlled by means of a heating blanket and kept at 37–38° C (rectal probe). The heart rate was derived from ECG. A Grass® 7P44B tachograph triggered by ECG signals provided beat-to-beat records of heart rate on a Grass® 7D polygraph.

The superficial peroneal nerve was used for stimulation. The nerve was desheathed and cut distally, and its central end was placed on bipolar electrodes in a pool of mineral oil. Stimulation was provided by a Grass® S88 stimulator with the following parameters: frequency—10 Hz, stimulus duration—0.5 ms, stimulus intensity—30 V, and duration of stimulation—20 s. Stimulations were provided every 15 min during an experiment, on the condition that heart rate (HR) baseline was in a steady state for at least 5 min before stimulation.

In every experiment, after an initial period of 30–40 min of halothane anesthesia, four inspired concentrations of halothane were used one after another: 1.5, 1.8, 2.1, and 2.4 vol%. The order of their administration was determined randomly. Each concentration was administered for 45 min. Halothane end-tidal concentration, baseline heart rate, and maximal heart rate increase during stimulation were determined 40–45 min following each change in inspired concentration.

In three additional experiments, the animals were intubated without a myorelaxant and maintained on

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Received from the Department of Anesthesiology, School of Medicine, University of Alabama in Birmingham, University Station, Birmingham, Alabama 35294. Accepted for publication May 24, 1984.

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halothane 1.8%. The heart rate responses were evoked before and after an intravenous bolus injection of pancuronium (80 µg/kg).

MAC multiples were calculated on the basis of data reported by Eger *et al.*³ The values were compared with the use of linear regression technique and Pearson *r* correlation coefficient.

Results

Stimulation of the superficial peroneal nerve at the lowest halothane concentrations (1.2–1.4 vol%, end-tidal) caused a profound increase in heart rate (fig. 1). The degree of cardiac acceleration at these concentrations ranged between 50% and 30% of baseline heart rate level. Maximal cardiac acceleration usually occurred before the end of the 20-s period of stimulation. Table 1 shows individual cardiac acceleration and baseline heart rate values at various end-tidal concentrations of halothane. In figure 2, cardiac acceleration was plotted against end-tidal halothane concentration. This demonstrates that the increase in heart rate caused by the somatic nerve stimulation was depressed progressively with the increase in halothane concentration. Relationship between the cardiac acceleration response and end-tidal halothane concentration may be described by the following equation: $y = 99.8 - 44.3x$. It was characterized by a high degree of correlation ($r = -0.93$, $P < 0.0001$, $n = 24$). Because baseline heart rate also was influenced by halothane concentration, correlation coefficients between all three variables (baseline heart rate, cardiac acceleration to the stimulation, and end-tidal

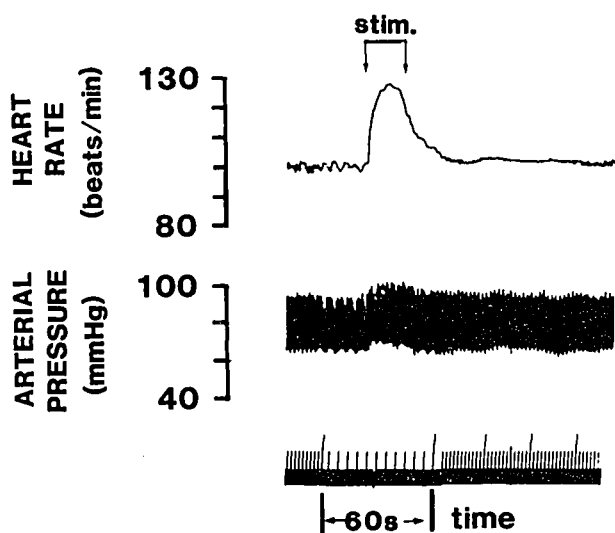


FIG. 1. Cardiac acceleration response to somatic nerve stimulation. The superficial peroneal nerve has been stimulated for 20 s with the following stimulus parameters: 10 Hz, 0.5 ms, 30 V. Halothane end-tidal concentration was 1.35% vol%.

TABLE 1. Halothane Dose-Response Data

Experiment	Inspired* Concentration (vol %)	End-tidal† Concentration (vol %)	Baseline‡ Heart Rate (beats/min)	HR Increase‡ to Stimulation (beats/min)
1	2.4	2.17	91	8
	1.5	1.37	69	23
	2.1	1.87	78	16
	1.8	1.73	77	14
2	1.8	1.50	72	24
	1.5	1.35	72	24
	2.4	2.07	95	7
	2.1	1.83	87	8
3	1.5	1.20	94	53
	1.8	1.53	91	34
	2.1	1.80	95	17
	2.4	2.00	99	12
4	2.1	1.83	105	22
	2.4	2.15	114	6
	1.8	1.75	91	16
	1.5	1.47	82	28
5	1.8	1.60	87	22
	2.4	2.15	108	4
	2.1	1.90	93	9
	1.5	1.40	74	32
6	1.5	1.30	80	32
	2.1	1.77	81	12
	1.8	1.55	84	18
	2.4	2.10	91	7

* Selected randomly.

† End-tidal concentration, baseline HR, and HR increase to the stimulation at 45 min following a change in inspired concentration.

halothane concentration) were compared. Correlation coefficient between baseline heart rate and end-tidal halothane concentration was 0.65 ($P < 0.001$). The weakest correlation was found between baseline heart rate and the cardiac acceleration to the stimulation ($r = -0.52$, $P < 0.01$).

In additional experiments when the animals were intubated without myorelaxant and maintained on halothane 1.8 vol%, the heart rate responses evoked before and after intravenous bolus injection of pancuronium 80 µg/kg were not different from one another. It also was found that pancuronium 80 µg/kg caused only a small increase in baseline heart rate (an increase of 3, 7, and 9 beats/min from a level of 90, 87, and 75 beats/min, respectively).

Discussion

A cutaneous nerve (the superficial peroneal nerve) was used in this study for stimulation. Parameters of stimulation (10 Hz, 0.5 ms, 30 V, 20 s) were selected to give maximal noxious stimulation. According to Sato *et al.*,⁴ with these parameters all C fibers (Group IV) should be excited. They investigated sympathetic re-

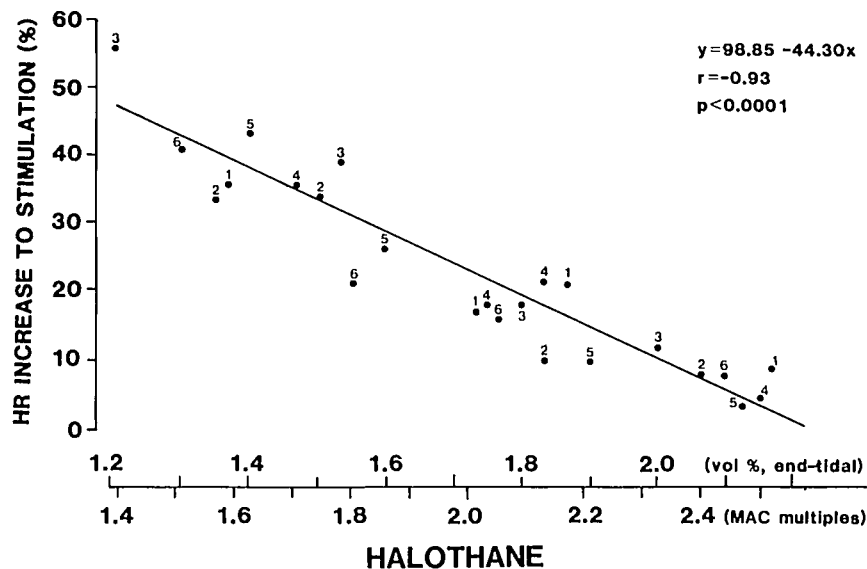


FIG. 2. Correlation of stimulation-induced cardiac acceleration with halothane end-expired concentration. Numbers above the dots represent experiment number. MAC multiples were calculated on the basis of data reported by Eger *et al.* (MAC—0.86 vol%).³ Relationship between y and x is described by the equation $y = 99.8 - 44.3x$.

sponses to cutaneous nerve stimulation and found that heart rate acceleration caused by noxious stimulation was mediated by the sympathetic cardiac nerves. It also was found that "although at first sight increases in heart rate seem to be coupled to pressor responses, in many cases heart rate changes were observed without any modifications of the blood pressure; in others, definite increases in heart rate were accompanied by hypotensive or mixed responses." This was the basis for the viewpoint that in contrast to the cardiac acceleration, blood pressure is only a very indirect and possibly quite inappropriate way of monitoring the central autonomic effects of somatosensory inputs.⁵

Pancuronium was used in this study for two reasons: first, to prevent responses to endotracheal tube and artificial respiration with a low concentration of halothane in the animals least sensitive to the anesthetic; second, to create experimental conditions most closely resembling typical clinical situation. Pancuronium is known to have vagolytic action and to affect heart rate. Therefore, it was appropriate to demonstrate that pancuronium cannot change significantly cardiac acceleration response to the stimulation by itself. We have found in an additional series of experiments that pancuronium 80 $\mu\text{g}/\text{kg}$ caused only a small increase in baseline heart (3–9 beats/min) and that the cardiac acceleration response was not changed by the drug. This correlates well with the observation by Kumagai *et al.* that even a complete vagotomy cannot change the magnitude of the heart rate increase evoked by cutaneous nerve stimulation in dogs.⁶ It also should be mentioned that Saxena and Bonta⁷ studied the effect of pancuronium in dogs

with a wide range of doses and found little changes in heart rate (at 0.05 mg/kg, heart rate increased $8 \pm 2\%$ and at 50.00 mg/kg, $9 \pm 11\%$).

Our data showed an excellent correlation between end-tidal concentration of halothane and the suppression of stimulation-induced cardiac acceleration ($r = -0.93$, $P < 0.0001$). Figure 2 demonstrates that at the 1.4 MAC level, the HR response to stimulation reached approximately 50% of baseline heart rate and, with an increase in the MAC, stimulation-induced cardiac acceleration gradually decreased until it was abolished completely at the 2.5 MAC level. There is evidence that these results might be transferable to humans. Roizen *et al.*⁸ have shown in patients that ED_{95} for blocking an increase in blood norepinephrine upon skin incision (MAC BAR_{95}) was 2.1 MAC for halothane–nitrous oxide combination.

Our data indicated that there was weak correlation ($r = -0.52$, $P < 0.01$) between baseline heart rate and stimulation-induced cardiac acceleration. It is interesting that, in rat experiments, no correlation was found between heart rate response to tail clamp and baseline heart rate at halothane concentrations within 1.5 to 2.4 vol% range.¹ Some correlation between baseline heart rate and stimulation-induced cardiac acceleration found in this study might have resulted from the independent effects of halothane on baseline heart rate and the cardiac acceleration.

Eger *et al.* pointed out that MAC represents a single point on a dose (anesthetic concentration)–response (central nervous system [CNS] depression) curve.^{9,10} Gradual increase in the dose of halothane beyond this

point (expressed in MAC multiples) caused in our experiments a proportional depression of cardiac acceleration to noxious stimulation. This suggests that suppression of heart rate increase to noxious stimulation may be used as a graded index of the depth of anesthesia for halothane. In fact, it confirms the everyday practice of anesthesiologists who are using increases in heart rate and arterial pressure caused by surgical stimulation to judge the adequacy of the depth of anesthesia.

The authors thank Edwin L. Bradley, Jr., Ph.D., of the UAB Department of Biostatistics for performing the statistical analysis of the data.

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