

Halothane Depresses Baroreflex Control of Heart Rate in Man

Peter C. Duke, M.D., F.R.C.P. (C),* Douglas Fownes, B.Sc.,† John G. Wade, M.D., F.R.C.P. (C)‡

Baroreflex control of heart rate was determined during three awake control situations and during two depths of halothane anesthesia in man. Baroreflex function was quantitated by calculating the pressor test slope from the R-R interval change on the ECG produced by a pharmacologically induced pressor response. During the three awake control situations the subjects breathed room air or 100 per cent O₂ spontaneously or 100 per cent O₂ with ventilation controlled. Mean (\pm SD) slopes obtained were 15.1 ± 4.5 , 15.6 ± 6.8 and 18.4 ± 9.9 , respectively. No significant difference in baroreflex function slope was observed. During light halothane anesthesia (0.7 per cent end-tidal) baroreflex function was significantly depressed (mean slope = 2.5 ± 1.5), and it was abolished at 1.1 per cent end-tidal halothane (mean slope = 0.03 ± 0.04). It is concluded that halothane anesthesia produces depression of baroreflex control of heart rate in man. (Key words: Anesthetics, volatile, halothane; Receptors, pressor; Reflexes, baro-.)

HALOTHANE ANESTHESIA induces hypotension without a compensatory tachycardia, suggesting some impairment of cardiovascular homeostatic mechanisms such as baroreflex function.¹

Studies of the effects of individual anesthetics on cardiovascular reflex control in man are lacking. Bristow *et al.* studied the effects of N₂O-halothane anesthesia on baroreflex control of heart rate in man, but only after premedication with meperidine and induction of anesthesia with thiopental.² They found that baroreflex function was depressed, but it is impossible to determine from their data what the effect of halothane alone on the reflex might be, because meperidine³ and thiopental⁴ are known to affect cardiovascular baroreflexes. Further, anesthetic depth was not controlled during their study, which we believe is essential for quantitation of drug-reflex interaction.

The purpose of the present study was to determine the effects of controlled depths of anesthesia with halothane in oxygen alone on the baroreflex in man. In addition, baroreflex function was studied in awake man breathing room air and compared with the effects of 100 per cent O₂ with spontaneous or controlled ventilation.

* Associate Professor of Anesthesia.

† Research Student Affiliate.

‡ Professor and Chairman of Department.

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Address reprint requests to Dr. Duke: Department of Anesthesia, 700 William Avenue, The University of Manitoba, Winnipeg 3, Manitoba, Canada.

Methods

Baroreflex function in man was assessed by the Pressor Test as described by Smyth, Sleight and Pickering.⁵ This provided quantitative assessment of baroreflex function. Details of the test are presented elsewhere,⁵ and only a brief description is included here. The test is based on the observation that a hypertensive stimulus reflexly slows heart rate. Direct arterial blood pressure and electrocardiogram (lead 2) are simultaneously recorded. A hypertensive stimulus sufficient to increase systolic blood pressure 20-25 torr or to lengthen significantly the pulse interval in response to a small increase in systolic blood pressure is produced by a rapid intravenous bolus injection of the direct arterial smooth muscle vasoconstrictor, angiotensin. One then plots in a beat-to-beat fashion the increase in systolic pressure against its immediately succeeding R-R interval (expressed in msec). As systolic pressure increases, the R-R interval lengthens. Continuous electrocardiographic and blood pressure tracings are obtained prior to and during the initial increase in systolic blood pressure. By using the method of least squares, a linear regression equation and coefficients for the two variables are calculated. The slope of this linear relationship represents an expression of baroreflex sensitivity, and is expressed in milliseconds of R-R interval change per torr increase in systolic blood pressure. Correlation coefficients above 0.75 with probability values less than 0.05 were accepted in the results.

Six healthy unpremedicated male patients ranging in age from 21 to 45 years were studied prior to minor surgical procedures. All studies were performed in accordance with institutional policies on human experimentation. Subjects were brought to the operating room two hours prior to scheduled operations. A radial-artery cannula was inserted percutaneously under local anesthesia. The catheter was connected to a Statham 23 De transducer by a high-pressure line (Cobe 40-104). The transduced signal was amplified and recorded on an Electronics for Medicine four-channel recorder. Mechanical and electrical calibrations were carried out before and after each experiment. All subjects were studied in the supine position. Baseline systolic blood pressure and electrocardiogram were recorded. Angiotensin, 5-8 μ g, was rapidly injected into a large vein. Each subject's sensitivity was tested by injection of graded doses of the vasopressor. Pressor tests were performed in duplicate

TABLE 1. Blood-gas, Circulatory and Slope Data (Mean \pm SD) for the Three Awake Control Situations

	Control Situation 1 Spontaneous Respiration, Air	Control Situation 2 Spontaneous Respiration, 100 Per Cent O ₂	Control Situation 3 Controlled Respiration, 100 Per Cent O ₂
P _{aO₂}	84 \pm 5	538 \pm 37	556 \pm 36
P _{aCO₂}	36 \pm 2	36 \pm 3	31 \pm 3
pH	7.46 \pm 0.03	7.47 \pm 0.04	7.50 \pm 0.05
Heart rate	70 \pm 7	68 \pm 10	68 \pm 7
Resting blood pressure	143 \pm 25	141 \pm 19	141 \pm 18
Δ blood pressure	17 \pm 4	20 \pm 5	20 \pm 3
Slope	15.1 \pm 4.5	15.6 \pm 6.8	18.4 \pm 9.9

TABLE 2. Blood-gas, Circulatory and Slope Data (Means \pm SD) for Control Situation 3 and Two Levels of Halothane Anesthesia

	Control Situation 3 Controlled Respiration, 100 Per Cent O ₂	Halothane .7 Per Cent	Halothane 1.1 Per Cent
P _{aO₂}	556 \pm 36	584 \pm 39	572 \pm 9
P _{aCO₂}	31 \pm 3	34 \pm 3	34 \pm 4
pH	7.50 \pm 0.05	7.46 \pm 0.05	7.46 \pm 0.04
Heart rate	68 \pm 7	69 \pm 6	70 \pm 11
Resting blood pressure	141 \pm 18	106* \pm 24.00	102* \pm 29
Δ blood pressure	20 \pm 3	24 \pm 2	25 \pm 3
Slope	18.4 \pm 9.9	2.5* \pm 1.5	0.03* \pm 0.04

* Significant, $P < .05$.

and the resultant slopes averaged. Intervals of 3–5 minutes were allowed between Pressor Tests to allow systolic blood pressure and heart rate to return to baseline levels.

Pressor Tests were performed on awake subjects 1) while spontaneously breathing room air; 2) while spontaneously breathing 100 per cent oxygen from a standard anesthetic circuit for at least 10 minutes; 3) while ventilation was controlled with 100 per cent O₂ by an Ohio ventilator placed in the anesthetic circuit (subjects breathing through a mouthpiece with a nose plug in place). The respirator was adjusted to provide a tidal volume and respiratory rate comfortable for the patient. Anesthesia was then induced by mask with halothane in 100 per cent oxygen. Succinylcholine (1 mg kg⁻¹) was administered intravenously and the trachea intubated.

End-tidal gases were sampled from the endotracheal tube and the halothane concentration determined with a Beckman IR 215-A infrared analyzer. The inspired concentration of halothane was adjusted to achieve the desired alveolar concentration of the anesthetic agent. Equilibration was considered complete when the end-tidal halothane concentration was within 10 per cent of the inspired halothane concentration. Pressor Tests were performed at two alveolar halothane concentrations: 1) 0.7 per cent halothane, considered a light level of halothane anesthesia (*i.e.*, <1 MAC), and 2) 1.1 per cent halothane, a moderate level of anesthesia (*i.e.*, approximately 1.25 MAC). Tidal volumes and respiratory rates were maintained as in awake con-

trol situation 3. At the conclusion of each test period, arterial blood was analyzed for P_{O₂}, P_{CO₂}, and pH in the usual manner.

Results

In the preanesthetic control studies, arterial blood P_{CO₂} and pH, initial heart rate, and resting blood pressure were similar (table 1). Respiratory alkalosis occurred in all three control situations. Arterial blood P_{O₂} was elevated in the oxygen-breathing studies, as expected. Average slopes obtained in the three control situations were not significantly different from each other. The data obtained in the 0.7 per cent and 1.1 per cent end-tidal halothane studies were compared with those for awake control situation 3 (table 2). Arterial blood P_{CO₂}, P_{O₂}, and pH and heart rate were similar for all three studies. Resting blood pressure decreased with increasing depth of halothane anesthesia. At 0.7 per cent end-tidal halothane, there was a marked reduction in the mean slope from the control value. At 1.1 per cent end-tidal halothane the mean slope value was almost zero (0.03). This indicates that with increasing depth of halothane anesthesia baroreflex function, expressed in terms of heart rate response, decreased. Figure 1 illustrates the mean slopes obtained at the two anesthetic depths and during the one control situation. During anesthesia the heart rate remained constant while blood pressure decreased from control by averages of 35 torr at 0.7 per cent halothane and 39 torr at 1.1 per cent halothane.

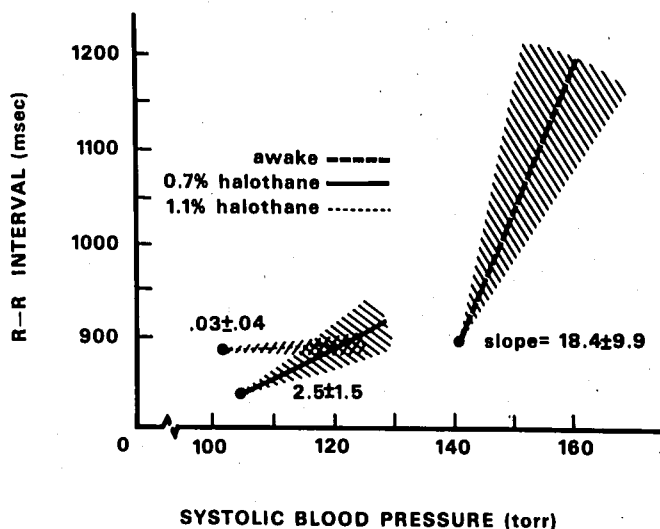


FIG. 1. Comparison of the mean (\pm SD) slope for awake control situation 3 with those for two levels of halothane anesthesia. Note that with increasing depth of anesthesia, systolic blood pressure and slope decrease.

This alteration in blood pressure would usually produce a reflex tachycardia. This did not occur in our studies, which indicates that resetting of the baroreflex occurs with halothane anesthesia.

Discussion

Bristow *et al.*, utilizing a similar quantitative method of baroreflex function testing, found that halothane, 0.5–1 per cent, in conjunction with nitrous oxide significantly depressed baroreflex function.² Their studies were performed in subjects in whom anesthesia was induced with 400–600 mg sodium thiopental 10 minutes prior to study. The study also showed that thiopental alone significantly alters baroreflex function, with a return towards control value within 4–6 minutes. Data confirming the full recovery of the baroreflex prior to the administration of halothane were lacking in their study. Similarly, nitrous oxide alone produced some depression of baroreflex function. Because of this polypharmacy, plus meperidine premedication, it is difficult to decipher what effect halothane alone might have had on baroreflex function. Another criticism of their study is that the inspired halothane concentrations varied, and one cannot be certain of the level of anesthesia in any particular subject at the time of study. Further evidence of the depressant effect of halothane on baroreflex function in man has been reported by Wayne *et al.*⁶ Utilizing a modified Valsalva maneuver, they showed that light and deep levels of halothane anesthesia depressed the normal circulatory responses in man.

It must be emphasized that the Pressor Test

measures only overall baroreflex activity in terms of heart rate response. One cannot define on the basis of such information where the locus or loci of altered activity may be. It may be in the afferent side of the baroreflex, in the brainstem or autonomic afferent pathways, or at the end organ or receptor level. There is some evidence from animal studies to show that halothane may have effects at all these levels.

Biscoe and Millar observed that halothane increased impulse discharges in single baroreflex units in the carotid sinus nerve of the cat.⁷ They concluded that halothane sensitized the baroreceptors, with the resulting sympathetic inhibition adding to the direct hypotensive and bradycardiac effect of halothane. Bristow *et al.* suggested that this observation could account for the resetting of the baroreflex.² Later it was shown that the level of sympathetic efferent firing does not change during halothane anesthesia in normal or in buffer-denervated animals.⁸

Price *et al.* concluded from isolation experiments in dogs that the predominant hemodynamic response of halothane was secondary to a central depression of the vasomotor centers and the baroreflexes.⁹ Price subsequently observed significant depression following the direct application of halothane to the vasomotor centers of the medulla.¹⁰

On the efferent side of the reflex halothane has been found to either increase¹¹ or decrease⁸ pre-ganglionic sympathetic impulse traffic. These divergent findings may be related to a species difference. Depression of sympathetic ganglionic transmission has also been shown to occur.^{12,13}

Despite these findings, two independent laboratories concluded that the major cardiovascular effects of halothane were due to its actions outside the central nervous system and that there was no significant alteration of baroreceptor function.^{8,14} Halothane directly depresses myocardial contractile force^{15,16} and vascular smooth muscle.^{17,18} Therefore, a simple explanation of a decreased heart rate in the presence of arterial hypotension and an intact baroreflex could be lack of "end-organ" responsiveness and insensitivity to baroreflex stimuli.

Does resetting of the baroreflex to function at lower blood pressures alter the ability of the baroreflex to respond to stimuli? There is some evidence against this possibility. First, although the baroreceptor response curve in animals is sigmoid over a very wide pressure range, the linear portion of the response curve is over a mean pressure range of 50 to 200 torr.¹⁹ Second, in three of our subjects anesthetized with halothane we maintained systolic blood pressures at awake control levels with continuous infusion of angiotensin. Slope values obtained prior to and after blood pressure correction were identical. Third, two of our subjects had little

change in resting systolic blood pressure when lightly anesthetized with halothane, but their Pressor Tests slopes were markedly depressed. Finally, Smythe *et al.*,⁵ using the same methods as ours, investigated the effects of normal physiologic sleep on resting blood pressure and baroreflex function.⁵ They observed that during sleep blood pressures fell to ranges comparable to those in our anesthesia studies but baroreflex function did not change and, if anything, became more sensitive.

In summary, our studies indicate that with increasing inspired oxygen concentrations, with or without controlled ventilation, there is no alteration of baroreflex function. With controlled ventilation subjects were slightly more alkalotic than when breathing spontaneously. This again did not affect baroreflex function. With the addition of low concentrations of halothane there was a marked depression of baroreflex function. At moderate depths of halothane anesthesia the reflex was abolished.

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