Baroreceptor Reflex Control of Heart Rate during Isoflurane Anesthesia in Humans

Karel J. Kotrla, M.D.,* Thomas J. Ebert, Ph.D.,† Eduards Vucins, M.D.,‡ Franz O. Igler, M.D., Ph.D.,§ Jill A. Barney, B.S.,¶ John P. Kampine, M.D., Ph.D.**

The effect of isoflurane alone (Group 1) and isoflurane following thiopental (Groups 2 and 3) on baroreflex control of heart rate in humans was investigated in this study. Phenylephrine (the pressor test) and sodium nitroprusside (the depressor test) were used to induce moderate changes in arterial blood pressure and to alter the stimulation of baroreceptor sites. In addition, graded neck suction was employed to examine carotid baroreflex control of heart rate. In Group 3 subjects, phenylephrine was infused continuously during anesthesia to maintain mean arterial blood pressure near control levels. The pressor- and neck-suction-derived baroreflex slopes were decreased progressively from awake to 1.0 and 1.5 MAC isoflurane. The slopes of the depressor responses were decreased at 1.0 MAC but showed little further depression at 1.5 MAC. For each method, the depression of baroreceptor slopes from control to 1.0 MAC and 1.5 MAC was similar among the three groups. Maintenance of arterial blood pressure (Group 3) and the utilization of thiopental (Group 2) did not significantly alter the depression of baroreflex responses during increasing levels of isoflurane anesthesia. Neck suction derived slopes compared favorably with the pressor test slopes (r = 0.75, P < 0.001). This study indicates that the depression of arterial baroreflex heart rate responses under isoflurane anesthesia are less pronounced than the depression of baroreflex responses noted by other investigators for halothane or enflurane. The neck suction technique appears to be a sensitive method useful in assessing the carotid sinus reflex in awake and anesthetized humans. (Key words: Anesthetics, volatile: isoflurane. Blood pressure: baroreceptor reflexes. Reflexes: baroreceptor.)

GENERAL ANESTHETICS have been shown to alter the arterial baroreflexes in both humans and animals. Baroreceptor reflexes were depressed by thiopental, halothane, halothane with nitrous oxide, and enflurane with or without nitrous oxide. However, baroreceptor reflexes were not depressed by methoxyflurane. The recent introduction of isoflurane a potent vasodilator into clinical practice stimulated our interest in its effects on this important blood pressure control mechanism.

Baroreflex control of heart rate can be studied in awake and anesthetized humans by the infusion of vasoactive drugs (usually phenylephrine or angiotensin). The classic technique known as the "pressor test" was described originally by Smyth, Sleight, and Pickering. These drugs increase blood pressure, stimulate baroreceptors, and produce a reflex slowing of the heart rate. Baroreflex sensitivity is defined by the slope of the relationship between arterial blood pressure and R–R interval. In addition, the infusion of a vasodepressor substance such as nitroprusside increases the heart rate, and the sensitivity of the baroreflexes to declining pressures is determined in a similar way to the pressor test.

Physiologic changes in arterial blood pressure simultaneously alter the stimulation at several baroreceptor sites and elicit an integrated reflex response through alterations of peripheral resistance, heart rate, blood volume, and cardiac output. Similarly, infusions of vasoactive substances change the vascular tone at all baroreceptor-containing areas and the firing pattern of many different
types of baroreceptors (i.e., aortic, carotid, cardiopulmonary, and splanchnic) are altered by this method.\textsuperscript{18}

The neck suction test developed by Eckberg et al.\textsuperscript{19,20} specifically stimulates carotid baroreceptors and thus offers an advantage in investigating the effects of anesthetics on baroreflex control mechanism. Stimulation of one set of baroreceptors may provide some insights about its relative importance compared with other baroreceptor regions involved in cardiovascular regulation. Therefore, in addition to the pressor and the depressor tests, we chose to employ the neck suction technique in the present study and compare it with the classical pressor test.

\textbf{Methods and Materials}

\textbf{Patient Selection and Study Groups}

Twenty-three unpremedicated ASA class I subjects, 20–35 years of age, were studied prior to elective surgery. All studies were performed in accordance with institutional policies on human experimentation, and informed consent was obtained from each patient.

The patients were divided into three groups. Group 1 consisted of seven patients who were anesthetized with isoflurane in 100% oxygen only. Group 2 consisted of six patients who were anesthetized with thiopental 4 mg/kg followed by inhalation of isoflurane in 100% oxygen. In Group 3, 10 patients were anesthetized as in Group 2, but their mean arterial blood pressures were maintained near control levels by continuous infusion of phenylephrine.

\textbf{Study Procedures}

Direct arterial BP (radial artery), ECG (Lead II), and neck chamber pressures were recorded simultaneously on a Grass Model 7 Polygraph (Grass Instruments, Quincy, Massachusetts) and base line recordings obtained. The neck suction was performed first and utilized an airtight flexible lead chamber rimmed with sponge rubber that was placed over the anterior two-thirds of the neck.\textsuperscript{9} A solenoid and a pressure transducer were attached to the neck chamber. Subatmospheric pressure was produced within the neck chamber by a vacuum motor. The level of negative pressure within the neck chamber was controlled by a voltage regulator. During expiratory apnea, five consecutive (R-wave triggered) ramped stimuli were applied, each lasting 0.40 s and beginning exactly 0.10 s after the peak of the R-wave of the ECG. This timing was chosen so that neck suction stimuli would be superimposed upon natural carotid arterial pulses.\textsuperscript{20} The five consecutive ramped neck suction were of increasing intensity, progressing from –10 to –50 mmHg. These stimuli are on the linear portion of the curve relating carotid sinus transmural pressure to R–R interval.\textsuperscript{21}

The pressor (A) and the depressor (B) tests were performed next (in that order): A) phenylephrine in a concentration of 30 mg/250 ml of D5W was infused at a rate of 0.6 mg/min to rapidly elevate mean arterial blood pressure by 20%; B) sodium nitroprusside solution in a concentration of 50 mg/250 ml of D5W was infused at a rate of 1 mg/min to lower the mean arterial blood pressure by 20%. A period of stabilization between the neck suction test, the pressor, and the depressor tests (usually 5 min) allowed the blood pressure and heart rate to return to pretest values.

The subjects were anesthetized in the supine position. The anesthetic sequence in Group 1 subjects consisted of preoxygenation, inhalational induction with isoflurane, and intubation following administration of succinylcholine 1 mg/kg. Group 2 and 3 subjects also were preoxygenated, but they were induced with sodium thiopental 4 mg/kg. Succinylcholine 1 mg/kg was given to facilitate intubation. Isoflurane was introduced following intubation. Inspired and end-tidal isoflurane concentrations were monitored continuously using a calibrated Perkin–Elmer Mass Spectrometer. Inspired concentrations were adjusted frequently to keep end-tidal concentrations at predetermined levels. To ensure anesthetic equilibration, the desired end-tidal concentrations were maintained constant for 10–15 min before the tests were performed. Constancy of ventilation and oxygenation was assured in all tests by frequent arterial blood gas analysis while awake and at both anesthetic levels. In addition, expired CO\textsubscript{2} levels were monitored continuously by a mass spectrometer. Baroreflex sensitivity was determined with neck suction, the pressor, and the depressor tests while awake at 1 MAC (1.34%) and 1.5 MAC (2%) isoflurane anesthesia, and changes in slopes were compared. In Groups 2 and 3, tests at both anesthesia levels were performed and measurements obtained at least 10 min following administration of thiopental and succinylcholine and in Group 1 at least 10 min following administration of succinylcholine. The total duration of these procedures (excluding anesthetic management) was about 45 min.

\textbf{Data Analysis}

The pressor and the depressor tests data were analyzed using least-squares linear regression analysis on the linear region (above threshold) of the sigmoid relation between blood pressure and R–R interval. Only the individual regression slopes with correlation coefficients greater than 0.6 were included in the group mean (90% of regression analyses resulted in correlation coefficients greater than 0.75). Only 4% of all regression analyses failed to meet this criterion, and in these cases individual slopes were estimated to facilitate data analysis.

Neck suction intensity and R–R interval analog signals
TABLE 1. Control Data—Awake Patients, 1 MAC and 1.5 MAC Isoflurane Anesthesia

<table>
<thead>
<tr>
<th></th>
<th>Awake (For Groups 1, 2, and 3)</th>
<th>1.0 MAC Isoflurane (For Groups 1, 2, and 3)</th>
<th>1.5 MAC Isoflurane (For Groups 1, 2, and 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>R-R Int.</td>
<td>1,108 ± 74</td>
<td>1,153 ± 91</td>
<td>942 ± 71*</td>
</tr>
<tr>
<td>SBP</td>
<td>132 ± 6</td>
<td>134 ± 6</td>
<td>137 ± 5</td>
</tr>
<tr>
<td>DBP</td>
<td>68 ± 2</td>
<td>73 ± 5</td>
<td>71 ± 3</td>
</tr>
<tr>
<td>MABP</td>
<td>89 ± 2</td>
<td>94 ± 6</td>
<td>95 ± 3</td>
</tr>
</tbody>
</table>

Data are means ± SEM. In each group, values at 1.0 and 1.5 MAC are significantly decreased from awake values (P < 0.05) except those indicated by † (not significant, P > 0.05). R–R intervals are expressed in milliseconds blood pressures in mmHg.

Depressor slopes decreased significantly in all groups at 1.0 MAC (ANOVA, Group 2 P < 0.05, Groups 1 and 3 P < 0.01). However, the depression from 1.0 to 1.5 MAC was smaller than for other tests (Fig. 3).

Baroreceptor reflex slopes of Groups 1 and 2 were significantly different at both levels of anesthesia (Figs. 1, 2, and 3), however, the degree of slope depression was not significantly different (Fig. 4). The interaction factor (Groups vs. Treatment) derived from ANOVA was used as a test of parallelism (between groups) of the slope depression from awake to 1.0 and 1.5 MAC isoflurane.22 For each procedure (neck suction, pressor and depressor tests) the interaction factor was not significant, indicating parallel depression of slopes between groups. Thus, prior administration of thiopental (Group 2) or maintenance of arterial blood pressure by phenylephrine infusion

Results

There were no significant differences in age, height, and weight in the three groups studied. While awake and at both levels of anesthesia, pH and P CO2 levels were within physiologic limits. The administration of 100% oxygen resulted in P O2 of 460 ± 33 mmHg at 1.0 MAC and 488 ± 17 mmHg at 1.5 MAC of isoflurane.

Awake arterial blood pressures were similar among the three groups. R–R intervals were significantly shorter in Group 3. In Groups 1 and 2 blood pressures and R–R intervals were decreased significantly from awake values at 1.0 MAC and 1.5 MAC (Table 1). In Group 3, subjects' systolic blood pressure declined significantly, but mean and diastolic blood pressures and R–R intervals were not changed from awake values (Table 1).

There was a significant difference between the awake control pressor slopes of Groups 1 and 2. Pressor test slopes were progressively and significantly decreased in all groups (ANOVA, Groups 2 and 3, P < 0.01, Group 1 P < 0.05) from awake to 1.5 MAC isoflurane (Fig. 1). Similarly, neck suction slopes decreased progressively and significantly in all groups (ANOVA, Groups 1, 2, and 3, P < 0.01) from awake to 1.5 MAC isoflurane (Fig. 2).

**FIG. 1.** The depression of phenylephrine slopes in Groups 1–3 from awake levels to 1.0 and 1.5 MAC isoflurane anesthesia. Baroreflex slopes of Groups 1 and 2 are significantly different (indicated by asterisk, P < 0.05). The depression of slopes from awake to 1.5 MAC is progressive and significant in all groups (Groups 2 and 3, P < 0.01, Group 1, P < 0.05).
Discussion

Circulatory homeostasis is altered by general anesthetic agents, and the effects of these agents could change arterial baroreceptor reflex function. Our investigation of a new general anesthetic, isoflurane, attempted to answer several questions. First, does isoflurane depress arterial baroreceptor reflexes, and if it does to what degree? Secondly, does the addition of thiopental to isoflurane anesthesia alter baroreceptor reflex function? Thirdly, during isoflurane anesthesia, does the maintenance of mean arterial blood pressure near awake control levels improve baroreceptor reflex sensitivity? Additionally, we wished to compare a new neck suction technique with the standard pressor test method for assessing human baroreceptor reflex function.

It has been demonstrated previously that baroreflexes may be affected by age, increased arterial $P_{CO_2}$, and hypertension. All of these factors were controlled in this study. Duke et al. have shown that increased arterial $P_{O_2}$ does not alter baroreflex responsiveness, and, therefore, an $F_{IO_2}$ of 1.0 was administered to all subjects along with isoflurane.

The possible influence of succinylcholine on baroreflex responses was not considered to be significant in view of the dose employed, its rapid metabolism, and the time interval between the injection and the data collection. It was noted that all subjects resumed spontaneous ventilation prior to tests carried out during anesthesia.

Awake control pressor slopes were larger than control depressor and neck suction slopes. We believe the difference between pressor and neck suction slopes is the result of a greater response to stimulation of many baroreceptor sites with the pressor test (i.e., aortic, carotid, cardiopulmonary, and splanchnic) versus the stimulation of primarily carotid baroreceptors with the neck suction technique. The difference between awake pressor and depressor slopes is a function of the sigmoid relation between blood pressure and heart rate. An increase in cardiac sympathetic tone produced by lowering arterial blood pressure elicits smaller changes in heart rate relative to the increase in parasympathetic tone produced by raising arterial blood pressure. Direct efferent sympathetic modulation of baroreceptor discharge also may result in differences between pressor and depressor slopes.

A significant difference was noted between the awake control pressor slopes of Groups 1 and 2, which, at the present time, we are unable to explain.

Pressor, depressor, and neck suction baroreflex slopes indicate that baroreflex function declines significantly at both levels of isoflurane anesthesia. The slopes derived from neck suction and depressor tests (Figs. 2 and 3) reveal a smaller change from control to 1.5 MAC (Fig. 4) than the slopes derived from pressor tests (Fig. 1).
BARORECEPTOR REFLEX CONTROL DURING ISOFLURANE

Fig. 4. Graph indicating changes in phenylephrine, neck suction, and sodium nitroprusside slopes at 1.0 MAC and 1.5 MAC isoflurane. For each method the depression of slopes is not significantly different among the three groups ($P > 0.05$).

Since control slopes for each method were different (as previously discussed) it was not expected that the absolute changes from control would be similar between methods. We do not believe that these differences detract from our demonstration of baroreflex depression with increasing depth of anesthesia.

In the study by Bristow et al., administration of thiopental produced a short-lived decrease in baroreflex sensitivity, associated with a tachycardia. He observed that within approximately 6 min following 400–600 mg of thiopental, the baroreflex slopes calculated during phenylephrine infusion returned to control levels. It is not clear from their work whether heart rates returned (within 6 min) to control levels. As noted above, there was a significant difference between the awake control pressor slopes of Group 1 and 2 subjects, but the pressor slopes during 1.0 MAC and 1.5 MAC isoflurane (analyzed by ANOVA) were lowered by about the same amount relative to the awake slopes (Fig. 4). There was also a parallel depression of neck suction and depressor slopes in Groups 1 and 2. Since all tests were performed at least 10 min following induction with thiopental and isoflurane (Group 2) or isoflurane (Group 1) similar baroreflex slope depression in the two groups for all three tests suggests that the effect of thiopental on baroreflex sensitivity had been dissipated. However, R–R intervals in Group 2 decreased more compared to R–R intervals of Group 1 under both levels of anesthesia (Table 1). Thus, a combination of isoflurane and thiopental may have a greater effect on baseline heart rates than isoflurane alone. The observation in animal studies that barbiturate anesthesia resets the heart rate to a higher level for a given blood pressure has been made by several other investigators. An increase in circulating catecholamines or augmented sympathetic activity could be responsible. No change in R–R intervals of Group 3 subjects seems to indicate that maintenance of mean arterial blood pressure at control levels prevents thiopental-induced tachycardia or tachycardia resulting from increasing depth of isoflurane anesthesia. This also could be a result of shorter R–R intervals in the awake subjects.

In Group 3 subjects, mean arterial blood pressure was maintained near control levels at 1.0 and 1.5 MAC isoflurane by continuous infusion of phenylephrine. Since the curve relating arterial blood pressure to R–R interval is sigmoid in nature, we thought that the hypotension

Fig. 5. A comparison of neck suction slopes with phenylephrine slopes for all three groups awake and at both levels of anesthesia. For each group the slopes declined in a linear and parallel fashion with increasing depths of anesthesia.
induced by anesthesia may have resulted in a depression of calculated baroreflex gain due to a shift to a flat region of this sigmoid curve. In other words, we wanted to differentiate between the effect of anesthetics on baroreflex sensitivity versus the effect of lowered blood pressure. Our data indicate that the support of mean arterial blood pressure did not change the depression of the baroreflex gain at 1.0 and 1.5 MAC isoflurane, which is comparable to the depression of baroreflex slopes in Groups 1 and 2. The baseline heart rates were different among groups studied with the shortest R–R intervals in Group 3. Theoretically, higher baseline heart rates could have a potentiating effect on the pressor responses and an inhibiting effect on depressor responses. This possibility is not demonstrated by Group 3 results.

The neck suction test, consisting of repetitive ramped carotid baroreceptor stimuli produced by a neck chamber proved to be a convenient way of testing baroreflex activity. Multiple trains of stimuli could be delivered in relatively short intervals (less than 1 min). The fact that this method is easily repeatable and provides tighter data is a distinct advantage when compared with the pharmacologic methods. It was well accepted by all subjects. Even though direct arterial blood pressure was monitored in this study, it is not essential for this technique.

In each group, there was a linear relationship between baroreflex slopes calculated for the neck suction and the pressor test (Fig. 5). The correlation coefficient derived by least-squares linear regression from all data (all subjects) under all experimental conditions was 0.75 (P < 0.001). We believe (but have not proven) that differences between

the neck suction and pressor tests are likely due to problems inherent in the pressor method. Pharmacologic manipulations of blood pressure may alter firing pattern of multiple baroreceptor units in the carotid sinus, aortic, and cardiopulmonary regions simultaneously. Furthermore, sympathetic nerve stimulation, phenylephrine, epinephrine, and angiotensin have all been shown to alter baroreceptor sensitivity by direct effects on the baroreflex region.

Since control baroreceptor slopes as well as patient selection and methods in our study were similar to those of other investigators, a comparison was made between the effects of isoflurane and halothane or enfurane on baroreflex responses to the pressor test (Fig. 6). Even though these studies were conducted in different laboratories, the data indicate that isoflurane preserves baroreflex regulation of heart rate better than either halothane or enfurane. While 1.25 MAC enfurane or halothane nearly abolishes baroreflex sensitivity, 1.0 MAC isoflurane diminishes baroreflex sensitivity to about 70% of control and 1.5 MAC isoflurane to 42% of control. The experimental evidence for smaller depression of baroreflex function during isoflurane anesthesia is supported by our own clinical experience as well as by others.

Better preservation of baroreflex responsiveness during isoflurane anesthesia may be an advantage in some clinical situations but detrimental in others. First, it might be interpreted that better-preserved baroreflex function is advantageous in the presence of hypovolemia. Secondly, it is possible that in certain clinical situations depressed baroreflex responsiveness would be preferable. For example, absence of reflex tachycardia in patients with coronary artery disease and myocardial ischemia reduces myocardial oxygen demands. It is our feeling that the ability of isoflurane to preserve baroreflex function should be considered when anesthetizing patients where maintenance of an optimal oxygen supply demand ratio to the myocardium is of great importance.

We conclude that isoflurane anesthesia depresses baroreflex control of heart rate in humans but to a substantially smaller degree than halothane or enfurane. There was no significant difference in the depression of baroreceptor gain with the addition of thiopental to the anesthetic regime. Furthermore, support of arterial blood pressure during 1.0 MAC and 1.5 MAC isoflurane anesthesia did not alter the depression of baroreflex gain. Lastly, the method of repetitive ramped carotid stimuli produced by a neck chamber proved to be a simple quantitative test that can be used to examine carotid baroreceptor–cardiac reflex physiology in awake and anesthetized humans.
assistance in this research project and Dr. Kalbfleisch, Assistant Professor, Department of Anesthesiology, for his help with statistical analysis. They also thank Mrs. Gloria Picucci and Mimi Mick for their help in the preparation of this manuscript.

References