Effects of Anesthesia on Baroreflex Control of Heart Rate in Man

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The effects of anesthesia on the setting and sensitivity of baroreceptor reflex control of heart rate in man were studied. Modest increases in systemic arterial blood pressure were produced transiently by small amounts of phenylephrine intravenously. The quantitative relationship between individual systolic arterial pressure pulses and subsequent cardiac cycle lengths was evaluated as an index of reflex performance.

Thiopental produced a decrease in baroreflex sensitivity, associated with tachycardia. Halothane and nitrous oxide resulted in marked reflex resetting, permitting the combination of bradycardia and reduced blood pressure. The mechanisms which may produce baroreflex resetting during anesthesia are discussed. We propose that barbiturate effects on heart rate control are achieved primarily in the central nervous system, and perhaps at the heart itself. Halothane and nitrous oxide could operate at baroreceptor sites in addition. (Key words: Baroreceptor; Baroreflex; Halothane; Thiopental; Nitrous oxide; Phenylephrine; Cardiovascular control; Heart rate; Blood pressure.)

There are extensive data describing the effects of anesthetics on the cardiovascular system, including many studies in animals. However, investigations in man of the influence of anesthesia on cardiovascular control mechanisms have been relatively few. The purpose of this work was to evaluate the effects of some commonly used anesthetic agents on the heart rate control system in man, to enlarge our understanding of the effects of anesthetics on the circulation.

Methods

Eight patients who were to have elective surgery gave informed consent for the experiment; one patient was studied on two occasions. Their ages ranged from 27 to 55 years, with an average of 39. Under local anesthesia with lidocaine, a braehial artery and antecubital vein were cannulated percutaneously with plastic tubing. Systemic arterial pressure (BP) was measured with a Statham P-23D strain gauge. The amplitude/frequency response of this system was tested with a sine-wave hydraulic pressure generator and was consistently flat to 15 cps. The electrocardiogram was recorded from standard limb leads, and a pneumograph around the chest detected the respiratory phase. All variables were recorded by an Elema-Schonander ink jet writer. Baroreflex control of heart rate was evaluated by the method of Smyth, Sleight and Pickering.1,2 Phenylephrine (Neosynephrine, 50 to 150 μg) was injected rapidly intravenously, producing a modest increase in BP, usually not more than 30 mm Hg systolic. The time from injection until the peak increase in pressure was approximately 20 to 30 seconds. Conscious subjects did not sense this degree of pressor effect, and were unaware of the injections. As discussed below, the relationship between the level of BP and the cardiac cycle length (pulse inter-
val) was evaluated quantitatively during the rising phase of BP. The pressure fell to pre-injection levels within two minutes after each dose of phenylephrine, and repeat injections were given during each experimental state.

There were nine experiments in the eight subjects. In eight of the experiments observations were made with the patient awake and subsequently during administration of various anesthetic agents, but before surgery began. In the remaining patient studies during anesthesia and wakefulness followed a testicular biopsy. The operations included inguinal herniorrhaphy, vein stripping and breast biopsy, and in no instance did the patients have signs of active systemic disease or evidence of cardiovascular disorders. One man had a permanent tracheostomy.

Neither atropine nor scopolamine was administered, although modest doses (50–75 mg) of meperidine (Demerol) were usually given for preoperative sedation. After control measurements, anesthesia was usually induced with 400–600 mg of sodium thiopental intravenously. In five subjects injections of phenylephrine were then made while the patient breathed room air, before inhalation anesthesia. Spontaneous ventilation was then maintained with an anesthetic mask with an inspired gas mixture of 70 per cent nitrous oxide and 30 per cent oxygen, with or without halothane (0.5 to 1 per cent).

Evaluation of the response of heart rate to a rise in pressure was done as described previously. Rapid intravenous injection of a small amount of phenylephrine produced a modest rise in BP, and cardiac slowing usually resulted as the baroreflex was stimulated. Plots were made of the relation between the systolic pressure level of each beat and the resulting pulse interval, as shown in figures 1 and 2. Pulse intervals during inspiration were excluded in order to avoid any potential effect of sinus arrhythmia, most likely to occur in the awake state. Plotting was done from the time of injection of phenylephrine until the peak pressure was achieved. The resulting relationship was linear, and the correlation coefficient and regression equation were calculated by standard formulae. Correlation coefficients were usually above 0.7, and only those regressions with probability values less than 0.05 were accepted in the results.

The distribution of points represented by the calculated regression line is a reflection of the sensitivity of baroreflex control of heart rate. The steeper the slope, the greater is the increase in pulse interval (decrease in heart

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**Fig. 1.** Brachial arterial pressure. The upper panel is the control, obtained just as 50 μg phenylephrine were injected, but before drug effect. The lower panel is taken from the tracing 20 seconds later when systolic pressure was approximately 12 mm Hg higher. Cardiac slowing is evident. From the time of injection until the peak of the pressor effect each systolic pressure was plotted against its subsequent pulse interval (e.g., systolic pressure a plotted against interval a, etc.). See fig. 2 and text.
rate) per unit rise in systolic BP. Slope units are given in milliseconds increase in pulse interval per mm Hg rise in systolic pressure.

As opposed to reflex sensitivity, we also define reflex resetting as a change in position of the line with or without a change in slope. To determine reflex resetting, a vertical line was also constructed at the level of the control systolic BP. Values for pulse interval at this pressure were then obtained for all other lines produced by other phenylephrine injections during various experimental states in that subject. This allowed observation of pulse interval at a constant reference systolic BP, as shown in Figure 3, and provided a quantitative means of describing the positions of the various plots on the graph.

Systolic BP was chosen as the test variable, both because of the ease of measurement and because it provided the most favorable correlations with pulse interval. We are mindful of other determinants of baroreceptor stimu-
Table 1. Results

<table>
<thead>
<tr>
<th></th>
<th>Number of Subjects</th>
<th>Pulse Interval (msec)*</th>
<th>Systolic Pressure (mm Hg)*</th>
<th>Diastolic Pressure (mm Hg)*</th>
<th>Baroreflex Slope (msec/kg rise)</th>
<th>Pulse Interval at Reference Pressure (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awake</td>
<td>5</td>
<td>878 ± 46</td>
<td>132 ± 10</td>
<td>75 ± 5</td>
<td>5.7 ± 1.5</td>
<td>787 ± 51</td>
</tr>
<tr>
<td>Thiopental Probability</td>
<td></td>
<td>689 ± 58</td>
<td>134 ± 11</td>
<td>80 ± 5</td>
<td>5.3 ± 0.9</td>
<td>712 ± 58</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;0.05</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Awake</td>
<td>8</td>
<td>864 ± 62</td>
<td>131 ± 6</td>
<td>75 ± 3</td>
<td>10.6 ± 1.6</td>
<td>853 ± 71</td>
</tr>
<tr>
<td>N₂O + halothane Probability</td>
<td></td>
<td>1028 ± 68</td>
<td>103 ± 5</td>
<td>62 ± 4</td>
<td>5.9 ± 1.7</td>
<td>1114 ± 44</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;0.02</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
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<tr>
<td>Awake</td>
<td>4</td>
<td>819</td>
<td>130</td>
<td>73</td>
<td>9.1</td>
<td>791</td>
</tr>
<tr>
<td>N₂O alone</td>
<td></td>
<td>899</td>
<td>114</td>
<td>71</td>
<td>7.3</td>
<td>1006</td>
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<tr>
<td>Halothane + N₂O</td>
<td>1060</td>
<td>98</td>
<td>58</td>
<td>58</td>
<td>6.7</td>
<td>1153</td>
</tr>
</tbody>
</table>

* Steady state values before phenylephrine effect. Means ± 1 standard errors of the means are listed, as well as the probability values from comparison of means. NS = not significant.

lution, such as the rate of rise of arterial pressure and pulse pressure. However, pulse pressure usually did not change in response to phenylephrine injection, and the shape of the pressure wave was not altered sufficiently to produce important effects.

Results

Thiopental

Five patients were evaluated before and during thiopental anesthesia. There were two consistent changes within two minutes after induction (table 1): an average increase in heart rate of 19 beats per minute and a decrease in sensitivity of the reflex (fig. 4). Thus, a unit change in BP resulted in a 40 per cent smaller alteration in heart rate after anesthesia. The baroreflex lines produced immediately after induction were usually displaced downward, in addition to being flattened. The actual BP before pressor injection was sometimes higher, and sometimes lower, than in the awake state. The rapidly changing state associated with the brief action of thiopental was shown by repeated injections of phenylephrine at two-minute intervals (fig. 4). The lines shifted progressively toward the original control level with each subsequent injection.

Halothane and Nitrous Oxide

Observations during combined nitrous oxide (N₂O) and halothane anesthesia in six subjects and halothane alone in two were combined and compared with the control state. The results were obtained ten minutes or more after injection of thiopental and are summarized in table 1 and figure 5. Significant alterations were found in all measured variables. Slowing of the heart rate and decrease in BP as steady-state measurements during halothane anesthesia were characteristic in our patients, as in patients reported by others.4-6 Resting heart rate fell from 69 to 58 and systolic BP decreased 28 mm Hg, on the average. The combination of lowered BP and slower heart rate by itself is indicative of resetting of the baroreceptor reflex, since a lower BP would usually produce tachycardia as the traditional manifestation of the baroreflex response. Reflex resetting was further demonstrated by injection of phenylephrine. Reflex lines showed gross resetting as well as decrease in slope, the latter indicating a decrease in sensitivity. The degree of resetting was partly masked by the decrease in slope, placing the lines closer than they would have been otherwise (fig. 3). Despite this, the pulse interval at the reference BP increased 261 msec. The changes were generally similar in the two subjects who received halothane alone (fig. 6) and those who received a combination of halothane and N₂O.

In four subjects, the effects of N₂O alone were compared with the effects of the combination of N₂O and halothane. Average values for all of the measurements with nitrous
oxide fell between those found awake and during the combination of halothane and N₂O. In these four subjects, the pulse interval at the reference pressure increased 215 msec with N₂O, and an additional 149 msec when halothane was added.

**Discussion**

Our study shows that the relationship in which heart rate decreases in response to a rise in blood pressure is altered during anesthesia, i.e., baroreflex sensitivity was consistently diminished by the three agents tested. The steady-state relationship between BP and heart rate can also be changed profoundly, and we have termed this “resetting.” We have not analyzed which parts of the reflex were primarily changed by the anesthetics, but possible sites include the baroreceptors and the afferent pathway, integrating centers in the nervous system and efferent sympathetic or vagal pathways.

Anesthetics have been shown to influence the central control of the circulation. Our observation that barbiturate anesthesia resets the heart rate at a higher value for a given BP has been made by others. We found no significant change in BP with the dose of N₂O and halothane in two subjects. Marked reflex resetting is evident, with bradycardia and lower systolic blood pressure. N₂O alone produces reflex lines midway between the control state and the combination of N₂O and halothane.
Fig. 6. Effects of halothane, given via a permanent tracheostomy for induction and maintenance of anesthesia for plastic operation upon the tongue. Left panel: resetting and decreased sensitivity soon after induction with halothane. Right panel: dashed lines were produced by phenylephrine after operation, just before halothane was discontinued. Injections of phenylephrine were then obtained 7, 9, 30 and 54 minutes after anesthesia was stopped. Reflex setting moved to the right, opposite in direction to the change with halothane.

Thiopental used in this study, and it seems likely that the decrease in pulse interval was caused at least partially by the observed decrease in baroreflex sensitivity; i.e., the vagal "brake" on the heart was less at any given level of BP during thiopental anesthesia. Support of this concept comes from animal experiments showing that barbiturate anesthesia can abolish the effects of carotid sinus stimulation. In addition, an increase in circulating catecholamines or augmented sympathetic activity could be responsible. The former has been suggested after induction with thiopental in dogs, and baroreflex sensitivity was found to be markedly decreased at the onset of exercise in man, a time of marked adrenergic activity. Thus, barbiturate effects upon the reflex could be explained largely by influences on central nervous system centers, with relative inhibition of the vagus and stimulation of the sympathetic system.

Afferent activity of single units of the carotid sinus nerve increases during ether anesthesia, with a higher discharge rate at any given sinus pressure, demonstrating that ether anesthesia can alter the sensing apparatus. More recently, halothane too was shown to increase the frequency of discharges in single fibers of the carotid sinus nerve at any given pressure, and this change could account for the marked reflex resetting we observed with this agent. Halothane also influences the different arm of the reflex arc, and has been found to inhibit transmission in sympathetic ganglia; overall postganglionic activity is still increased above the control state, however. This latter evidence is difficult to interpret with regard to our studies because of the consistent bradycardia we observed. In view of the recognized negative inotropic effect of halothane, the possibility remains that it has a direct depressant influence on the heart's responsiveness to accelerator stimuli. The slow heart rate during halothane anesthesia is reversed by atropine, however, suggesting dependence largely upon vagal effects rather than a direct influence.

Species differences with N₂O may occur since reflex resetting with 80 per cent N₂O was directionally similar to that seen with halothane in our studies, whereas no effect was seen when the gas was inhaled by cats.

It is unlikely that changes in blood gas tensions were responsible for the observed effects upon the baroreflex during anesthesia, since hypercapnia with or without hypoxia causes resetting in the opposite direction to that observed with nitrous oxide or halothane. Furthermore, there is little effect on baroreflex sensitivity wrought by these changes in arterial gas tension, in contrast to the consistent alteration in sensitivity observed in our studies with anesthesia.

The present report does not answer all the questions about the phenomena we observed,
but provides some insight into control of heart rate during anesthesia and provides a method for studying autonomic changes during anesthesia.

References


