Effects of Anesthesia on the Canine Carotid Chemoreceptor Reflex

MICHAEL ZIMPFER, SIU PO SIT, AND STEPHEN F. VATNER

SUMMARY We studied the effects of α-chloralose (100 mg/kg, iv), Na pentobarbital (25 mg/kg, iv) and halothane (1 vol% and 2 vol%) on the response to carotid chemoreceptor stimulation (CCRS) in eight chronically instrumented dogs. CCRS was accomplished by means of intracarotid injections of nicotine while ventilation was held constant in the unanesthetized state and following administration of one of three different anesthetics. In the conscious state, CCRS elicited intense bradycardia and peripheral vasoconstriction as reflected by a 173 ± 14% increase in initial cardiac cycle length and a 216 ± 22% increase in mean iliac vascular resistance. Each anesthetic, studied on separate days, attenuated these responses to CCRS strikingly (P < 0.01). For instance, after α-chloralose, CCRS increased iliac resistance by only 55 ± 14% and cardiac cycle length by only 27 ± 13%. After Na pentobarbital, CCRS increased iliac resistance by 12 ± 4% and cardiac cycle length by 8 ± 5%. After inhalation of halothane (1 vol%), CCRS increased iliac resistance by 26 ± 7% and cardiac cycle length by 11 ± 8%, whereas halothane (2 vol%) abolished these responses to CCRS. Thus, general anesthesia interferes severely with carotid chemoreceptor control of the circulation. Whereas halothane and Na pentobarbital altered responses to CCRS the most, we found that even α-chloralose, which has been thought to maintain or augment reflex responses, was able to depress the response to CCRS strikingly.


The majority of experiments concerned with cardiovascular physiology in general, and neural control of the circulation in particular, have been conducted in anesthetized animals, often following extensive surgery. It remains controversial whether general anesthesia alone, i.e., in the absence of surgical manipulation, exerts any consistent effects on reflex control of the circulation. It is generally thought that baroreceptor reflex responses are enhanced by α-chloralose anesthesia (Brown and Hilton, 1956; Armstrong et al., 1961), whereas barbiturate anesthesia depresses these responses (Armstrong et al., 1961; Cox and Bagshaw, 1979). The effects of anesthesia on cardiovascular responses to stimulation of the arterial chemoreceptor reflex have not been studied as extensively.

The objective of the present investigation was to examine for the first time the effects of three commonly used anesthetics (Na pentobarbital, α-chloralose, and halothane) on cardiac and peripheral vascular responses to stimulation of one of the most powerful cardiovascular reflexes, the carotid chemoreceptor reflex. It is well recognized that...
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stimulation of the carotid chemoreceptor reflex elicits intense bradycardia and peripheral vasoconstriction (Comroe, 1964). Moreover, recent studies in conscious dogs indicated that the most intense peripheral vasoconstriction following carotid chemoreceptor reflex stimulation (CCRS) occurs in the iliac bed (Rutherford and Venner, 1978). Accordingly, the present investigation was concerned with the extent to which three anesthetics affected reflex bradycardia and iliac vasoconstriction in chronically instrumented dogs. To eliminate not only the antagonistic effects of activation of pulmonary inflation reflexes, but also the complicating influences of respiratory depression induced by general anesthesia, experiments also were conducted with ventilation controlled as has been done previously (Rutherford and Venner, 1978).

Methods

The response to CCRS was studied in eight mongrel dogs weighing 25-31 kg, in the conscious state, and during general anesthesia with three different anesthetics. Through a midline laparotomy under Na pentobarbital anesthesia (25 mg/kg, iv) the animals were instrumented with electromagnetic flow transducers (Zepeda Instruments) and a hydraulic cuff occluder around one of the common iliac arteries. Heparin-filled Tygon catheters were chronically implanted in the aorta and in one of the main carotid arteries with the tip just proximal to the carotid sinus, ensuring that the carotid arteries remained patent. Arterial blood pressure was measured with a Statham P23 Db strain gauge manometer (Statham Instruments), connected to the aortic catheter. Iliac blood flow was measured with an electromagnetic flow meter system (Benton Instruments). Occlusive zero flow was determined repeatedly throughout the experiments by inflating the previously implanted hydraulic occlusive cuff. The electromagnetic flow probes were calibrated by means of timed collections of blood when the animals were killed. Arterial samples from the aortic catheter were collected in iced, heparinized syringes, and arterial blood gases were measured with a Radiometer acid-base analyzer (PHM 71 Mk2) and blood microsystem (BMS Mk2) Radiometer.

The experiments were conducted 2-4 weeks after the operation when the dogs were vigorous and healthy. Recordings of iliac blood flow, arterial blood pressure, and heart rate were obtained continuously from the unsedated dogs in the conscious state, as well as in the anesthetized state. CCRS was accomplished by injection of nicotine (0.2-0.4 µg/kg) into the carotid catheter. In all experiments, the same dose of nicotine was injected in the conscious and anesthetized states. Since the chemoreceptor discharge normally fluctuates with the respiratory cycle (Biscoe and Purves, 1967; Fitzgerald et al., 1969), care was taken to perform the different injections of nicotine at the end-expiratory phase. In all dogs the effects of CCRS were examined in the conscious state with spontaneous ventilation. In three dogs the effects of CCRS also were examined after administration of either Na pentobarbital, 25 mg/kg, iv, or α-chloralose, 100 mg/kg, iv, or halothane 1 and 2 vol% and with spontaneous ventilation. Responses to CCRS also were compared in dogs before and after each of the anesthetics, but with respiration controlled under both conditions, to eliminate complicating influences due to variations in baseline levels of arterial blood gases, which could alter the responses to CCRS, as well as to avoid the documented antagonistic cardiovascular effects induced by secondary stimulation of pulmonary inflation reflexes (Venner and McRitchie, 1975; Rutherford and Venner, 1978; Venner and Rutherford, 1978; Venner et al., 1980).

To examine the effects of CCRS with ventilation controlled, succinylcholine was infused (100 µg/kg per min, iv) after an initial dose of 1 mg/kg, iv. Ventilation was controlled by a respirator, using a gas mixture of O2 and N2 (FiO2 = 0.3). Minute ventilation was adjusted to maintain arterial pH values within the normal range for unanesthetized animals, while arterial P O2 was maintained at a slightly higher and arterial PCO2 at a slightly lower level to ensure that the chemoreceptors were stimulated only minimally prior to injections of nicotine. To eliminate any distress associated with intubation or initiation of succinylcholine, sodium thiamylal (4 mg/kg, iv) was administered prior to intubation. Furthermore, 2 ml of a 2% lidocaine solution (Xylocaine) were administered through the cricothyroid membrane to anesthetize the trachea and the undersurface of the larynx, as is done in some patients. In addition the endotracheal tubes were coated with a local anesthetic ointment (Xylocaine 2%). Responses to CCRS were examined at least 30-60 minutes after the sodium thiamylal. This period is sufficient to exclude most, but not all, residual effects of this anesthetic. Since these dogs were not anesthetized, care was taken not to perform any intervention or experiment that was not tolerated by the conscious dogs in the absence of succinylcholine, as has been done previously in conscious rabbits (Korner et al., 1969; Korner et al., 1973) and dogs (Venner and McRitchie, 1975; Venner and Rutherford, 1978; Rutherford and Venner, 1978; Venner et al., 1980). It is important to note that tachycardia, a prominent feature of the canine response to discomfort, was not observed in the present study. Prior to inception of these experiments, the protocol was reviewed by the Animal Care Committee of the institution and was found to conform to the guidelines for research on experimental animals.

After three responses to CCRS had been obtained in the unanesthetized state, the animals were anesthetized with either α-chloralose (100 mg/kg, iv), as a 10% solution, dissolved in polyethylene glycol, or Na pentobarbital, (25 mg/kg, iv), or halothane 1 vol% followed by halothane 2 vol%. Only one of the three anesthetics was administered on a
single day. At least 48 hours elapsed before a second experiment was conducted. The sequence of anesthetics was randomized. The infusion of succinylcholine was maintained throughout the entire experiment. Control experiments indicated that neither prolonged succinylcholine infusion nor the vehicle for α-chloralose affected the response to CCRS. The halothane vaporizer was calibrated against an infrared analyzer (Beckman gas analyzer). After a steady level of anesthesia had been achieved (20 minutes for α-chloralose and 30 minutes for Na pentobarbital and halothane), CCRS was repeated at least three times over the subsequent 30–60 minutes.

The data were recorded on a multichannel tape recorder and played back on a direct-writing oscillograph. Mean iliac blood flow and mean arterial pressure were obtained with electronic resistance-capacitance filters with two second time constants. Mean iliac resistance was calculated as the quotient of mean arterial pressure and mean iliac blood flow. For the purpose of illustration, mean iliac resistance was computed using operational amplifiers configured for a divider circuit. Data for mean iliac blood flow and mean arterial pressure were averaged at the point of the peak increase in mean arterial pressure following CCRS. The bradycardia was evaluated at a rapid paper speed by comparing the pulse interval for the first beat following CCRS to the average of eight control beats prior to CCRS. The first beat following CCRS occurred prior to the rise in arterial pressure and thus avoided the complicating influences of arterial baroreceptor-mediated bradycardia. Sinus rhythm was confirmed by lead II of the electrocardiogram.

Average values ± SEM are reported throughout. Responses to CCRS were compared to control using Student's t-test for paired comparisons, while baseline values and responses to CCRS after each anesthetic were compared to the unanesthetized values using analysis of variance (Armitage, 1971).

**Results**

In conscious dogs with spontaneous respiration, CCRS elicited a biphasic cardiovascular response. The first phase was characterized by bradycardia and an increase in iliac resistance. The second phase closely followed the increases in ventilation, which occurred secondary to chemoreceptor stimulation, and was characterized by tachycardia and a decrease in iliac resistance. As shown previously (Rutherford and Vatner, 1978), the early phase was mediated primarily by the chemoreceptor reflex while the later phase was mediated by pulmonary inflation reflexes. Whereas responses to CCRS were attenuated severely by general anesthesia, it was unclear whether the attenuation was due to an effect on chemoreceptor or pulmonary inflation reflexes or to changes in arterial blood gases, induced by the depressant effects of anesthesia on ventilation. Accordingly, the remainder of the data are concerned with responses during controlled ventilation. Under these conditions, arterial blood gases were not significantly different in any of the states studied (Table 1). The average data for control values and responses to CCRS, as well as significant changes to CCRS and differences in response to CCRS before and after each anesthetic, are indicated in Table 2.

**Effects of Anesthesia on Baseline Values**

*Table 2*

α-Chloralose did not affect mean arterial pressure, iliac blood flow, or resistance, and tended to increase the baseline cardiac cycle length, but not significantly. Na pentobarbital increased heart rate, reduced mean iliac resistance, and increased iliac blood flow significantly. Halothane, both at 1 vol% and 2 vol%, reduced cardiac cycle length, mean arterial pressure, and iliac resistance significantly.

**Effects of Anesthetics on Cardiac Cycle Length**

The first beat following CCRS was compared to an average of eight control beats. In unanesthetized dogs, CCRS increased cardiac cycle length by 1189 ± 97 msec. Na pentobarbital, α-chloralose, and halothane 1 vol% reduced these responses to CCRS significantly and by similar amounts, whereas halothane (2 vol%) abolished the response.

**Effects of Anesthetics on Iliac Vascular Resistance**

In unanesthetized dogs, CCRS increased iliac vascular resistance strikingly (216 ± 22%). Moreover, these increases were similar on the three

<table>
<thead>
<tr>
<th>Arterial Blood Gases</th>
<th>Po2 (mm Hg)</th>
<th>PCO2 (mm Hg)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unanesthetized</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-Chloralose</td>
<td>108.4 ± 4.1</td>
<td>33.0 ± 2.6</td>
<td>7.40 ± 0.01</td>
</tr>
<tr>
<td>Na pentobarbital</td>
<td>103.2 ± 3.3</td>
<td>31.1 ± 1.0</td>
<td>7.41 ± 0.01</td>
</tr>
<tr>
<td>Unanesthetized</td>
<td>96.1 ± 6.8</td>
<td>34.1 ± 1.4</td>
<td>7.40 ± 0.02</td>
</tr>
<tr>
<td>Unanesthetized</td>
<td>109.1 ± 5.4</td>
<td>34.3 ± 1.7</td>
<td>7.40 ± 0.02</td>
</tr>
<tr>
<td>Halothane 1 vol%</td>
<td>126.4 ± 4.6</td>
<td>33.1 ± 2.3</td>
<td>7.39 ± 0.01</td>
</tr>
<tr>
<td>Halothane 2 vol%</td>
<td>119.0 ± 4.6</td>
<td>32.4 ± 1.5</td>
<td>7.40 ± 0.01</td>
</tr>
<tr>
<td>Halothane 2 vol%</td>
<td>116.5 ± 5.5</td>
<td>31.5 ± 1.3</td>
<td>7.39 ± 0.01</td>
</tr>
</tbody>
</table>
Table 2: Effects of Anesthetics on Responses to Carotid Chemoreceptor Stimulation (CCRS)

<table>
<thead>
<tr>
<th></th>
<th>Cardiac cycle length (msec)</th>
<th>Mean arterial pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Δ with CCRS</td>
</tr>
<tr>
<td>Unanesthetized</td>
<td>684 ± 43</td>
<td>1175 ± 112*</td>
</tr>
<tr>
<td>a-Chloralose</td>
<td>825 ± 88</td>
<td>180 ± 85†</td>
</tr>
<tr>
<td>Unanesthetized</td>
<td>684 ± 33</td>
<td>1209 ± 188*</td>
</tr>
<tr>
<td>Na Pentobarbital</td>
<td>487 ± 26†</td>
<td>44 ± 28†</td>
</tr>
<tr>
<td>Unanesthetized</td>
<td>702 ± 60</td>
<td>1187 ± 213*</td>
</tr>
<tr>
<td>Halothane 1 vol%</td>
<td>557 ± 57†</td>
<td>60 ± 26†</td>
</tr>
<tr>
<td>Halothane 2 vol%</td>
<td>526 ± 50†</td>
<td>8 ± 8†</td>
</tr>
</tbody>
</table>

Mean iliac flow (ml/min) Mean iliac resistance (mm Hg/ml per min)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Δ with CCRS</th>
<th>Control</th>
<th>Δ with CCRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unanesthetized</td>
<td>130 ± 10</td>
<td>-63 ± 10*</td>
<td>0.95 ± 0.09</td>
<td>1.85 ± 0.39*</td>
</tr>
<tr>
<td>a-Chloralose</td>
<td>126 ± 11</td>
<td>-27 ± 6†</td>
<td>1.06 ± 0.13</td>
<td>0.56 ± 0.14†</td>
</tr>
<tr>
<td>Unanesthetized</td>
<td>125 ± 11</td>
<td>-64 ± 9*</td>
<td>1.00 ± 0.14</td>
<td>2.07 ± 0.39*</td>
</tr>
<tr>
<td>Na Pentobarbital</td>
<td>165 ± 15†</td>
<td>-10 ± 4†</td>
<td>0.70 ± 0.08‡</td>
<td>0.08 ± 0.03†</td>
</tr>
<tr>
<td>Unanesthetized</td>
<td>114 ± 6</td>
<td>-62 ± 4*</td>
<td>1.00 ± 0.05</td>
<td>2.23 ± 0.28*</td>
</tr>
<tr>
<td>Halothane 1 vol%</td>
<td>127 ± 16</td>
<td>-17 ± 5†</td>
<td>0.77 ± 0.08‡</td>
<td>0.25 ± 0.07†</td>
</tr>
<tr>
<td>Halothane 2 vol%</td>
<td>113 ± 20</td>
<td>0 ± 0†</td>
<td>0.67 ± 0.09‡</td>
<td>0 ± 0‡</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM.
* Responses to CCRS significantly different from control, P < 0.01.
† Control or response to CCRS significantly different from unanesthetized, P < 0.01.
‡ Control or response to CCRS significantly different from unanesthetized, P < 0.05.

Figure 1: Responses to CCRS with nicotine (Nic 0.2 μg/kg) are shown on measurements of phasic and mean arterial pressure, phasic and mean iliac blood flow, and computed mean iliac resistance in an unanesthetized dog with controlled ventilation in the lefthand panel, and in the same dog after the addition of a-chloralose, 100 mg/kg, in the right hand panel. The iliac constriction induced by CCRS was depressed considerably by a-chloralose anesthesia. The increase in heart period, which occurred in the unanesthetized state prior to an increase in arterial pressure, occurred in this dog following chloralose administration after arterial pressure rose.
separate days (Table 2). The increases in iliac resistance with \( \alpha \)-chloralose (Fig. 1) (55 ± 14%), Na pentobarbital (Fig. 2) 12 ± 4%, and halothane 1 vol% (Fig. 3) (28 ± 7%) were significantly less than that observed in unanesthetized dogs, whereas halothane 2 vol% abolished the response (Fig. 3).

Discussion

It is generally held that anesthesia with \( \alpha \)-chloralose enhances activity of neural reflexes, whereas barbiturates exert the opposite effect. To a great extent this concept is based on studies by Armstrong et al. (1961) and Brown and Hilton (1956) who found that \( \alpha \)-chloralose augmented baroreceptor reflex responses, whereas barbiturate anesthesia depressed these responses. More recently these topics were investigated by Cox and Bagshaw (1979) and Hosomi and Sagawa (1979). The results of these studies are not entirely consistent with the generally held viewpoint noted above, in that Cox and Bagshaw (1979) found depressed responses to carotid occlusion after either \( \alpha \)-chloralose or Na pentobarbital, whereas Hosomi and Sagawa (1979) found that Na pentobarbital did not affect responses of arterial pressure and heart rate to a rapid withdrawal of 10% of blood volume. The extent to which halothane affects baroreceptor reflexes also remains controversial. On the one hand, Bagshaw and Cox (1977) concluded that baroreceptor control of the circulation was well preserved with halothane, and Bristow et al. (1969) found that, whereas baroreflex sensitivity was depressed by thiopental, it was only reset by halothane. On the other hand, Duke et al. (1977) concluded that halothane depressed baroreflex sensitivity, and Cox and Bagshaw (1979) observed that responses to carotid occlusion were depressed by this anesthetic.

The effects of anesthetics on chemoreceptor reflexes have been studied much less extensively. During anesthesia with \( \alpha \)-chloralose, an exaggerated sensitivity in response to CCRS was described by Dripps and Dumke (1943) in terms of increases in respiratory minute volume. Biscoe and Millar (1968) felt that pentobarbital did not affect carotid chemoreceptor discharge significantly, whereas halothane depressed the response. Duffin et al. (1976) also found that halothane depressed chemoreceptor reflexes, since the anesthetic depressed the normal
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**Figure 3** Responses to CCRS with nicotine (Nic 0.2 μg/kg) are shown on measurements of phasic and mean arterial pressure, phasic and mean iliac blood flow, and computed mean iliac resistance in an unanesthetized dog with controlled ventilation in the lefthand panel and in the same dog after the addition of halothane 1 vol% and 2 vol% (righthand panel). The iliac constriction and bradycardia induced by CCRS was depressed considerably by 1 vol% halothane anesthesia, whereas, 2 vol% of halothane abolished these responses.

respiratory response to two breaths of oxygen. It is important to note that none of these studies were concerned with the cardiovascular effects of chemoreceptor stimulation.

In the present investigation, it was found that increases in both cardiac cycle length and iliac vascular resistance in response to CCRS were strikingly depressed by all three anesthetics studied, i.e., by α-chloralose, Na pentobarbital, and halothane 1 vol%. Halothane at a concentration of 2 vol% abolished any detectable cardiovascular effects of CCRS. This study represents the first quantitative assessment of the extent to which anesthesia depresses cardiovascular responses to CCRS. Thus, the current results are not in contradiction to prior studies, since previous quantitative data in this area are lacking. However, it is of interest that Pelletier and Shepherd (1972) noted parenthetically that venous constrictor responses to chemoreceptor stimulation were depressed by supplemental doses of α-chloralose.

Since CCRS increases respiratory drive and stimulates pulmonary inflation reflexes secondarily (Daly and Scott, 1958; Daly and Scott, 1962; Vatner and McRitchie, 1975; Rutherford and Vatner, 1978; Vatner and Rutherford, 1978), and also because of the well known respiratory depressant effects of general anesthesia, the effects of the different anesthetic agents on the carotid chemoreceptor reflex were compared in this investigation in the anesthetized state with those obtained on the same day in the conscious dog with controlled normoventilation.

In the present investigation, only the responses of the iliac bed and cardiac rate to CCRS were examined. These were selected, since they are the most dramatic responses to CCRS. We previously have shown that the iliac bed is most sensitive to stimulation of the carotid chemoreceptors in the conscious dog (Rutherford and Vatner, 1978). It is also important to note that the bradycardia was examined for only the first beat after CCRS, since later beats could well be contaminated by bradycardia mediated through baroreceptor reflexes, as arterial pressure rises following CCRS. In contrast, arterial pressure either remained constant or fell at the time of initial cardiac rate response to CCRS. It
is recognized that the effects of CCRS on iliac vascular resistance were modulated by arterial baroreceptor reflexes. However, the arterial baroreceptors would tend to diminish the iliac vasoconstriction most in the unanesthetized dogs, in which the rise in arterial pressure was greatest. Thus, it is conceivable that differences in response to CCRS in conscious and anesthetized dogs were underestimated in this investigation. It should also be noted that failure of iliac vascular resistance to rise appropriately with CCRS was not due to an elevated baseline pressure caused by the anesthetic, i.e., reaching a "ceiling" level prior to CCRS. In fact, halothane and Na pentobarbital decreased iliac vascular resistance significantly, while α-chloralose did not exert a significant effect.

Whereas each anesthetic studied depressed the iliac vascular and bradycardiac responses to CCRS strikingly, this study was not designed to determine the location in the reflex loop at which the anesthetic exerted its depressant action. All general anesthetics affect the central nervous system, and, therefore, this potential locus for the depressed response cannot be excluded. It is also of interest that the study of Biscoe and Millar (1968) showed that halothane depressed chemoreceptor discharge, locating one source of reflex depression at the receptors or in the afferent neural transmission. Both efferent arms of the autonomic nervous system, i.e., the parasympathetic and sympathetic, manifested depressed responses to CCRS. This conclusion is based on the findings that depressed responses to CCRS were observed not only for heart rate, which is mediated by increased parasympathetic tone to the heart (Daly and Scott, 1958; Daly and Scott, 1962; Rutherford and Vatner, 1978), but also for iliac vascular resistance which is mediated by increased sympathetic tone to the periphery (Daly and Scott, 1962; Rutherford and Vatner, 1978).

In summary, whereas it is well recognized that general anesthesia exerts a variety of effects on almost every aspect of the cardiovascular system and its control, the extent to which anesthetics depress responses to CCRS have not been quantitated. Although halothane and Na pentobarbital altered responses to CCRS the most, even α-chloralose anesthesia, which has been thought to maintain or augment reflex responsiveness, was found to depress both chemoreceptor reflex responses of heart rate and iliac vascular resistance strikingly.

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