

Halothane Induces Depressor Responses to Noxious Stimuli in the Rat

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The effect of halothane on hemodynamic responses to noxious stimuli was investigated in anesthetized male Sprague-Dawley rats. It was found that increasing the end-tidal halothane concentration from sub-MAC to supra-MAC levels was frequently associated with a reversal of the mean arterial pressure response to a noxious stimulus from a pressor response to depressor response. The depressor responses could be produced by noxious stimuli at several sites but were of greatest frequency (100%) and magnitude (up to -80 mmHg) after clamp application at the base of the tail. The depressor responses were often, but not always, accompanied by decreases in heart rate. The correlation coefficient between the changes in heart rate and the changes in mean arterial pressure caused by noxious stimuli was +0.61 (n = 9). The authors further characterized the depressor responses in an additional 18 rats. The depressor responses were not influenced by vagotomy or muscarinic cholinergic blockade and were associated with concurrent decreases in both cardiac output and systemic vascular resistance. The hemodynamic changes associated with the depressor responses were consistent with a centrally mediated withdrawal of sympathetic tone. Knowledge of this effect of halothane on the arterial blood pressure and heart rate responses to noxious stimuli may be important for correctly interpreting animal responses to noxious stimuli in the presence of general anesthetic agents, particularly because animals are frequently used to characterize both the potency and the hemodynamic effects of anesthetic agents. The presence of depressor responses also indicates that mean arterial pressure responses to noxious stimuli cannot be used as a linear index of anesthetic depth in rats anesthetized with halothane. (Key words: Anesthesia; depth. Anesthetics; volatile: halothane. Noxious stimuli; blood pressure; depressor response.)

NOXIOUS STIMULI in the awake animal result not only in the conscious perception of pain, but also in a purposeful movement (withdrawal) response and in an autonomic response that affects almost every organ system but that is manifest most clearly in the cardiovascular system with changes in heart rate (HR) and systemic blood pressure.¹ One measure of the potency of an anesthetic agent is its ability to prevent or obtund these responses.

Traditionally, purposeful movement responses have been used to assess anesthetic potency. The minimum alveolar concentration (MAC) of an agent that prevents movement in response to a standard noxious stimulus in

50% of subjects is now the most commonly used and understood measure of anesthetic potency.² However, the ability to prevent pain perception, movement, and autonomic responses may comprise different components of "anesthesia" that do not have a direct relationship to one another.^{3,4} In modern anesthetic practice, with the widespread use of neuromuscular blocking drugs, the ability of an anesthetic agent to prevent HR and systemic blood pressure responses to noxious stimuli would appear to be a more clinically relevant index of anesthetic potency than the ability to prevent purposeful movement.

Indeed, there has been increasing interest in measuring the effects of anesthetic agents on hemodynamic responses to noxious stimuli in both humans and animals.⁵⁻⁷ However, in animal studies performed so far, only HR responses have been examined, on the pretext that "blood pressure is only a very indirect and possibly quite inappropriate way of monitoring the central autonomic effects of somatosensory input."⁷ This pretext is based on the observation of variable pressor, depressor, and mixed arterial blood pressure responses to afferent nerve stimulation in laboratory animals.^{8,9} Nevertheless, HR responses to noxious stimuli should not be interpreted independently because changes in arterial blood pressure may produce changes in HR through the baroreceptor reflex.¹⁰ If hemodynamic responses to noxious stimuli are to be used to assess anesthetic potency, it is necessary to know the responses of both HR and arterial blood pressure.

The aim of the current study was to examine the effect of halothane on both HR and arterial blood pressure responses to standardized noxious stimuli in the rat in order to determine whether halothane has predictable effects on hemodynamic responses to noxious stimuli that can be used to assess anesthetic depth in the rat. Because previous studies in the rat have used many different sites of noxious stimulation,^{2,11} stimulation-site-related variability of hemodynamic response was also examined.

Methods

EXPERIMENTAL PREPARATION

All studies conformed with the "Guiding Principles in the Care and Use of Animals" of the American Physiological Society. Male Sprague-Dawley rats (Charles River Laboratories, Wilmington, Massachusetts 01887) (weight = 584 ± 18 g, mean ± SEM) (n = 9) were anesthetized

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with 2% halothane (vol/vol) in O₂ in a plexiglas induction chamber. After tracheostomy, controlled ventilation was started with the use of a pressure cycled ventilator (Analytical Specialties SAR-2, St. Louis, Missouri) and a non-rebreathing circuit. Anesthesia was continued with an inspired halothane concentration of 1.5% in O₂. Bilateral vagotomy was performed to prevent vagal influences. Carotid artery pressure and central venous pressure (CVP) were monitored with the use of intravascular catheters (PE-50 tubing) filled with heparinized saline and connected to Gould P23ID[®] transducers that were calibrated to a mercury column. Rectal temperature was servo controlled at 37° C with the use of a heating mattress. The end-tidal fraction (FET) of CO₂ and halothane (H) was measured by mass spectrometry (1100 MGA[®], Perkin-Elmer Pomona, California) with the use of a respiratory waveform monitoring technique.¹² Ventilation was adjusted to maintain FET_{CO₂} at 5.0 ± 0.5% (mean ± range). Continuous recordings of aortic pressure and heart rate and intermittent recordings of FET_{CO₂} and FET_H were made on a Gould 2800[®] recorder.

GROUP 1

After instrumentation, the FET_H was reduced to 0.75% and allowed to equilibrate for 30 min. Noxious stimuli were applied at five different sites in random order (base-tail; mid-tail; tip-tail; fore-foot pad; hind-foot pad). Stimuli to the tail were applied by a 20-cm rubber-shod tubing clamp (Pilling Instruments, Fort Washington, Pennsylvania; model 35-1375), clamped to the second ratchet. Stimuli to the footpads were applied by a 12-cm surgical hemostat (American V. Mueller, Edison, New Jersey; model SU-2700), also clamped to the second ratchet. All stimuli were applied in a similar manner on each occasion. Each stimulus was applied for 60 s and the maximum change in HR, mean arterial pressure (MAP), and CVP during the period of stimulation was determined. The MAP was allowed to stabilize for 5 min between stimuli. After recordings had been made from all five sites, the FET_H was increased by 0.25% and again allowed to equilibrate for 30 min. By repeating the sequence described above, data were collected from stimulation at all five sites, at five FET_H levels from 0.75 to 1.75%, at intervals of 0.25%. At FET_H = 1.75% data were only collected from seven rats because severe hypotension developed in two (MAP < 30 mmHg).

For statistical purposes, one ΔMAP response value (average of ΔMAP responses from all five sites) was calculated for each rat at each FET_H. The ΔMAP responses at each FET_H ≥ 1.0% were compared with the ΔMAP responses at 0.75% (which was used as the control) with the use of one-tailed paired *t* tests. Because multiple tests were performed on the same sample, the Bonferroni method for

simultaneous multiple comparisons was used, and only *P* values less than or equal to 0.01 were considered significant.¹³ The ΔMAP responses at FET_H = 0.75% (sub-MAC) and FET_H = 1.25% (supra-MAC) were also analyzed with the use of one-tailed one-sample *t* tests (H₀: μ ≤ 0 at FET_H = 0.75%, H₀: μ ≥ 0 at FET_H = 1.25%) to determine whether the mean changes in MAP were positive or negative. Similarly, the ΔMAP responses at each of the five sites, and at each FET_H, were analyzed with the use of one-tailed one-sample *t* tests to determine whether the mean responses were positive or negative. The correlation coefficient between the ΔHR and ΔMAP responses to noxious stimuli was also calculated, as was the correlation coefficient between the changes in CVP and MAP, with the use of simple linear regression.

GROUP 2

Because the Group 1 data frequently displayed depressor responses to noxious stimuli at FET_H of 1.0% or greater, supplemental experiments were performed on additional rats to further characterize the depressor responses. These rats were prepared in the same manner as those in Group 1 except for the additional interventions that are outlined below. Noxious stimuli in the Group 2 rats were applied only at the base of the tail because this was the site that produced the highest incidence and magnitude of depressor responses in Group 1 (see "Results"). Statistical analyses in the Group 2 experiments also used the Bonferroni method to reduce α when multiple simultaneous comparisons were made.¹³

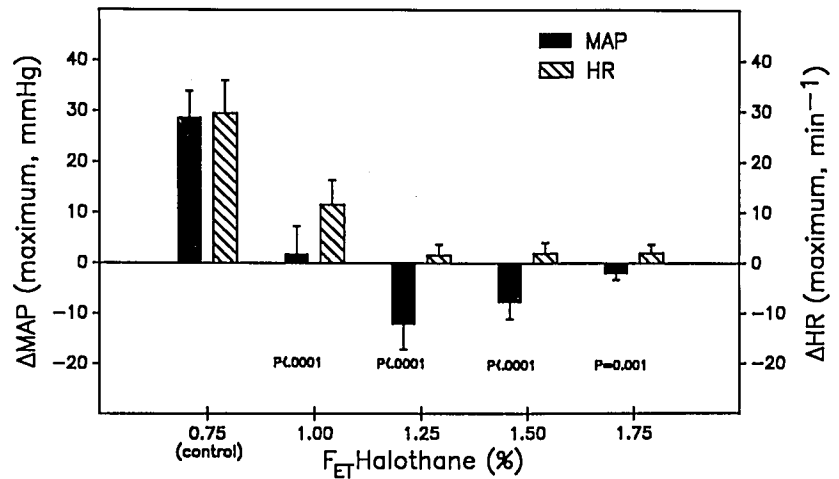
Group 2a: Effect of Vagotomy

To determine whether similar responses occurred in rats with intact vagus nerves, six rats (weight = 434 ± 28 g) were prepared in the manner described above except that initially the vagi were left intact. Base-tail clamp was applied at FET_H of 0.75% and 1.25%. Base-tail clamp was repeated after bilateral vagotomy but in reverse order (1.25%, 0.75%). (The order was reversed after vagotomy to determine whether the depressor response in general could revert to a pressor response if the FET_H was reduced to the control level.) The ΔMAP and ΔHR responses to base-tail clamp before and after vagotomy were compared with the use of paired *t* test with α = 0.0125.

Group 2b: Effect of Cholinergic Blockade

At an FET_H of 1.0%, base-tail clamp was applied to six vagotomized rats (weight = 530 ± 46 g), before and after the administration of atropine 0.1 mg · kg⁻¹ iv. Muscarinic cholinergic blockade was confirmed by the absence of an arterial pressure response to acetylcholine 5 μg · kg⁻¹ iv. The ΔMAP and ΔHR responses to base-tail clamp before

FIG. 1. Group 1 data. The effect of halothane on mean arterial pressure (Δ MAP) and heart rate (Δ HR) responses to noxious stimuli at all five sites of stimulation combined. Bars indicate mean \pm SEM, $n = 9$. (P values obtained from one-tailed paired t tests comparing Δ MAP responses at each $F_{ET_H} \geq 1.0\%$ with the control.) Refer to table 1 for prestimulus MAP and HR data.



and after atropine were compared with the use of a paired t test with $\alpha = 0.025$.

Group 2c: Effect on Cardiac Output and Systemic Vascular Resistance

In an additional six rats with intact vagus nerves (weight = 429 ± 13 g), cardiac output (CO) was estimated with the use of an electromagnetic blood flowmeter (Statham Instruments Inc., Oxnard, California; model SP-2202) placed acutely on the ascending aorta. The flowmeter was introduced through a wide sternotomy incision and placed around the aorta in a position that did not affect baseline MAP. CO and MAP were measured during base-tail clamp at F_{ET_H} of 0.75% and 1.25%. After pentobarbital overdose-induced cardiac arrest, the flowmeter was calibrated *in situ* by inserting a cannula through a left ventricular incision into the ascending aorta and recording the measured aortic flow during known infusion rates from a calibrated syringe pump (Harvard Apparatus, Southnatick, Massachusetts; model 907).

Systemic vascular resistance (SVR) was then calculated with the use of standard formulae. Δ MAP, Δ CO, and

Δ SVR responses at both F_{ET_H} levels were analyzed with the use of one-tailed one-sample t tests with $\alpha = 0.01$, according to the following null hypothesis: $H_0: \mu \leq 0$ at $F_{ET_H} = 0.75\%$, $H_0: \mu \geq 0$ at $F_{ET_H} = 1.25\%$.

Results

GROUP 1

Figure 1 displays the effect of halothane on the mean Δ MAP and Δ HR responses to noxious stimuli at all sites of stimulation combined. Table 1 gives the corresponding values for the prestimulation and poststimulation MAP and HR. There were statistically significant reductions in the absolute magnitude of the Δ MAP responses to noxious stimuli at all F_{ET_H} levels greater than control (0.75%). Moreover, increasing the F_{ET_H} was frequently associated with a reversal of the direction of the Δ MAP response from pressor to depressor. An example of a typical pressor and depressor response in the same rat is given in figure 2. The depressor responses were of a similar duration to the pressor responses, both typically attaining their maximum change during the period of stimulation and re-

TABLE 1. The Effect of Halothane on Mean Arterial Pressure (MAP) and Heart Rate (HR) in Group 1

	End-tidal Halothane (%)				
	0.75	1.00	1.25	1.50	1.75
MAP (mmHg)					
Prestimulation	100 \pm 3	86 \pm 3	87 \pm 3	75 \pm 3	56 \pm 3
During stimulation	128 \pm 4	89 \pm 4	76 \pm 3	68 \pm 3	53 \pm 3
Δ MAP	28 \pm 5	2 \pm 5	-11 \pm 3	-8 \pm 3	-3 \pm 2
Range of Δ MAP (min, max)	-80, +80	-65, +60	-60, +25	-55, +15	-25, +5
HR (min^{-1})					
Prestimulation	356 \pm 5	346 \pm 5	344 \pm 4	339 \pm 4	332 \pm 6
During stimulation	386 \pm 7	358 \pm 5	346 \pm 4	340 \pm 4	334 \pm 6
Δ HR	29 \pm 4	11 \pm 3	1 \pm 2	1 \pm 2	2 \pm 1
Range of Δ HR (min, max)	-20, +100	-25, +70	-30, +35	-15, +35	-10, +25

Values indicate mean \pm SEM of measurements from all five stimulation sites in all nine rats.

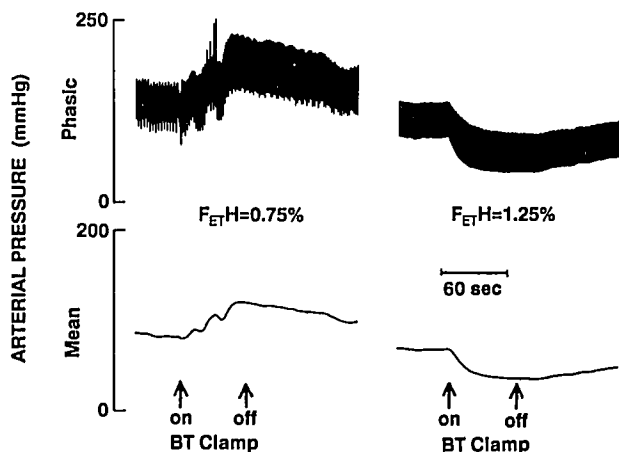


FIG. 2. Typical mean arterial pressure responses to base-tail clamp at end-tidal halothane fractions (F_{ET_H}) of 0.75% (sub-MAC) and 1.25% (supra-MAC).

turning to their baseline prestimulus value within 5 min. The reversal of the response was statistically significant because the mean control Δ MAP response ($F_{ET_H} = 0.75\%$) was positive ($P < 0.001$), whereas the mean Δ MAP response at $F_{ET_H} = 1.25\%$ was negative ($P = 0.011$).

Figure 3 demonstrates that increasing the F_{ET_H} was associated not only with a reduction in the frequency of positive Δ MAP and Δ HR responses to noxious stimuli, but also with an increase in the frequency of negative Δ MAP and Δ HR responses to noxious stimuli up to an F_{ET_H} of 1.25%. At $F_{ET_H} \geq 1.25\%$, both positive and negative Δ MAP and Δ HR responses decreased as nil responses (changes less than 1% of prestimulation value) to noxious stimuli increased.

Figure 4 demonstrates that there was a modest positive correlation between Δ MAP and Δ HR responses to noxious stimuli ($r = +0.61$), however, there was only a weak

correlation between Δ MAP and Δ CVP responses to noxious stimuli ($r = +0.25$).

Figure 5 displays the effect of halothane on the mean Δ MAP responses to noxious stimuli at each of the five sites of stimulation separately. At $F_{ET_H} = 0.75\%$ (control), all the mean Δ MAP responses were positive. However, at $F_{ET_H} \geq 1.25\%$, most of the mean Δ MAP responses were negative. At $F_{ET_H} = 1.25\%$, four of the five sites had negative mean Δ MAP responses (these were only statistically significant at the base-tail [$P < 0.001$] and the hind-foot [$P = 0.009$]). At $F_{ET_H} = 1.5\%$, all five sites had negative mean Δ MAP responses (only at the base-tail was this statistically significant [$P = 0.003$]). Table 2 gives the data for the frequency and magnitude of the depressor responses. The greatest frequency and magnitude of depressor responses was produced by stimuli at the base-tail. However, depressor responses were observed after stimuli at *all* sites, including the tip of the tail, which had a 33% incidence of depressor responses at $F_{ET_H} = 1.0\%$ and $F_{ET_H} = 1.25\%$.

GROUP 2a

The effect of vagotomy is displayed in figure 6. There was no significant difference between either Δ MAP or Δ HR responses to base-tail clamp measured before and after vagotomy. Figure 6 also displays that the depressor response is reversible because it can revert to a pressor response if the F_{ET_H} is reduced to the control level.

GROUP 2b

The effect of muscarinic cholinergic blockade is displayed in figure 7. There was no significant difference between either Δ HR or Δ MAP responses to base-tail clamp before and after establishing muscarinic cholinergic blockade.

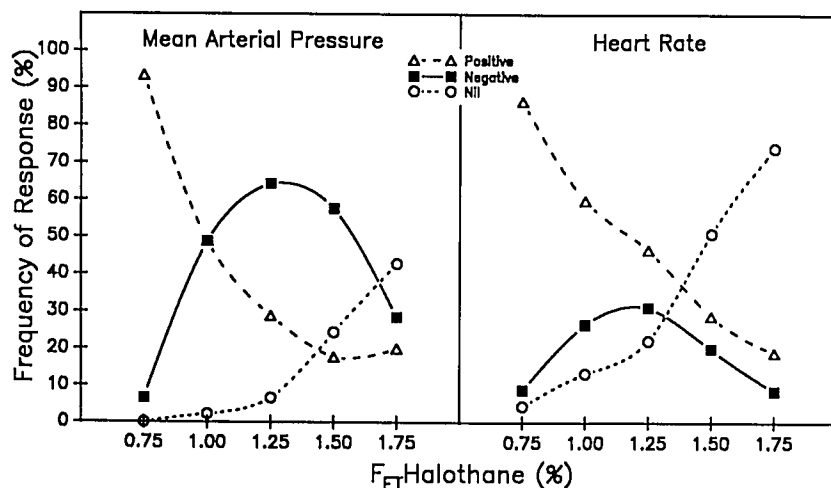


FIG. 3. Group 1 data. The effect of halothane on the frequency of positive, negative, and nil (changes less than 1.0% of prestimulation value) mean arterial pressure (MAP) and heart rate (HR) responses to noxious stimuli at all five sites of stimulation combined.

GROUP 2c

The effect of base-tail clamp on CO and SVR is displayed in figure 8. At $F_{ET_H} = 0.75\%$, base-tail clamp produced increases in MAP, CO, and SVR, whereas at $F_{ET_H} = 1.25\%$, base-tail clamp produced decreases in all these variables. The reductions in ΔMAP and ΔCO at $F_{ET_H} = 1.25\%$ were statistically significant, however, other values did not attain statistical significance.

Table 3 gives the prestimulation (baseline) hemodynamic data for the Group 2 rats. The prestimulation MAP in all Group 2 experiments was similar to the prestimulation MAP at the same F_{ET_H} level in Group 1.

Discussion

Our results demonstrate that halothane induces depressor responses to noxious stimuli in the rat. The normal awake ΔMAP response to noxious stimuli in the rat appears to be pressor (increase in MAP), but at a certain end-tidal concentration of halothane there is often a reversal of this pressor response to a depressor response (decrease in MAP). The depressor response itself reverts

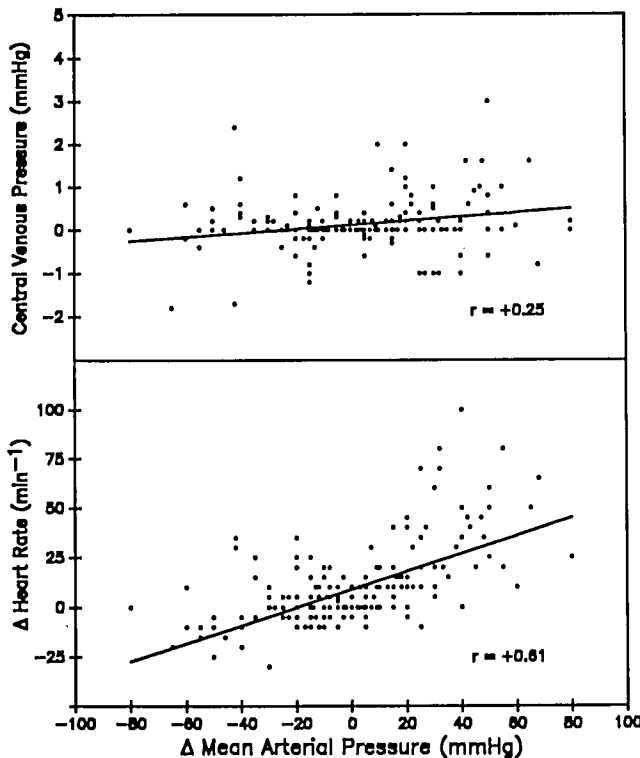


FIG. 4. Group 1 data. Top panel: The correlation between the mean arterial pressure responses (ΔMAP) and central venous pressure responses (ΔCVP) to noxious stimuli ($y = 0.11 + 0.005x$). Bottom panel: The correlation between mean arterial pressure responses (ΔMAP) and heart rate responses (ΔHR) to noxious stimuli ($y = 8.9 + 0.45x$). Both panels present data from all five sites of stimulation in all nine rats.

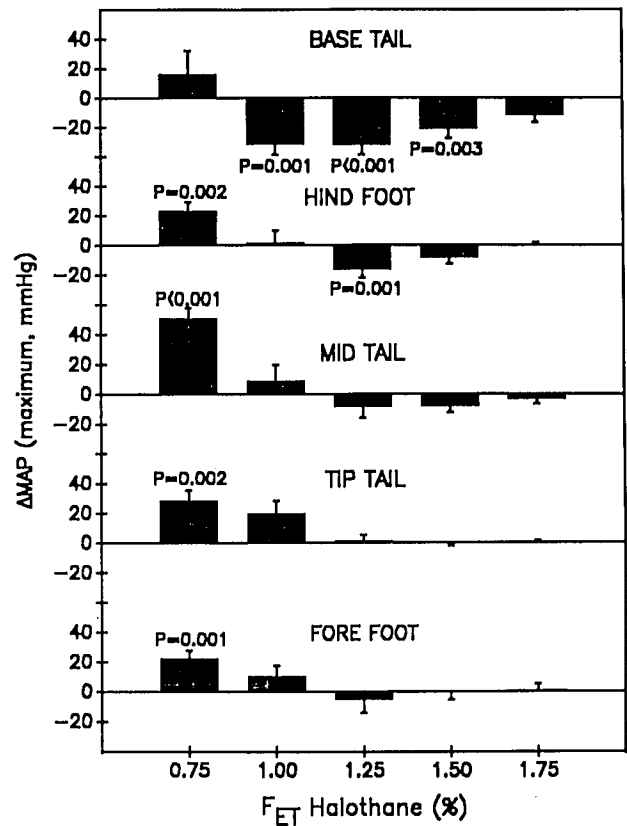


FIG. 5. Group 1 data. The effect of halothane on mean arterial pressure (ΔMAP) responses to noxious stimuli applied at different sites. Bars indicate mean \pm SEM, $n = 9$. P values obtained from one-tailed one-sample t tests (only P values ≤ 0.01 are presented).

to a pressor response if the F_{ET_H} is reduced to the control level. The F_{ET_H} at which depressor responses first occur varies between individual rats and the site of stimulation (fig. 5). However, at $F_{ET_H} = 0.75\%$ almost all responses are pressor, whereas at $F_{ET_H} \geq 1.25\%$, most responses are depressor. As such, the conversion from a pressor to a depressor response occurs at or near the halothane MAC value of 0.97%, which has been previously observed for rats of similar age and weight in our laboratory.¹² Increasing the F_{ET_H} above 1.25% results in a reduction of both pressor and depressor responses to noxious stimuli. Decreases in HR in response to noxious stimuli also occur but are less frequent than decreases in MAP (fig. 3).

The assumption that the MAP and HR increase in response to noxious stimuli in the awake state is supported by our own observations of almost exclusive increases in MAP and HR at the lowest F_{ET_H} studied (0.75%) and by previous reports of increased MAP and HR in response to noxious stimuli in unanesthetized animals.⁹ $F_{ET_H} = 0.75\%$ was chosen as our control because it is less than the reported MAC for the rat^{2,12} but is still high enough to prevent conscious perception of pain and to reduce reflex movement during stimulation. However, because

TABLE 2. The Effect of Halothane on the Frequency and Magnitude of Depressor Mean Arterial Pressure Responses at Different Sites

	F _{ET} Halothane				
	0.75% (Control) (n = 9)	1.00% (n = 9)	1.25% (n = 9)	1.50% (n = 9)	1.75% (n = 7)
Base-tail	22% (-61 ± 19)	100% (-32 ± 7)	100% (-32 ± 7)	100% (-22 ± 6)	70% (-18 ± 3)
Hind-foot	11% (0)	33% (-10 ± 3)	77% (-12 ± 3)	44% (-10 ± 1)	14% (0)
Mid-tail	0% (0)	44% (-20 ± 3)	66% (-21 ± 3)	77% (-13 ± 3)	42% (-9 ± 6)
Tip-tail	0% (0)	33% (-8)	33% (-26 ± 7)	22% (-22 ± 5)	0% (0)
Fore-foot	0% (0)	33% (-13 ± 4)	55% (-23 ± 10)	33% (-14 ± 8)	14% (-20)
Average (all sites)	7% (0)	48% (-13 ± 4)	66% (-23 ± 10)	55% (-14 ± 8)	28% (-20)

Values indicate percentage of responses that are depressor at each site. The magnitudes of the depressor response at each site are given

in parentheses (mean ± SEM, mmHg).

individual MAC values were not measured, it is possible that FET_H = 0.75% exceeded MAC for a small proportion of the rats studied.

The likelihood of obtaining a pressor or a depressor response depends not only on the FET_H, but also on the site of noxious stimulation. In our study, stimuli to the base-tail were associated with the highest incidence of depressor responses, and stimuli to the tip-tail were associated with the lowest. These site-related differences in the frequencies of the depressor responses are difficult to explain but may result, in part, from different sensitivities to noxious stimuli at different sites. Our stimuli to the tail were applied in a similar manner to stimuli in previous MAC studies in the rat, which have been shown to be supramaximal in obtaining movement responses.² However, Mazze *et al.* have observed that the same noxious stimulus results in a higher MAC when applied to the base-tail than it does when applied to the mid-tail.¹¹ This suggests that the base-tail is more sensitive than the mid-tail and indicates that equal stimuli, even though "supramaximal," may result in different magnitudes of response

at different sites. One possible explanation for the low incidence at the tip-tail may relate to a failure of our tail clamp to achieve a "supramaximal" stimulus at that site. The tail clamp was applied in a similar manner on each occasion. However, the diameter of the tail is smaller at the tip, and the clamp application may have been less intense at this site. Similarly, variations in the size of the perceived stimulus at other sites may have contributed to the overall site-related variability of response. Further work is necessary to determine the influence of the site of stimulation on the incidence of depressor responses. However, our results show that depressor responses can be produced by noxious stimuli at many different sites in the rat (table 2) and that the depressor responses are not limited to a local, site-related reflex. Moreover, other investigators have observed depressor responses at multiple sites in other species.^{8,9}

The mechanism of the depressor response is unclear but appears to be consistent with a central withdrawal of sympathetic tone. McLennan observed depressor responses to afferent nerve stimulation in rabbits anesthe-

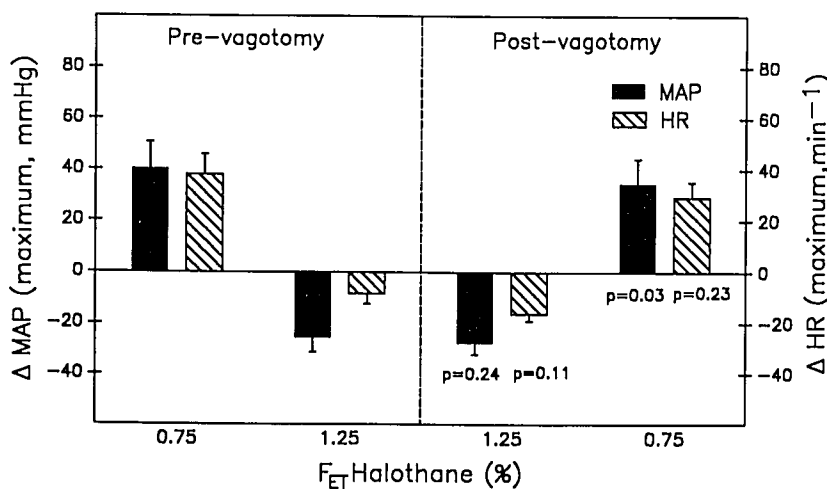
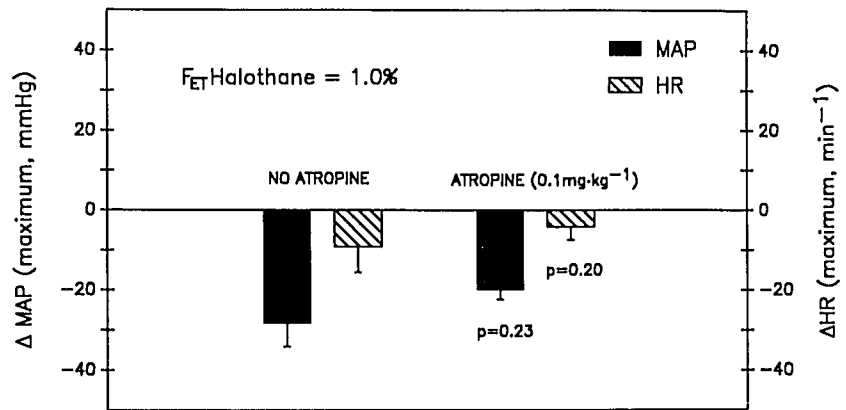


FIG. 6. Group 2a data. The effect of vagotomy on mean arterial pressure (Δ MAP) and heart rate (Δ HR) responses to base-tail clamp. Bars indicate mean \pm SEM, n = 6. (P values obtained from paired t tests comparing post-vagotomy values with prevagotomy values.) Refer to table 2 for prestimulus data.

FIG. 7. Group 2b data. The effect of muscarinic cholinergic blockade on mean arterial pressure (Δ MAP) and heart rate (Δ HR) responses to base-tail clamp. Bars indicate mean \pm SEM, $n = 6$. (P values obtained from paired t tests comparing values before and after the administration of atropine.) Refer to table 2 for prestimulus data.



tized with diethyl ether.⁹ He found that the depressor responses were associated with a reduction in sympathetic discharge from the renal nerve and concluded that the depressor responses resulted from a reduction in sympathetic outflow from the vasomotor center. Although we did not measure sympathetic outflow directly, we did find that, during the depressor response, there were concurrent decreases in CO and SVR (fig. 8), which would be consistent with a reduction in sympathetic output from the central nervous system. As such, our data support the conclusion of McLennan and expand the applicability of his findings to the rat and to halothane.

An alternative hypothesis is that the depressor responses result from active rather than passive vasodilation. Our results show that the depressor responses do not result from a vagal reflex (fig. 6) nor are they cholinergically mediated (fig. 7). Moreover, active vasodilation is more likely to be associated with a concurrent increase in CO rather than a decrease. Nevertheless, there are a number of other possible mediators of active vasodilation^{14,15} that need to be investigated before an active component to the depressor response can be completely discounted.

Our results also show that depressor responses do not result from reductions in heart rate alone and are not related to changes in central venous pressure. Despite the positive correlation ($r = +0.61$) between Δ MAP and Δ HR responses to noxious stimuli, large decreases in MAP were occasionally observed with no changes in heart rate or even with small increases (fig. 4), indicating that depressor responses can occur independent of changes in HR. The poor correlation ($r = +0.25$) between Δ MAP and Δ CVP responses to noxious stimuli indicates that the depressor responses are not related to a decrease in CVP.

Even if the hemodynamic mechanism of depressor responses can be established, there is still a need to determine how they can be induced by anesthetic agents. Noxious stimuli in the awake subject elicit an autonomic and hormonal response that equips the subject for a "fight or flight."¹⁶ That an anesthetic agent is able to obtund or abolish this response is expected. However, that an anesthetic agent should reverse this response is surprising,

particularly because anesthetic-induced depressor responses have not been described in humans. Further investigation is necessary to elucidate the mechanism by which halothane or other anesthetic agents induce depressor responses to noxious stimuli and to determine in which species this phenomenon can be observed. Moreover, continued investigation of depressor responses may be useful to examine not only the mechanisms by which halothane modifies hemodynamic responses to noxious stimuli, but also to examine mechanisms of hypotension and vasodilation during anesthesia.

The high incidence of depressor responses in the presence of halothane in the current study and the previous observations of depressor responses to noxious stimuli in other animals with the use of other anesthetic agents has important implications for small animal research. All investigators using rats or other laboratory animals should be aware of possible anesthetic-induced depressor responses to their interventions, which may confound their results and which will not be evident unless blood pressure is monitored. For example, examining movement re-

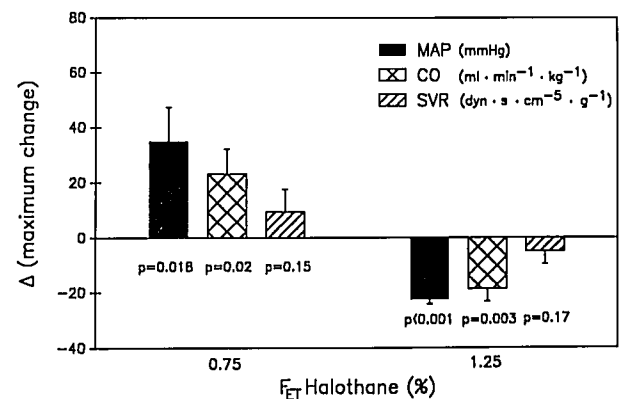


FIG. 8. Group 2c data. The effect of halothane on mean arterial pressure (Δ MAP), cardiac output (Δ CO), and systemic vascular resistance (Δ SVR) responses to base-tail clamp. (Note that the SVR units are per gram body weight, not per kilogram). Bars indicate mean \pm SEM, $n = 6$. (P values obtained from one-tailed one-sample t tests). Refer to table 2 for prestimulus data.

TABLE 3. Prestimulation (Baseline) Hemodynamic Data in Group 2

2A. Effect of Vagotomy F_{ET} Halothane	Prevagotomy		Postvagotomy	
	0.75%	1.25%	0.75%	1.25%
MAP (mmHg)	93 ± 6	82 ± 7	99 ± 6	85 ± 6
HR (min ⁻¹)	340 ± 14	322 ± 6	355 ± 10	338 ± 5
2B. Effect of Muscarinic Blockade	No Atropine		Atropine	
MAP (mmHg)	84 ± 3		87 ± 4	
HR (min ⁻¹)	317 ± 8		315 ± 8	
2C. Effect on Cardiac Output and Systemic Vascular Resistance F_{ET} Halothane	0.75%		1.25%	
MAP (mmHg)	82 ± 8		85 ± 6	
CO (ml · min ⁻¹ · kg ⁻¹)	140 ± 10		120 ± 12	
SVR (dyn · s · cm ⁻⁵ · g ⁻¹)	48 ± 6		60 ± 7	

Values indicate mean ± SEM (n = 6 in each subgroup).

sponses to tail clamping has been a common method of assessing the potency of anesthetic agents (MAC) in the rat, and it has been shown that interference with central catecholamine neurotransmitter release reduces halothane MAC in rats.¹⁷ Moreover, it has been shown that hypotension can also reduce MAC.² Our results demonstrate that, at least when halothane is used, base-tail clamping induces decreases in MAP of up to 80 mmHg and that this most likely results from a reduction of central sympathetic output. As such, it is possible that depressor responses may have confounded previous measurements of MAC in rats. Similarly, previous studies on the effect of anesthetic agents on HR responses to noxious stimuli in rats (which did not measure blood pressure) may have been confounded by large and unobserved decreases in MAP.⁶

In conclusion, halothane not only reduces the magnitude of pressor responses to noxious stimuli in the rat, but at a certain end-tidal concentration, at or near MAC, halothane frequently converts the pressor response to a depressor response. This effect is most consistently demonstrated by stimuli at the base of the tail. The depressor response is often, but not always, accompanied by decreases in HR and is associated with reductions in both CO and SVR. The presence of depressor responses indicates that MAP responses to noxious stimuli cannot be used as a linear index of anesthetic depth in the rat and that monitoring of both MAP and HR is necessary to correctly interpret data from animal experiments involving the application of noxious stimuli.

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