Yonsei Medical Journal
Vol. 45, No. 3, pp. 492 - 500, 2004

Effect of Enflurane on the Baroreflex Control of Heart Rate in Decerebrate Rats

Ki-Young Lee, Sang Bum Nam, Youn Woo Lee, Dong Woo Han, Nam Ryong Cho, and Jong Seok Lee

Department of Anesthesiology and Pain Medicine and Anesthesia and Pain Research Institute, Yonsei University College of Medicine, Seoul, Korea.

Volatile anesthetics alter the arterial baroreflex (BRX) but its mechanisms are poorly understood. This study was designed to determine the effect of 1 and 2 minimal alveolar concentrations (MAC) of enflurane on the BRX parameters in unanesthetized brain stem-intact and decerebrate rats. Under enflurane anesthesia, the femoral artery and both femoral vein were catheterized for pressor (phenylephrine) and depressor (nitroprusside) drug delivery and continuous blood pressure measurements. Decerebration was performed at midcollicular level. BRX tests were performed in 3 time periods; before enflurane (conscious brain-intact), during 1 or 2 MAC enflurane exposure 1 hour after a sham operation or a decerebration operation, and 2 hours after the termination of enflurane (zero enflurane). Mean arterial pressure (MAP) and heart rate (HR) were fitted to a sigmoid logistic equation, the Boltzman equation. The curve of best fit was obtained with a computer program. 1 MAC and 2 MAC of enflurane shifted MAP-HR baroreflex curves to the left in the all groups and significantly attenuated the baroreflex range. The slope of conscious intact period and zero enflurane period of each group did not change significantly, but during the enflurane period the slope was significantly lowered. Enflurane depressed the baroreflex sensitivity (slope) and the HR range in a similar dose-dependant manner in both brain stem-intact and decerebrate rats. Such results draw into question whether the suprapontine sites contribute to enflurane's actions on cardiovascular autonomic regulation.

Key Words: Baroreflex, enflurane, decerebration

Received December 29, 2003
Accepted May 14, 2004

This study was supported by a faculty research grant of Yonsei University College of Medicine for 2000. (No. 2000-04)

Reprint address: requests to Dr. Jong Seok Lee, M.D., Department of Anesthesiology and Pain medicine, Yongdong Severance Hospital, Yonsei University College of Medicine, 146-92 Dogok-dong, Kangnam-gu, Seoul 135-720, Korea. Tel: 82-2-3497-3524, Fax: 82-2-3463-0940, E-mail: jonglee@yumc.yonsei.ac.kr

INTRODUCTION

It is well known that volatile anesthetics, such as enflurane, alter the arterial baroreflex (BRX) in both human[1-3] and animals,[4-6] but its mechanisms are poorly understood. Enflurane has been shown to cause myocardial depression,[7] and the depression of blood pressure[8,9] and cardiac output.[8] However, it is not known whether the suprapontine central nervous system (CNS) regulatory sites are involved for heart rate (HR) - BRX depression effects of enflurane. The autonomic nervous system reflex has sensors, afferent pathways, CNS integration, and efferent pathways to the receptors and efferent organs.[10] Cardiovascular afferents converge initially on the dorsomedial portion of the nucleus tractus solitarius (NTS).[11-13] Reflex experiments in conscious and anesthetized animals suggests that the NTS, particularly the medial portions, is absolutely essential to BRX integrity.[14] Lesions or pharmacological blocked of the NTS effectively eliminate BRX responses. Electrical or pharmacological (e.g. excitatory amino acid) activation of the medial NTS mimics BRX responses by evoking decreases in HR, blood pressure (BP) and sympathetic nerve activity. Infracollicular or midcollicular decerebration has no effect on BRXs for some anesthetics (e.g., ketamine, isoflurane), whereas other agents (e.g., althesin) depressed the HR-BRX to a greater degree after decerebration.[15,16] Although the effect of decerebration upon the cardiovascular and respiratory response were examined in decerebrate animal, there have been no reports determining the effect of enflurane anesthesia on BRX parameters in decerebrate rats. Therefore, we hypothe-

sized that the suprapontine CNS sites are not required for depression of the BRX control of HR during enflurane anesthesia. To verify the aforementioned hypothesis, we experimented with the BRX control of HR on brain stem-intact rats and decerebrate rats during anesthesia with 1 minimal alveolar concentration (MAC) and 2 MAC enflurane. We also tested the BRX in unanesthetized and decerebrate rats after the completion of anesthesia.

MATERIALS AND METHODS

Preparation for study of conscious rats

Our experiments adhered to the "Guiding Principles in the Care and Use of Animals" of the American Physiological Society. The experiments were performed in 24 male Sprague-Dawley each weighing between 300 g and 400 g (339 ± 22.8 g). For anesthetic induction the rats were placed in a box containing 5% enflurane in 100% oxygen for 6 minutes. They were then transferred to an inclined platform, intubated with a 16 gauge intravenous catheter, and adequate anesthesia was maintained with enflurane (2.5%) and oxygen. The left and right femoral veins were canulated with polyethylene catheters 10 (PE 10) for the drug administration. The left femoral artery was similarly catheterized with PE 50 for continuous blood pressure measurements and blood sampling. The catheters were kept patent with a heparinized saline and they were routed subcutaneously to the neck and externalized. Three stainless wire electrodes were placed under the skin for electrocardiographic monitoring. Rats were treated prophylactically with a subdermal injection of amoxicillin (150 mg/kg) on the day of surgery and every other day thereafter. The BRX studies were performed 24 h after the preparatory surgery.

Experimental protocol

The rats were divided into four groups (n=6 in each group). A sham operation as a control was performed in two groups and decerebration was performed in another two groups. The effects of 1 or 2 MAC enflurane (rat, 2.21 or 4.42%)[17] were studied in each group. BRX tests were performed in 3 time periods of before, during and after 1 or 2 MAC enflurane exposures. During the sham or decerebration operations, anesthesia was maintained with 2.5% enflurane. When these preparations were completed, enflurane was adjusted to achieve an end-tidal concentration of 1 or 2 MAC.

The rats were ventilated with a stroke volume of 10 ml/kg body weights at a respiratory rate of 60 breaths/min, or to keep the end-tidal CO_2 at about 30 mmHg. End-tidal CO_2, inspired O_2, enflurane concentration, and ECG were monitored continuously while the rats were intubated (Vitalmax 4100, PaceTech Inc., Clearwater, FL, USA). Arterial blood samples were collected for the measurement of arterial blood gas tensions and plasma concentrations of Na^+ and K^+ before each experiment period, and these parameters were measured using a blood gas analyzing system (GEM Premier 3000, Instrumentation Laboratory, Lexington, MA, USA). If signs of respiratory depression were observed with this procedure, the experiment on this rat was stopped and the data was excluded from the present study. Body temperature was maintained at 37℃ by a temperature-controlled heating table. After initial conscious intact measurements were taken, including the BRX tests, the rats were anesthetized, and either a decerebration or a sham operation was then performed. When these measurements were completed, anesthesia was halted, and the animals were allowed to recover for 2 h (zero enflurane). The rats were then extubated and the BRX test was repeated in the absence of enflurane.

BP and HR measurements and baroreceptor reflex studies

On the day of the experiment, each rat was placed in a rat restrainer. The arterial catheter was connected to a pressure transducer to monitor the pulsatile arterial pressure. The blood pressure signal was digitally sampled by a data acquisition system (PowerLab; AD Instruments, Colorado Springs, CO, USA). Changes of MAP and HR were elicited by injecting i.v. 0.2-10 μg/kg of phenylephrine and 1-50 μg/kg sodium nitroprusside, and these injections were given with a 10 μl

or 50 μl glass syringe according to the method of Head and McCarty.[18] Mean arterial pressure (MAP) and HR were recorded continuously before the onset of injection and during the peak HR of each injection. Arterial pressure was raised and lowered by alternating injections of graded (1-50 μl i.v) doses of phenylephrine and nitroprusside respectively. A sufficient time was allowed for both the MAP and HR to return to resting values between each injection.

Peak values of MAP and HR were fitted by nonlinear regression analysis to the logistic sigmoidal equation (Boltzman's equation). The logistic equation was as follows:

$HR = A_1 - A_2/[1 + e^{(MAP - Xo)}/dx] + A_2$,

Where A_1 = higher HR, A_2 = lower HR, A_1-A_2 = HR range, Xo = BP_{50} (MAP at half the HR range), dx = a curvature coefficient that is independent of range. The average gain (G) or slope of the curve was given by

$G = -(A_1-A_2)/dx \times 4.56$.

The curve of best fit was obtained with a computer program (Origin 6.1; Origin Labs, Northampton, MA, USA), which utilized a least-squared iterative routine based on the Botlzman's equation. Individual stimulus-response curves and thus, the parameters estimate and gain values were generated for each rat. All curves were forced to go through the average basal values of MAP and HR. In every case, the correctness of fit was determined by the percentage of the total sums of squares that were accounted for by the model. The parameter estimates were averaged for separate treatment groups. Finally, the averaged parameter estimates were used to generate a single stimulus-response curve for each treatment group for the graphic presentation of results.

Decerebration

The rats were decerebrated at the midcollicular level by a modification of the Faber et al's technique (Fig. 1).[19] Under enflurane anesthesia, the tracheas of the rats were intubated and placed in the stereotaxic instrument (DJ 2-204, Korea Daejong Co, Seoul, Korea). After the midline

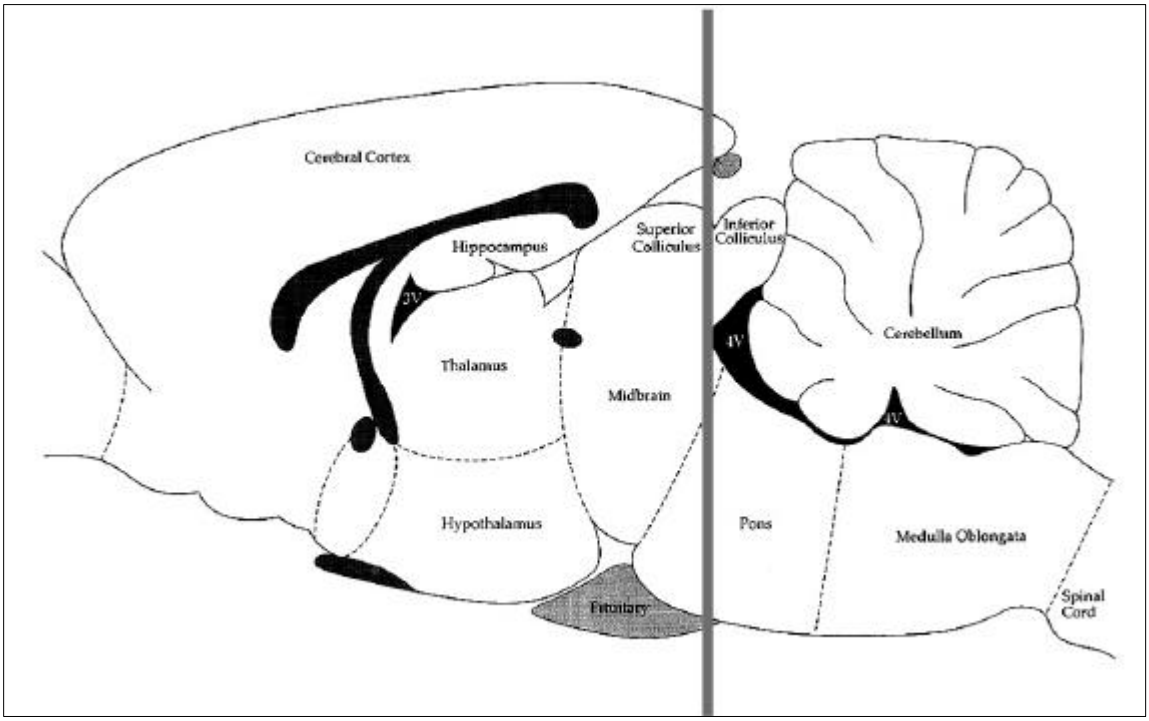

Fig. 1. A schematic representation of the midcollicular transection modified from the method of Paxinos and Watson.20 The area 6.5 mm posterior to the bregma was transected. The heavily stippled line represents the target transection lesion. CNS structures rostral to the line, i.e., cerebral cortex, hippocampus, thalamus, hypothalamus and midbrain were physiologically and anatomically isolated from the pons and medulla.

incision was made, the muscle and skin was retracted to the sides to expose the cranium. The cranium was removed laterally 6.5 mm posterior to the bregma with a power-driven No. 8 dental burr drill. After removal of the dura, the tip of a hooked-knife blade was set on the midline 6.5 mm caudal from the bregma, and then the lateral edge of the blade was placed at the lateral extent of the craniotomy furrow, according to the atlas of Paxinos and Watson.[20] The knife was slowly lowered through the brain until an ipsilateral blink reflex was observed. The knife was then moved medially until the tip was just beyond the midline, at which point it was raised to transect the brain. The knife was then removed and the same procedure followed on the other side. Sham operations were performed with identical procedures in the non-decerebrate rats with the exception of the decerebration knife cut. After these BRX experiments the brains in the experimental rat groups were removed and examined to verify the presence of a complete midcollicular brain stem transection. If the decerebration was incomplete, the data were excluded from the present study.

Statistical analysis

Measurement data of resting MAP and HR, slope, dx, A_1, A_2, BP_{50} were averaged. MAP-HR BRX curves were obtained in each condition (before intervention, during enflurane anesthesia, and zero enflurane) in each animal. Comparisons among mean values of the parameters were made within and between groups by repeated-measures of two-way analysis of variance. For significant interactions, the Scheffe F test was used for post hoc comparisons (StatView, SAS Institute Inc., Cary, NC, USA). *P* values of less than 0.05 were considered significant. All data are expressed as means ± SD.

RESULTS

The average values of basal MAP and HR

Table 1. Average Values of Resting MAP, HR, and Baroreflex Parameters in Intact and Decerebrate rats

Group		Brain-stem Intact			Decerebrate		
		Conscious Intact	Enflurane	Zero Enflurane	Conscious Intact	Enflurane	Zero Enflurane
1 MAC	Basal MAP (mmHg)	115 ± 2.0	97 ± 6.7*†	123 ± 3.3	120 ± 3.1	88 ± 4.8*†	120 ± 7.3
	Basal HR (beats/min)	354 ± 9.6	274 ± 7.3*†	358 ± 7.9	371 ± 16.1	278 ± 11.8*†	326 ± 16.5
	A1 (beats/min)	474 ± 12.8	281 ± 28.3*†	496 ± 13.3	522 ± 18.6	305 ± 27.8*†	513 ± 36.5
	A2 (beats/min)	220 ± 27.3	212 ± 34.5	190 ± 14.3	224 ± 23.4	232 ± 30.1	188 ± 42.5
	HR range (beats/min)	254 ± 20.1	69 ± 21.5*†	306 ± 12.3	298 ± 16.2	73 ± 18.3*†	325 ± 29.5
	BP50 (mmHg)	120 ± 8.5	113 ± 9.7	130 ± 7.8	127 ± 8.9	131 ± 5.9	134 ± 15.8
	Slope (beats/min/mmHg)	-3.7 ± 0.85	-1.9 ± 0.32*†	-3.3 ± 0.4	-3.1 ± 0.78	-1.8 ± 0.18*†	-3.1 ± 0.32
2 MAC	Basal MAP (mmHg)	118 ± 4.0	80 ± 3.1*†‡	125 ± 3.1	116 ± 1.9	72 ± 2.0*†‡	119 ± 2.0
	Basal HR (beats/min)	346 ± 6.8	258 ± 4.5*†	347 ± 8.0	354 ± 8.9	239 ± 13.8*†	328 ± 8.1
	A1 (beats/min)	460 ± 28.5	259 ± 17.3*†‡	460 ± 23.8	455 ± 33.6	237 ± 28.4*†‡	452 ± 34.7
	A2 (beats/min)	244 ± 30.5	242 ± 10.2	220 ± 15.3	185 ± 26.3	223 ± 21.6*†	180 ± 20.8
	HR range (beats/min)	216 ± 33.3	17 ± 13.7*†‡	240 ± 34.5	269 ± 30.5	14 ± 5.8*†‡	272 ± 42.1
	BP50 (mmHg)	121 ± 9.3	80 ± 5.6*†‡	132 ± 30.5	133 ± 4.5	70 ± 9.7*†‡	111 ± 7.8
	Slope (beats/min/mmHg)	-2.6 ± 0.4	-0.7 ± 0.1*†‡	-2.5 ± 0.3	-2.9 ± 0.6	-0.5 ± 0.1*†‡	-3.3 ± 0.3

Values are mean ± SD. N = 6 in each group.
*$p<0.05$ between enflurane and conscious intact; †$p<0.05$ significant difference from zero enflurane; ‡Significanct difference between. respective 1 and 2 minimum alveolar concentration (MAC; $p<0.05$). MAP = Mean Arterial Pressure; HR = Heart Rate. A1 = upper HR. plateau; A1 = upper HR plateau; A1 = upper HR plateau; A2 = lower HR plateau; HR range = difference between upper and lower HR. plateau; BP50 = MAP at half HR range.

during the conscious intact period were similar among all groups (Table 1). The values of conscious intact and zero enflurane periods were similar in brain intact rats and decerebrate rats. Enflurane caused a reduction in the basal MAP at the 1 and 2 MAC enflurane anesthetized periods in a dose dependent manner in the sham rats as well as in decerebrate rats. Enflurane decreased the basal HR, but there was no significant difference between the 1 and 2 MAC enflurane.

The effects of 1 or 2 MAC enflurane on BRX function parameters after the sham operation or decerebration are shown in Fig. 2. Each curve represents an average of 6 curves for brain intact, 1 or 2 MAC enflurane after the sham operation or decerebration, and 2 hours after the enflurane anesthesia was finished. At 1 MAC and 2 MAC sham, in comparing the pre-decerebration (conscious intact) to post decerebration (zero enflurane) the BRX parameters (slope, HR range, A_1, A_2, and BP_{50}) were quite similar. However, at 2 MAC decerebrate, enflurane shifted BP_{50} to a lower pressure (Fig. 2, Table 1). Enflurane depressed the HR range and BRX sensitivity in a

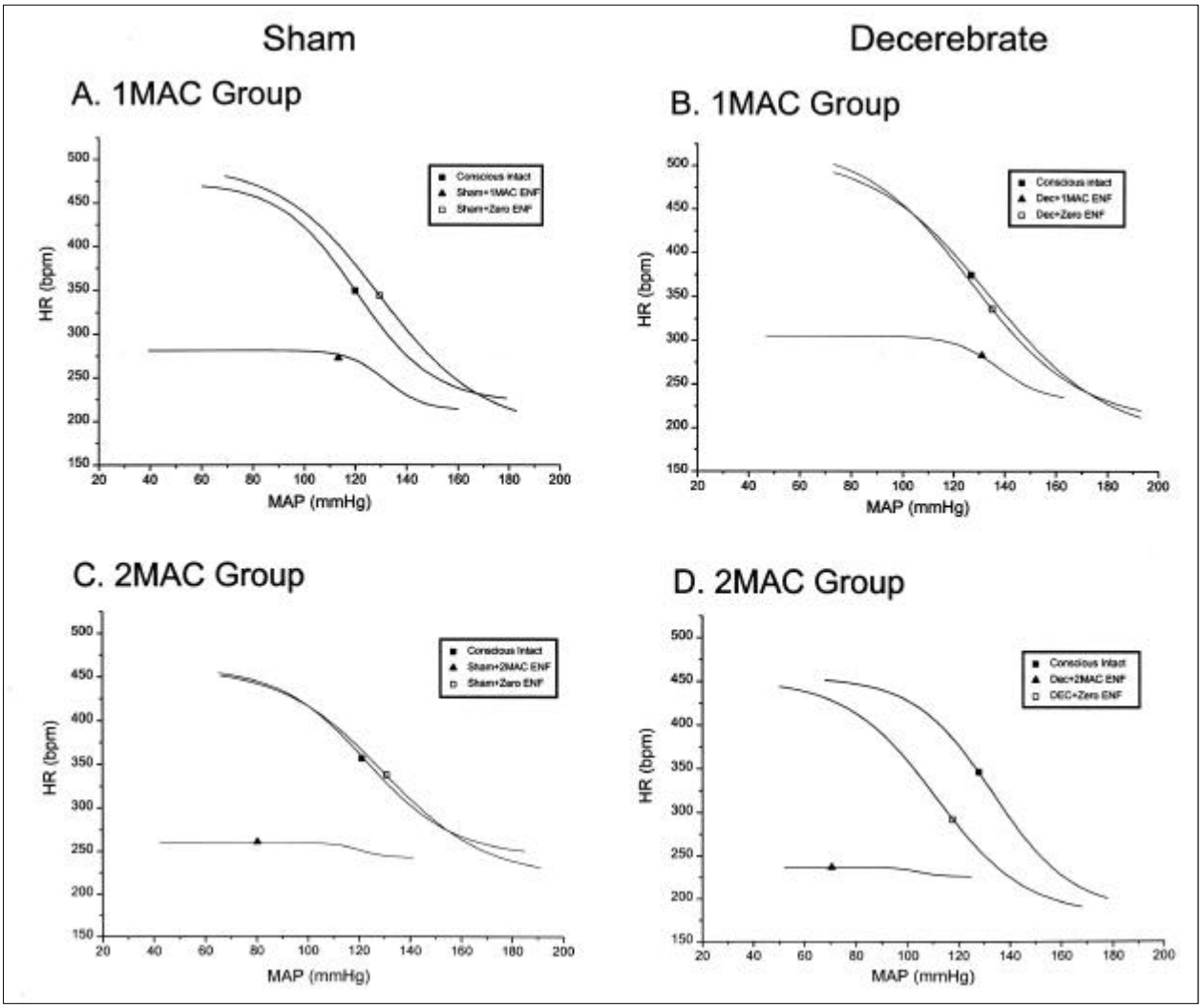

Fig. 2. Effects of enflurane on mean arterial pressure -heart rate baroreflex curves for brain intact/sham (A and C) and decerebrate (B and D) rats. Each panel shows curves for the following conditions: (1) before enflurane (conscious intact); (2) during enflurane (1 or 2 minimum alveolar concentration exposure after sham or decerebration; and (3) after recovery from enflurane (zero enflurane). Note that even 1 MAC enflurane depressed the tachycardia portion of the curves to a greater extent than the bradycardia portion. The curves represent an average baroreflex curve for six animals. Closed circles indicate the resting level of MAP and HR for each curve. bpm = beats/min.

similar dose-dependant manner in both brain stem intact and decerebrate rats. At 1 MAC, enflurane reduced the BRX-HR range by predominantly depressing the upper plateau (A_1) and sparing the lower HR plateau (A_2). At this enflurane level, decreasing the BP with nitroprusside evoked little increase in HR, whereas phenylephrine-induced increases in BP elicited a substantial decrease in HR. At 2 MAC, enflurane depressed the upper plateaus and shifted BP_{50} to a lower pressure for both intact and decerebrate rats. At this enflurane level, the low plateaus were significantly shifted upward for the decerebrate rats.

Arterial blood gas tensions (pHa, $PaCO_2$, PaO_2), electrolytes (Na^+ and K^+), and hematocrit showed similar basic characteristics between the brain intact and decerebrate rats (Table 2). However, PaO_2 was higher during the enflurane anesthesia period compared with other time periods because oxygen was administered together with the enflurane. PaO_2 of the zero enflurane period was higher compared to the conscious intact period because supplemental oxygen was administered by a mask.

DISCUSSION

In this study, we examined not only a standard BRX test, but also the responses produced after decerebration of the rats under enflurane anesthesia and a non-anesthetic state. We observed that enflurane depressed the BRX control of HR similarly, whether the suprapontine portions of the brain were intact or not. This finding is consistent with a previous study using other anesthetics.[15,16] Since enflurane depressed the BRX function equally both in intact and decerebrate rats for a given MAC, anesthetic depression of the BRX clearly does not require the suprapontine CNS regulatory sites such as cortex, thalamus or hypothalamus. Our results, however, did not identify the sites of enflurane BRX depression

Table 2. Arterial Blood Gases, Hematocrit, Plasma Sodium and Potassium Concentration

		Brain-stem Intact			Decerebrate		
		Conscious Intact	Enflurane	Zero Enflurane	Conscious Intact	Enflurane	Zero Enflurane
1 MAC	pHa	7.46 ± 0.03	7.48 ± 0.02	7.51 ± 0.03	7.48 ± 0.03	7.51 ± 0.02	7.45 ± 0.05
	$PaCO_2$ (mmHg)	36 ± 3	33 ± 1	34 ± 5	35 ± 1	34 ± 3	37 ± 3
	PaO_2 (mmHg)	81 ± 1‡	510 ± 28*†	152 ± 21	84 ± 5‡	487 ± 59*†	168 ± 68
	O_2 Sat (%)	97 ± 1	99.9*†	98 ± 2	97 ± 1	100*†	98 ± 2
	HCO_3 (mmol/L)	31 ± 2	28 ± 1	27 ± 2	30 ± 1	27 ± 2	28 ± 3
	Na^+ (mEq/L)	144 ± 2	142 ± 2	144 ± 1	143 ± 1	140 ± 1	145 ± 5
	K^+ (mEq/L)	4.1 ± 0.4	4.0 ± 0.8	4.5 ± 0.7	4.3 ± 0.2	4.3 ± 0.2	4.0 ± 0.3
	Hematocrit	44 ± 2	44 ± 2	43 ± 1	43 ± 4	45 ± 3	43 ± 4
2 MAC	pHa	7.51 ± 0.01	7.49 ± 0.03	7.47 ± 0.04	7.48 ± 0.04	7.51 ± 0.04	7.45 ± 0.06
	$PaCO_2$ (mmHg)	35 ± 2	32 ± 2	36 ± 6	38 ± 3	33 ± 3	38 ± 6
	PaO_2 (mmHg)	85 ± 6‡	460 ± 68*†	190 ± 43	79 ± 5‡	475 ± 28*†	184 ± 77
	O_2 Sat (%)	97 ± 1	99.9*†	97 ± 2	97 ± 1	99 ± 1†	98 ± 2
	HCO_3 (mmol/L)	30 ± 1	28 ± 1	28 ± 3	30 ± 2	29 ± 3	29 ± 2
	Na^+ (mEq/L)	145 ± 2	141 ± 3	142 ± 3	144 ± 2	141 ± 4	145 ± 5
	K^+ (mEq/L)	4.1 ± 0.4	4.4 ± 0.6	3.9 ± 0.4	4.1 ± 0.2	4.5 ± 0.5	3.9 ± 0.4
	Hematocrit	44 ± 3	43 ± 2	43 ± 2	45 ± 2	43 ± 1	44 ± 2

Mean ± SD *$p<0.05$ Significant difference from zero enflurane; †$p<0.05$ Significant difference between enflurane and conscious intact; ‡$p<0.05$ between zero enflurane and conscious intact; N = 6 in each group.

within the BRX pathways. Seagard et al. and other investigators have documented that anesthetics work at multiple sites along the reflex chain, including carotid baroreceptors, afferent nerve pathways within the central nervous system, ganglia, efferent nerve pathways and the neuro effector junction.[4,21,22] BRX control of HR can be accomplished with the CNS structure in or below the pons,[12,15,16] and volatile anesthetics can depress the medullary cardiovascular centers.[23,24] Direct microinjection of halothane into the medulla in decerebrate dogs depressed BP responses to electrical stimulation of medullary pressor and depressor areas.[23] In dissociated NTS neurons (at the first synapse of the afferent baroreceptors fiber terminals in the medulla) of the rat, halothane and enflurane reduced the glutamate induced excitatory responses and enhanced the GABA responses.[24] Such results support the notion that the supramedullary sites do not contribute to alterations in the BRX control of HR during enflurane anesthesia.

The present investigation did not assess sympathetic and parasympathetic contributions to the changes in BRX characteristics that occurred with decerebration or with enflurane. Our data, however, suggests that enflurane depresses the sympathetic components of the HR-BRX because enflurane decreased BRX tachycardia elicited by decreases in BP, whereas reflex bradycardia occurring for increases in BP remained largely unaffected. These bradycardic BRX responses are primarily due to the activation of parasympathetic activity, while the tachycardic BRX responses often involve both sympathetic activation and vagal inhibition.[18] We examined the relationship between MAP and HR using graded bolus i.v. doses of vasopressor (phenylephrine) and depressor (sodium nitroprusside) drugs to produce reflex bradycardia and tachycardia. This method of BRX measurement offers a more comprehensive assessment, including the direct measurement of the full pressure-response range of the BRX in each condition.[18]

Studies in both man1 and animals[5] have been demonstrated that enflurane anesthesia may depress the BRX. Enflurane might potentially depress BRX control of HR by affecting any of several components of the pathway: the sensory limb at the arterial baroreceptor or at the vessel wall in which these sensory endings are embedded, the CNS portions of the reflex including synaptic transmission or associated ion channel, and the efferent pathways and/or the peripheral effectors themselves such as cardiac myocytes. These findings are generally similar to the reports of experiments with isoflurane.[16,25] Although isoflurane has a better preservation of baroreflex responsiveness than does halothane and enflurane, all these anesthetics diminish baroreflex sensitivity.[1,4,26,27]

Hypotension induced by inhalation anesthetics is caused by vasodilatation, decreased cardiac output due to myocardial depression, and decreased sympathetic nervous system tone. With enflurane, the decreased basal level of sympathetic nerve activity could contribute to enflurane-induced cardiac depression or a reduction of peripheral vascular tone, which may result in hypotension.[26] In the present study, enflurane caused a significant decrease in the blood pressure of rats in a dose-dependent manner and HR was decreased, but there was no significant difference between 1 MAC and 2 MAC enflurane.

Many factors can influence the HR-BRX performance. Potentially complicating factors such as an acid-base abnormality,[28] changes in Na^+,[29,30] K^+,[30] and plasma concentration or blood pressure[31-34] might alter the BRX control of HR. In our study, these parameters remained within normal ranges during enflurane period, except for an increased PaO_2.

Decerebration preparation is commonly used in cardiovascular and neurological studies when an unanesthetized animal model preparation is required. Transection at the midcollicular level disrupts all spinal and lower cranial nerve (V through XII) sensory input to the thalamus, hypothalamus and cortex. Since the major cardiovascular regulation centers are located in the pons and medulla, decerebrate preparation at the midcollicular level has been shown to have only minimal effects on resting cardiovascular parameters and on reflex responses to BRX and chemoreceptor stimulation in most species. Our midcollicular decerebration did not alter resting MAP, HR or HR-BRX, and this result was consistent with previous reports.[16,35,36] However, there

are conflicting reports on the effects of decerebration on MAP and HR. Sapru et al.[37] reported that midcollicular decerebration decreased MAP and HR in adult Wistar rats. In another study, MAP and HR were increased in Sprague-Dawley rats,[38,39] whereas Faber at al's[19] study found that MAP was slightly lower and HR was significantly higher than the values for conscious unrestrained rats. Decerebration does not alter respiration in rats. Although we did not determine the respiratory rate and per-minute ventilatory volume, the blood $PaCO_2$, PaO_2 and pH were not significantly different among the experiment periods within the groups. These data together with the observations by Sapru et al.[37] and Faber et al.[19] for midcollicular decerebrate rats provide evidence that, with the exception of HR change, decerebration does not significantly alter the cardiovascular or respiratory homeostatic mechanism in the rat.

In summary, when the influence of enflurane anesthesia was removed in decerebrate rats (zero enflurane), injections of graded doses of phenylephrine and nitroprusside did not alter HR-BRX function, and enflurane depressed the HR-BRX control in a dose dependent manner. Although we did not identify the specific sites of the BRX pathways, the results suggest that enflurane depresses HR-BRX function by acting on sites at or below the pontine CNS regulatory sites. Future studies will be aimed at the cellular targets and mechanisms affected within the brain stem, and these targets are likely to include the neurotransmitter receptors and ion channels involved in synaptic transmission and the excitability on neurons involved in BRX control within the NTS, the ventrolateral medulla and nucleus ambigus.

REFERENCES

1. Morton M, Duke PC, Ong B. Baroreflex control of heart rate in man awake and during enflurane and enflurane-nitrous oxide anesthesia. Anesthesiology 1980;52:221-3.
2. Kotrly KJ, Ebert TJ, Vucins E, Igler FO, Barney JA, Kampine JP. Baroreceptor reflex control of heart rate during isoflurane anesthesia in humans. Anesthesiology 1984;60:173-9.
3. Takeshima R, Dohi S. Comparision of arterial BRX function in humans anesthetized with enflurane or isoflurane. Anesth Analg 1989;69:284-90.
4. Seagard JL, Elegbe EO, Hopp FA, Bosnjak ZJ, von Colditz JH, Kalbfleisch JH, et al. Effects of isoflurane on the baroreceptor reflex. Anesthesiology 1983;59:511-20.
5. Skovsted P, Price HL. The effects of ethrane on arterial pressure, preganglionic sympathetic activity, and barostatic reflexes. Anesthesiology 1972;36:257-62.
6. Sellgren J, Biber B, Hemriksson BA, Martner J, Ponten J. The effects of propofol, methohexitone and isoflurane on the baroreceptor reflex in the cat. Acta Anesthesiol Scand 1992;36:784-90.
7. Shimosato S, Sugai N, Iwatsuki N, Etsten BE. The effect of ethrane on cardiac muscle mechanics. Anesthesiology 1969;30:513-8.
8. Dobkin A, Henrich RG, Israel JS, Levy AA, Neville JF Jr, Ounkasem K. Clinical and laboratory evaluation of a new inhalation agent: Compound 347 (CHF2-O-CF2-CHF-CL). Anesthesiology 1968;29:275-87.
9. Botty C, Brown B, Stanley V, Stephen CR. Clinical experiences with Compound 347, a halogenated anesthetic agent. Anesth Analg (Clev) 1968;47:499-505.
10. Barash PG, Cullen BF, Stoelting RK. Clinical anesthesia, 4th ed. Philadelphia: Lippincott-Raven Publishers; 2001. p.280-2.
11. Kumada M, Terui N, Kuwaki T. Arterial barorecetpr reflex: its central and peripheral neural mechanisms. Prog Neurobiol 1990;35:331-61.
12. Loewy AD. Central autonomic pathways. In: Loewy AD, Spyer KM, editors. Central Regulation of Autonomic Functions. New York: Oxford Univ. Press; 1990. p.88-103.
13. Van Giersbergen PLM, Palkovits M, De Jong W. Involvement of neurotransmitters in the nucleus tractus solitarius in the rabbit. Brain Res 1992;72:789-824.
14. Reis DJ. The brain and hypertension: reflections on 35 years of inquiry into the neurobiology of the circulation. Circulation 1984;70(SIII):31-45.
15. Blake DW, Korner PI. Effects of ketamine and althesin anesthesia on baroreceptor-heart rate reflex and hemodynamics of intact and pontine rabbits. J Auton Nerv Syst 1982;5:145-54.
16. Lee JS, Andreson MC, Morrow DR, Chang KSK. Isoflurane depresses BRX control of heart rate in decerebrate rats. Anesthesiology 2002;96:1214-22.
17. Mazze RI, Rice SA, Baaen JM. Halothane, isoflurane, and enflurane MAC in pregnant and nonpregnant female and male mice and rats. Anesthesiology 1985;62: 339-41.
18. Head GA, McCarty R. Vagal and sympathetic components of heart rate range and gain of the baroreceptor-heart rate reflex in conscious rats. J Auton Nerv Syst 1987;21:203-13.
19. Faber JE, Harris PD, Wiegman DL. Anesthetic depression of microcirculation, central hemodynamics, and respiration in decerebrate rats. Am J Physiol 1982;243: H837-43.
20. Paxinos G, Watson C. The rat brain in stereotaxic coordinates, 4th ed. San Diego: Academic Press; 1998.

figure 79-96.
21. Seagard JL, Hopp FA, Bosnjak ZJ, Osborn JL, Kampine JP. Sympathetic efferent nerve activity in conscious and isoflurane-anesthetized dogs. Anesthesiology 1984;61: 266-70.
22. Segard JL, Hopp FA, Donegan JH, Kalbfleisch JH, Kampine JP. Halothane and the carotid sinus reflex: Evidence for multiple sites of action. Anesthesiology 1982;57:191-202.
23. Price HL, Price ML, Morse HT. Effects of cycloprofane, halothane and procaine on the vasomotor center of the dog. Anesthesiology 1965;26:55-60.
24. Wakamori M, Ikemoto Y, Akaike N. Effects of two volatile anesthetics and a volatile convulsant on the excitatory and inhibitory amino acid responses in dissociated CNS neurons of the rat. J Neurophysiol 1991;66:2014-21.
25. Bell LB. Baroreflex modulation by isoflurane anesthesia in normotensive and chronically hypertensive rabbits. Adv Pharmacol 1994;31:389-408.
26. Saeki Y, Hasegawa Y, Shibamoto T, Yamaguchi Y, Hayashi T, Tanaka S, et al. The effects of sevoflurane, enflurane, and isoflurane on baroreceptor-sympathetic reflex in rabbits. Anesth Analg 1996;82:342-8 .
27. Muzi M, Ebert TJ. Randomized, prospective comparison of halothane, isoflurane, and enflurane on BRX control of heart rate in humans. Adv Pharmacol 1994;31:379-87.
28. Watanabe Y, Dohi S, Iida H, Ishiyama T. The effects of bupivacaine and ropivacaine on BRX sensitivity with or without respiratory acidosis and alkalosis in rats. Anesth Analg 1997;84:398-404.
29. Ferrario CM, Tramposch A, Kawano Y, Brosnihan KB. Sodium balance and the reflex regulation baroreceptor function. Circulation 1987;75(Suppl I)I:141-8.
30. Andresen MC, Kuraoka S, Brown AM. Individual and combined actions of calcium, sodium, and potassium ions on baroreceptors in the rat. Circ Res 1979;45: 757-63.
31. Kedzi P. The baroreceptors in hypertension and hypotension, Baroreceptors and Hypertension. Toronto: Pergamon Press; 1967. p.301-8.
32. Bristow JD, Honour AJ, Pickering GW, Sleight P, Smyth HS. Diminished BRX sensitivity in high blood pressure. Circulation 1969;39:48-54.
33. Boerbom LE, Werner PH, Donergan JH, Zuperku EJ, Bonchek LI, Kampine JP. Coarctation of the aorta and baroreceptor resetting. A study of carotid baroreceptor stimulus response characteristics before and after surgical repair in the dog. Circ Res 1981;48:365-71.
34. Igler FO, Donegan JH, Hoo KC, Korns ME, Kampine JP. Chronic localized hypotension and resetting of carotid sinus baroreceptors electrophysiological and histological studies in the dog. Circ Res 1981;49:649-54.
35. Korner PI, Uther JB, White SW. Central nervous integration of the circulatory and respiratory responses to arterial hypoxemia in the rabbit. Circ Res 1969;24: 757-76.
36. Chai CY, Share NN, Wang SC. Central control of sympathetic cardiac augmentation in lower brain stem of the cat. Am J Physiol 1963;205:749-53.
37. Sapru HN, Krieger AJ. Cardiovascular and respiratory effects of some anesthetics in the decerebrate rat. Eur J Pharmacol 1979;53:151-8.
38. Gomes C, Trolin G. Circulatory effects of decerebration in the unanesthetized spontaneously hypertensive rat. Acta Physiol Scand 1980;108:201-3.
39. Trolin G. Involvement of a-adrenergic receptors at different levels of the central nervous system in the regulation of blood pressure and heart frequency. Acta Physiol Scand Suppl 1975;430:3-41.