Halothane Anesthesia Attenuates Cardiopulmonary Baroreflex Control of Peripheral Resistance in Humans

Thomas J. Ebert, M.D., Ph.D.,* Karel J. Kotrlý, M.D., † Edwards J. Vucins, M.D.;‡ Christine Z. Pattison, M.D.,§ John P. Kanipe, M.D., Ph.D.¶

The effects of halothane anesthesia on cardiopulmonary (low pressure) baroreflex control of peripheral resistance were studied in 10 ASA class I young men. Graded (−5, −7.5, −10, −12.5 mmHg) lower body negative pressure (LBNP) was used to produce progressive decreases in thoracic blood volume and central venous pressure. These stimuli activate reflexes from cardiopulmonary baroreceptors. Volunteers were studied while awake and during 1 MAC (0.75%) and 1.25 MAC (0.93%) halothane anesthesia. Heart rate (6%) in 0.9% normal saline was infused into patients before baseline recordings were initiated. Blood pressure, stroke volume, cardiac output, and systemic and forearm vascular resistance decreased and forearm blood flow increased during halothane anesthesia. In awake subjects, LBNP did not alter heart rate or blood pressure, but stroke volume and cardiac output decreased. Blood pressure was maintained by cardiopulmonary baroreflex-mediated increases in peripheral resistance. In anesthetized subjects, decreases in stroke volume and cardiac output during LBNP were similar to awake responses, however, hypotension occurred because reflex resistance increases were markedly attenuated. The authors conclude that halothane anesthesia blunts cardiopulmonary baroreflex resistance responses provoked by mild decreases in thoracic blood volume in humans. (Key words: Anesthetics, volatile: halothane. Blood pressure: reflex control. Measurement techniques: plethysmography, forearm, impedance. Receptors: baroreceptors, cardiopulmonary. Reflexes: baroreflexes, cardiopulmonary.)

ACUTE REGULATION of arterial blood pressure is mediated by arterial (high pressure) and cardiopulmonary (low pressure) baroreceptor reflexes. Most inhalational anesthetic agents are known to markedly attenuate arterial baroreflex function in humans.1-3 There are no reports of the effects of anesthesia on human cardiopulmonary baroreflex function. Furthermore, there is but one report that addresses this issue in experimental animals.5

Cardiopulmonary baroreceptors sense slight reductions in thoracic blood volume and initiate sustained reflex increases in peripheral vascular resistance to maintain arterial pressure.6-8 This reflex is activated during hemorrhage, well before initiation of arterial baroreflex responses.6,7,9 Therefore, cardiopulmonary baroreflex adjustments may be essential for maintaining cardiovascular homeostasis during anesthesia (particularly since arterial baroreflexes are blunted). Knowledge of how anesthetics alter cardiopulmonary baroreflex function in humans may be important and perhaps critical for choosing the appropriate anesthetic for surgical procedures in hypovolemic patients or surgical procedures in which rapid blood loss might occur.

The objective of this study was to determine the effect of halothane anesthesia on cardiopulmonary baroreflex control of peripheral resistance in humans. We used low-level lower body negative pressure to reduce thoracic blood volume and decrease the stimulation of low-pressure baroreceptors. Our data reveal that halothane anesthesia produces a marked blunting of cardiopulmonary baroreflex control of peripheral resistance in humans.

Materials and Methods

This investigation was approved by the institution's human research review committee. Ten ASA class I unmedicated subjects (22–57 yr) volunteered to be studied before elective surgery. All subjects gave informed consent before participation. Heart rate, forearm blood flow, and arterial pressure were determined by ECG, Hg-in-Silastic strain gauge plethysmography, and radial artery cannulation, respectively. Central venous pressure was monitored from a central venous catheter inserted through the right external jugular vein. The position of this catheter in the intrathoracic region was confirmed by characteristic respiratory variations in the waveform.

Stoke volume was determined by impedance cardiography.10 We have previously described and validated this technique.11 Briefly, the method involves placement of four electrode bands circumferentially around the neck and thorax, application of alternating current (100 kHz, 4 mA) to the outer two electrodes, and measurement of changes in thoracic impedance from the inner two electrodes.10,11 Stroke volume and cardiac output calculated from noninvasive impedance waveforms correlate well with invasive measurements obtained with the Fick,12,13 dye,14-17 and thermal18,19 dilution methods. However, stroke volume changes are more reliably determined by the impedance method than absolute stroke volumes.11,14-16,19 Therefore, absolute values of stroke vol-

* Resident in Anesthesiology and Assistant Professor of Physiology.
† Associate Professor of Anesthesiology.
‡ Assistant Professor of Anesthesiology.
§ Resident in Anesthesiology.
¶ Professor and Chairman of Anesthesiology and Professor of Physiology.

Received from the Department of Anesthesiology, Medical College of Wisconsin Affiliated Hospitals, Milwaukee, Wisconsin, and the Veterans Administration Medical Center, Milwaukee, Wisconsin. Accepted for publication July 26, 1985.

Address reprint requests to Dr. Ebert: Department of Anesthesiology, VA Medical Center, 5000 W. National Avenue, Milwaukee, Wisconsin 53213.
HALOTHANE ATTENUATES CARDIOPULMONARY BAROREFLEXES

<table>
<thead>
<tr>
<th>Table 1. Baseline Hemodynamic Data (prior to LBNP)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
</tr>
<tr>
<td>Cardiac output (/min)</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyn · s · cm⁻¹)</td>
</tr>
<tr>
<td>Forearm blood flow (ml · min⁻¹ · 100 ml⁻¹)</td>
</tr>
<tr>
<td>Forearm vascular resistance (mmHg · ml⁻¹ · min · 100 ml)</td>
</tr>
<tr>
<td>Central venous pressure (mmHg)</td>
</tr>
<tr>
<td>Impedance Z₀ (ohms)</td>
</tr>
</tbody>
</table>

All values are mean ± SEM.
Stroke volume, cardiac output and systemic vascular resistance are relative values derived from impedance cardiography.

* Significant change from awake, P < 0.05.
† Significant change from awake, P < 0.01.

ume and calculated values of cardiac output and systemic vascular resistance provided in this report are relative estimates. The more accurately detected changes in these variables (depicted in figs. 2 and 3), are the critical values used to interpret the influence of halothane on cardiopulmonary baroreflex function. Baseline transthoracic impedance (Z₀) was used as an index of thoracic blood volume changes in this study.²⁰²¹

Lower body negative pressure (LBNP) consisted of enclosing the body, below the iliac crests, in an airtight box.²⁰²² Subatmospheric pressure was created by an industrial vacuum source (noise insulated), controlled by a voltage regulator and sensed by a vacuum gauge that previously had been calibrated against a mercury manometer. Forearm blood flow was determined by a temperature compensated Hg-in-Silastic strain gauge and saddle.²³ A venous occluding cuff was placed on the upper arm and an arterial occluding cuff placed about the wrist. Inflation curves (10 s) were obtained at 20-s intervals.²⁰ Inspired and end-tidal halothane concentrations and CO₂ were monitored continuously by a mass spectrometer. Arterial blood pH and P₇.₃ were maintained within physiologic ranges by controlled ventilation adjustments based upon frequent arterial blood gas sampling.

Analog data were transcribed on a strip chart recorder and converted to digital format by hand analysis on a digitizing board in line with a digital computer. Mean arterial pressure cardiac output and systemic and forearm vascular resistance were calculated.

PROCEDURES

Subjects were supine throughout the study. Electrodes, forearm strain gauge, and arterial and venous catheters were placed, and 500 ml of colloid (6% hetastarch in 0.9% NaCl) was administered intravenously. This volume loading was precautionary. Our preliminary studies indicated that because many patients were mildly hypovolemic following the routine preoperation NPO orders, there were in some anesthetized volunteers, excessive declines in blood pressure upon exposure to mild levels of LBNP. By administering fluids before testing, we were able to apply greater gradations of LBNP and avoided unreasonable hypotension. Subjects were positioned in the LBNP box, and a trial run was initiated to familiarize the volunteer with the procedure. Baseline recordings were obtained during three brief (10 s) relaxed end-expiratory breath holds (at 2-min intervals). Lower body negative pressure was applied in progressive 3-min steps (−5, −7.5, −10, and −12.5 mmHg) and breath-hold data were obtained at the second and third minute of each LBNP level. Subjects then were preoxygenated with 100% O₂, anesthetized with halothane in O₂, and intubated after intravenous succinylcholine (1 mg/kg). Subjects were ventilated manually at individualized rates and volumes so that arterial blood gas concentrations were maintained at preanesthesia levels. Twenty minutes after intubation, baseline data were collected and LBNP tests were repeated at identical intervals (and during end-expiratory apnea) as described for awake conditions. Six subjects initially were studied at 1.0 MAC (0.75%) levels and then studied 10 min after establishing 1.25 MAC (0.93%) levels. The order of testing was reversed in the other four patients.

STATISTICAL ANALYSIS

Baseline data (prior to LBNP) were averaged, and the two stress readings at each LBNP level were averaged. Baseline hemodynamic variables while awake and anesthetized were compared by Student's t tests for paired observations. Responses to LBNP were compared with analysis of variance. We assumed P values less than 0.05 to be significant.

Results

Resting hemodynamic variables obtained from average baseline readings before LBNP exposure are provided in table 1. There were no differences in heart rate, central...
Central venous pressure decreased linearly with step increases in LBNP, as depicted in figure 1. These decreases were slightly greater with increasing MAC of halothane, such that most of the reductions during 1.25 MAC halothane were significantly greater than awake responses. A similar but nonsignificant trend was noted when thoracic impedance Zo was plotted. (Zo increases are inversely proportional to thoracic blood volume decreases).

We chose to analyze the cardiovascular responses (to LBNP) as a function of changes in central venous pressure, since pressure is an important stimulus to baro-(pressure) receptors. Figure 2 reveals that heart rate and blood pressure were unchanged by LBNP in awake patients. However, mean arterial pressure decreased progressively with graded LBNP at both halothane levels. During 1.0 MAC halothane, heart rate was slightly (but significantly) increased compared with awake responses. In each experimental situation, stroke volume and cardiac output decreased progressively with increasing LBNP. However, stroke volume and cardiac output reductions were significantly less during 1.25 MAC halothane than when patients were awake or receiving 1.0 MAC halothane. Pre-LBNP stroke volume and cardiac output values were lower at 1.25 MAC halothane than at awake or 1.0 MAC halothane conditions. Therefore, analysis of the percent change from control failed to reveal significantly greater differences in the stroke volume and cardiac output reductions during 1.25 MAC halothane.

Figure 3 indicates that as halothane concentration is increased, there is a progressive blunting of the resistance responses to LBNP. Reflex forearm vascular resistance increases in awake patients were markedly diminished when anesthetized ($P < 0.01$). There were no differences in the forearm resistance responses at 1.0 and 1.25 MAC halothane. Since baseline (pre-LBNP) resistance values were less in anesthetized (vs. awake) conditions, we repeated our analyses with the use of percent changes. This also revealed a significant difference between responses from awake and anesthetized subjects.

**Discussion**

The major finding of this study is that cardiopulmonary baroreflex control of peripheral resistance is markedly attenuated by halothane anesthesia in humans. This is qualitatively similar to the effect of halothane anesthesia on human arterial baroreflex control of heart rate. These combined findings indicate that baroreflexes may not contribute importantly to cardiovascular regulation during 1.0 MAC and 1.25 MAC halothane anesthesia.

**Baseline Hemodynamics**

Heart rate was unchanged during halothane anesthesia, despite a reduction in mean arterial pressure (when reflex tachycardia would be expected). This confirms previous studies, which demonstrate that halothane blanks arterial...
baroreflex control of heart rate. Stroke volume and cardiac output during 1.0 MAC halothane were unchanged from awake values. Earlier reports demonstrated reductions in stroke volume and cardiac output during halothane. We considered that an increase in circulating catecholamines early after intubation may have contributed to maintaining stroke volume and cardiac output near awake levels. However, this seemed unlikely, since we allowed a 20-min period of stabilization after intubation before recording baseline data. Furthermore, four of 10 subjects in this study were tested initially (after intubation) at 1.25 MAC levels before 1.0 MAC testing. In these individuals, stroke volume and cardiac output were decreased at 1.25 MAC but unchanged from awake values during 1.0 MAC testing. The maintenance of stroke volume at 1.0 MAC halothane may have been related to the mild volume loading of subjects before the study. Because the impedance method is very reliable when used to detect stroke volume changes in humans, our data indicate that 1.0 MAC halothane anesthesia does not decrease stroke volume or cardiac output in young healthy men preloaded with 500 ml colloid. However, at 1.25 MAC halothane, these variables did decrease, and this is probably related to a direct effect of higher concentrations of halothane on myocardium.
and a decrease in sympathetic efferent activity to the heart.28,29

Systemic and forearm vascular resistance decreased with anesthesia. This is most likely due to reduced sympathetic activity to vascular beds.29,30 an impaired release of norepinephrine from sympathetic terminals,31,32 and a direct effect of halothane on vascular smooth muscle.32-34 As a result of this vasodilation, forearm blood flow increased during halothane.

Baseline (pre-LBNP) central venous pressure was unchanged by halothane. Eger et al.34 reported a nonsignificant trend of right atrial pressure increases during halothane anesthesia, which might have been due to slight decreases in forearm venous compliance. However, other data indicate that whole-body venous compliance increases with halothane,35 probably because of reductions in venous smooth muscle tone.32,33 Thoracic impedance, an index of thoracic blood volume, was not altered during anesthesia. Thus, two independent methods, impedance Zo and central venous pressure measurements, suggest that central venous pressure and volume were unchanged during halothane anesthesia. Therefore, it is likely that the initial baseline (pre-LBNP) stimulus to low-pressure baroreceptors was similar when patients were awake and while anesthetized.

**RESPONSES TO LOWER BODY NEGATIVE PRESSURE**

Central venous pressure decreased and thoracic Zo increased progressively with graded increases in LBNP (fig. 1). There was a tendency for central venous pressure decreases to be greater during halothane anesthesia. Therefore, we chose to plot the hemodynamic responses to LBNP as a function of the changes in central venous pressure, since these changes are probably a better index of the stimulus at cardiopulmonary baroreceptor sites than the absolute level of LBNP. We reason that the greater decreases in central venous pressure at equivalent LBNP intensities during halothane are due to increases in lower-extremity venous compliance resulting in more caudal blood pooling during anesthesia.

In general, heart rate, stroke volume, and cardiac output responses to LBNP were similar when patients were awake and while anesthetized. We noted a slight reduction in heart rate during LBNP in awake volunteers. This is thought to be due to a reverse Bainbridge effect.20 There was a slight (2 beats/min) increase in heart rate during LBNP at 1.0 MAC halothane, which was significant when compared with the bradycardia noted while awake. This was not evident during 1.25 MAC halothane.

In awake humans, LBNP at levels less than 20 mmHg does not produce hypotension or eliciting increases in heart rate, which suggests that arterial baroreflexes are not activated.6-8 In support of this contention, Thames et al.9 have demonstrated in experimental animals that arterial baroreceptor afferent traffic is unchanged during small reductions in blood volume that are sufficient to activate cardiopulmonary baroreflexes. In out investigation, blood pressure and heart rate were unchanged during LBNP in awake volunteers, despite substantial reductions in central venous pressure, thoracic blood volume, stroke volume, and cardiac output. Blood pressure was maintained by reflexes from cardiopulmonary baroreceptors, which produced sustained increases in vascular resistance (noted in fig. 3). When subjects were anesthetized with increasing MAC halothane, reflex systemic vascular resistance increases were progressively attenuated and reflex forearm vascular resistance increases provoked by LBNP were markedly attenuated. The stroke volume and cardiac output reduction during LBNP was similar in patients while awake and anesthetized. Therefore, the blood pressure decline produced by LBNP when the patient is anesthetized can be accounted for primarily by the diminished reflex increases in peripheral resistance. This blood pressure reduction did not elicit a reflex tachycardia (since arterial baroreceptors were also blunted).1,2

Despite the critical role of cardiopulmonary baroreceptor reflexes in maintaining blood pressure during slight changes in central blood volume, there have been no previous studies investigating the effects of anesthetics on human cardiopulmonary baroreflex function. A previous report, from our department, on cardiopulmonary baroreflex function in dogs during halothane anesthesia provided findings that support our results.5 In this investigation, vagal afferent nerve activity from the heart was increased by acute coronary artery occlusion. The increased afferent traffic (opposite of LBNP, which decreases vagal afferent traffic) produced reflex decreases in resistance in the isolated perfused gracilis muscle. These decreases were attenuated progressively by increasing concentrations of inspired halothane. Therefore, it appears that in both humans and animals, halothane anesthesia blunts cardiopulmonary baroreflex regulation of peripheral resistance.

The mechanism of this attenuation of low-pressure baroreflex resistance responses is not known. We do know that multiple sites in the pathways mediating high-pressure baroreflex responses are altered by inhalational anesthetics.28 Despite sensitization of baroreceptors by halothane, there appears to be a reduction in central, preganglionic, and cardiac responses to arterial baroreceptor stimulation in animals anesthetized with halothane.29 Similar multiple mechanisms may be involved in the attenuation of cardiopulmonary baroreflex function during halothane.

There are several limitations to be considered in interpreting the results of this study. Baseline peripheral resistance decreased when halothane concentrations were
increased (table 1). Thus, absolute changes in resistance provoked by cardiopulmonary baroreflex activation during anesthesia may have been less because of a more dilated vascular bed. However, the law of initial resistance values mitigates against this possibility. For example, Myers and Honig demonstrated that as baseline resistance is decreased, the response to vasocostructor influences is increased. Therefore, our demonstration of blunt resistance responses from a dilated vascular bed is profound and strengthens our conclusions.

Inhalational induction and maintenance of anesthesia with halothane alone is uncommon in clinical practice. Nitrous oxide often is added to the anesthetic regimen. We did not study the effect of halothane–nitrous oxide anesthesia on cardiopulmonary baroreflex function in humans. Nitrous oxide provides sympathetic activation and may improve arterial baroreflex function when combined with halothane. Conceivably, the combination of halothane and nitrous oxide anesthesia improves cardiopulmonary baroreflex regulation of arterial pressure.

In this study, subjects were volume loaded with 500 ml of colloid. This helped prevent excessive hypotension when LBNP was applied during anesthesia. Thus, in normovolemic or slightly hypovolemic patients (particularly chronic hypovolemia in the elderly) who may not be adequately volume loaded before induction, the blunting of cardiopulmonary baroreflex function by halothane may result in more dramatic hypotension than demonstrated in this investigation.

In summary, cardiopulmonary baroreflexes are important (perhaps major) regulators of blood pressure during slight changes in thoracic blood volume. We examined the function of this reflex during halothane anesthesia in young men and demonstrated that halothane significantly attenuated cardiopulmonary baroreflex resistance increases provoked by small graded decreases in central venous pressure. The attenuated resistance responses resulted in significant cardiovascular compromise; blood pressure declined precipitously during LBNP when patients were anesthetized but was well maintained in awake individuals. Moreover, reduction of baseline blood pressure during halothane anesthesia may be a result of the failure of cardiopulmonary baroreflexes to elicit vasocostriction.

The combination of halothane-induced attenuation of arterial and cardiopulmonary baroreflex function suggests that this anesthetic may not be ideal for surgical procedures in which rapid blood loss may occur. We qualify this statement with the knowledge that nitrous oxide is commonly part of the halothane anesthetic regimen in clinical practice and the effect of this regimen on cardiopulmonary baroreflex function was not tested. Furthermore, we do not know if other inhalational anesthetics blunt cardiopulmonary baroreflexes to a similar degree. Therefore, we cannot provide recommendations at this time for optimum anesthetic agents for surgery in hypovolemic patients or surgery in which rapid blood loss may occur.

One situation where halothane anesthesia may be useful is when controlled hypotensive anesthesia is planned. The blunted baroreflexes produced by this agent help prevent compensatory reflex adjustments to vasodilator administration.

The authors thank Dr. James J. Smith, Jill Barney, Anna Stadnik, and Leanne Groban for their time and support of this research. They also are thankful for the temporary loan of several pieces of equipment essential to this investigation.

References

15. Dennison JC, Maher JT, Reeves JT, Cruz JC, Cymerman A,