Influence of chloralose anesthesia on cardiovascular function in trained dogs

ROBERT H. COX

Bockus Research Institute and Department of Physiology, University of Pennsylvania, Philadelphia, Pennsylvania 19146

Chloralose is a widely used anesthetic agent for neurophysiological experiments involving the central nervous system and for experiments on neural control of the circulatory system. While it is known that chloralose causes hyperactivity of certain neural activities and neural-related reflex effects on the circulation (2, 3, 5), little is known of what chloralose does to the circulatory system itself. In a review of the circulatory effects of anesthetics, Greisheimer (9) reported that chloralose had been found to augment the activity of certain neural activities and neural-related reflexes controlling heart rate and arterial blood pressure in the dog but that no observations had been reported of its effects on peripheral resistance. Greisheimer reported further that chloralose produces tachycardia and increases arterial blood pressure in the dog but that no observations had been made on the hemodynamic alterations produced by acute chloralose anesthesia in trained, chronically instrumented mongrel dogs. In addition, the hemodynamic responses to intravenous injections of norepinephrine and isoproterenol were only slightly affected by chloralose. With the former drug, the results suggest that the mechanoreceptor reflexes controlling heart rate are exaggerated by chloralose. No direct action on vascular smooth muscle could be demonstrated.


The acute hemodynamic responses to chloralose anesthesia were determined in nine trained, chronically instrumented mongrel dogs. They were instrumented for the measurement of ascending aorta pressure and blood flow, and left ventricular and central venous pressures. The acute administration of chloralose was associated with transient changes in hemodynamic variables of which returned to preanesthesia control levels about 15 min after the beginning of the administration of chloralose. The cardiovascular responses to the intravenous injection of norepinephrine and isoproterenol were obtained before and 60 min after the induction of anesthesia. These procedures were performed to gain some insight into alterations in cardiovascular regulatory mechanisms produced by chloralose in the intact animal.

METHODS

Fifteen healthy, adult, mongrel dogs averaging 22 kg in body weight were selected for these experiments. Successful experiments were performed on nine dogs (six were the same animals used in a companion study (7)). A detailed description of the methods employed in this study have been given elsewhere (7).

<table>
<thead>
<tr>
<th>Exp No.</th>
<th>Dogs</th>
<th>MAP (mm Hg)</th>
<th>CO (liters/min)</th>
<th>PR (mm Hg)</th>
<th>dP/dt (mm Hg/sec)</th>
<th>SV (ml)</th>
<th>LV dP/dt (mm Hg/sec)</th>
<th>aorta blood flow (ml/sec)</th>
<th>LVEDP (mm Hg)</th>
<th>VP (mm Hg)</th>
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<td></td>
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<tr>
<td>2</td>
<td>20 F</td>
<td>92 ± 0.2</td>
<td>2.7 ± 0.2</td>
<td>844 ± 37</td>
<td>9.0 ± 1.2</td>
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<tr>
<td>4</td>
<td>20 M</td>
<td>99 ± 0.3</td>
<td>2.0 ± 0.2</td>
<td>820 ± 41</td>
<td>16.2 ± 1.2</td>
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<tr>
<td>5</td>
<td>21 M</td>
<td>98 ± 0.3</td>
<td>3.1 ± 0.3</td>
<td>948 ± 42</td>
<td>7.8 ± 1.2</td>
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<tr>
<td>6</td>
<td>23 M</td>
<td>112 ± 0.1</td>
<td>3.3 ± 0.1</td>
<td>900 ± 23</td>
<td>7.4 ± 1.2</td>
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<tr>
<td>9</td>
<td>14 M</td>
<td>109 ± 0.1</td>
<td>4.2 ± 0.1</td>
<td>535 ± 19</td>
<td>6.1 ± 0.1</td>
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<tr>
<td>10</td>
<td>90 M</td>
<td>99 ± 0.2</td>
<td>4.1 ± 0.1</td>
<td>947 ± 30</td>
<td>8.4 ± 1.2</td>
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<tr>
<td>11</td>
<td>19 F</td>
<td>87 ± 0.1</td>
<td>3.2 ± 0.1</td>
<td>953 ± 35</td>
<td>7.8 ± 1.2</td>
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<tr>
<td>12</td>
<td>18 F</td>
<td>100 ± 0.1</td>
<td>3.8 ± 0.1</td>
<td>879 ± 31</td>
<td>9.0 ± 1.2</td>
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</tr>
<tr>
<td>13</td>
<td>19 F</td>
<td>69 ± 0.1</td>
<td>3.4 ± 0.1</td>
<td>410 ± 32</td>
<td>6.4 ± 1.2</td>
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<tr>
<td>Avg</td>
<td>19</td>
<td>98 ± 0.2</td>
<td>3.6 ± 0.1</td>
<td>862 ± 32</td>
<td>2.8 ± 0.8</td>
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</tbody>
</table>

Values are means ± se. MAP = mean arterial pressure. CO = cardiac output. PR = peripheral resistance. T = heart period. SV = stroke volume. LV dP/dt = left ventricular pressure derivative. dQ/dt = ascending aorta flow derivative. LVEDP = left ventricular end diastolic pressure. VP = mean central venous pressure.

With these facts in mind, and because of the importance of making measurements in trained, chronically instrumented animals, the experiments reported herein were performed. It was the purpose of these experiments to determine the hemodynamic alterations produced by acute chloralose anesthesia in trained, chronically instrumented dogs. In addition, the hemodynamic responses to intravenous injections of norepinephrine and isoproterenol were obtained before and after the induction of anesthesia. These procedures were performed to gain some insight into alterations in cardiovascular regulatory mechanisms produced by chloralose in the intact animal.

With the facts in mind, and because of the importance of making measurements in trained, chronically instrumented animals, the experiments reported herein were performed. It was the purpose of these experiments to determine the hemodynamic alterations produced by acute chloralose anesthesia in trained, chronically instrumented dogs. In addition, the hemodynamic responses to intravenous injections of norepinephrine and isoproterenol were obtained before and after the induction of anesthesia. These procedures were performed to gain some insight into alterations in cardiovascular regulatory mechanisms produced by chloralose in the intact animal.
FIG. 1. Transient hemodynamic response to chloralose anesthesia. Hemodynamic variables are arterial pressure (AP) in mm Hg, mean arterial pressure (MAP) in mm Hg, ascending aorta flow (AQ) in liters/min, cardiac output (CO) in liters/min, peripheral resistance (PR) in $10^5$ dynes sec cm$^{-2}$, aortic flow derivative (DQDT; $dQ/dt$ in text) in liters/sec$^2$, stroke volume (SV) in ml, heart period (T) in seconds, the left ventricular pressure (LVP) in mm Hg, left ventricular end diastolic pressure (LVDPDT; LV dP/dt in text) in mm Hg/sec, and venous pressure (VP) in mm Hg. Slow-speed record shows acute hemodynamic response to chloralose induction, while faster speed records show values at specific times after induction.

Arch, left ventricle, and inferior vena cava with the use of Statham P23Gb monometers and previously implanted catheters. The data were recorded on an ink recorder (Brush model 200) and on magnetic tape (Sangamo model 471RB). After stabilization, initial control recordings were made and the responses to intravenous bolus injections of $l$-norepinephrine bitartrate (Levophed; Winthrop Laboratories, N.Y.C.) (5 and 10 $\mu$g) and isoproterenol hydrochloride (Isuprel; Winthrop Laboratories) (1 and 2 $\mu$g) were obtained. After recovery, the animals were anesthetized with $\alpha$-chloralose (H. P. Rossiger and Co., N.Y.C.) (100 mg/kg). The hemodynamic responses to anesthesia were followed for 60 min and then the drug injections were repeated. No attempt was made to maintain the animals in a particular stage of anesthesia. The anesthetic dose employed (100 mg/kg) is that usually reported for experimental procedures (15), and no supplemental anesthesia was administered. Also, no attempt was made to produce uniform levels of anesthesia in the individual animals. The doses of drugs utilized herein were those which, in preliminary experiments, were found to produce significant hemodynamic and reflex responses without causing arousal or excitement of the animals. The experimental data recorded on magnetic tape were analyzed using special-purpose analog circuitry as previously described (7).

RESULTS

Control values of some important hemodynamic variables from the individual animals are given in Table 1. Included in the table are the mean values and standard deviations from the individual experiments as well as the average of the mean values (at the bottom) and the standard errors of the means. These data are similar to values obtained previously in this laboratory as well as to data published in the literature.
Effects of anesthesia. Figure 1 shows typical analog responses to the acute injection of chloralose in one dog. High-speed records are shown for control conditions and at 5, 15, and 30 min after the beginning of anesthesia induction. The induction of anesthesia was performed during the period of time indicated by the dark bar at the bottom of the chart. It is apparent that the acute effects of chloralose are manifest before anesthesia induction was completed. In

**TABLE 2. Hemodynamic parameters before and 60 min after chloralose anesthesia**

<table>
<thead>
<tr>
<th>TIME</th>
<th>MAP, mm Hg</th>
<th>CO, liters/min</th>
<th>FR, $10^3 \times$ dynes cm$^{-2}$</th>
<th>T, msec</th>
<th>SV, ml</th>
<th>LV dP/dt, $10^3 \times$ dynes cm$^{-2}$</th>
<th>dQ/dt, liters/sec</th>
<th>LVEDP, mm Hg</th>
<th>VP, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>101 $\pm$ 3</td>
<td>2.4 $\pm$ 0.2</td>
<td>3.9 $\pm$ 0.4</td>
<td>820 $\pm$ 2</td>
<td>33 $\pm$ 2</td>
<td>3.1 $\pm$ 0.2</td>
<td>8.9 $\pm$ 2</td>
<td>5.1 $\pm$ 0.2</td>
<td>2.5 $\pm$ 0.2</td>
</tr>
<tr>
<td>60 min</td>
<td>110 $\pm$ 7</td>
<td>2.3 $\pm$ 0.2</td>
<td>4.2 $\pm$ 0.5</td>
<td>729 $\pm$ 4</td>
<td>27 $\pm$ 2</td>
<td>3.1 $\pm$ 0.2</td>
<td>5.4 $\pm$ 3</td>
<td>3.0 $\pm$ 0.8</td>
<td></td>
</tr>
</tbody>
</table>

Values are means $\pm$ se. MAP = mean arterial pressure. CO = cardiac output. FR = peripheral resistance. T = heart period. SV = stroke volume. LV dP/dt = left ventricular pressure derivative. dQ/dt = ascending aorta flow derivative. LVEDP = left ventricular end-diastolic pressure. VP = mean central venous pressure.
CARDIOVASCULAR RESPONSES UNDER CHLORALOSE

**FIG. 4.** Peak percentage responses to norepinephrine averaged from all experiments. Open circles represent values before, and closed squares after, chloralose anesthesia. Vertical lines show SEM. Any significant differences are indicated by relevant P values given above norepinephrine dose level. Arrows indicate time of injection.

This animal these effects included a transient hypotension, tachycardia, peripheral vasodilatation, and an increase then decrease in cardiac output, among others. Venous pooling as well as myocardial depression are associated with the acute response. The sinus arrhythmia present before anesthesia is suppressed during the acute response. After this acute response, the hemodynamic variables slowly return to the control values. A summary of the analog responses 2, 5, 15, 30, and 60 min after anesthesia are given in Fig. 2. The individual variables are given as percentages of the initial preanesthesia control values. In general, the acute effects of chloralose anesthesia last about 15 min. By that time, the hemodynamic variables return to control levels and are not significantly different from the control values for 60 min. The control values and values 60 min after the initiation of induction are summarized in Table 2. None of these hemodynamic variables shows significant differences under the two conditions.

**FIG. 5.** Average percentage transient responses to 10 μg of norepinephrine before (open circles) and after (closed circles) chloralose anesthesia. Vertical lines are SE. Data points are averaged every 5 sec after norepinephrine injection. Significant differences (P < 0.05) are indicated by an asterisk above or below pertinent points. Symbols used are same as those defined in Fig. 1. Ordinates of each variable are percent of control values.

**FIG. 5.** See adjoining column for legend.
Norepinephrine responses. Figure 3 shows an example of analog responses to a 5 µg intravenous injection of norepinephrine before and about 60 min after anesthesia. The curves on the left show the responses before chloralose. The slow-speed tracings show the complete responses while the faster tracings show the various hemodynamic variables before injection and during the peak inotropic and chronotropic responses. The curves on the right represent similar responses after anesthesia.

A summary of the average values of the control and peak responses to 5 and 10 µg of norepinephrine from the various experiments is given in Fig. 4. The open circles represent values averaged over all the experiments before anesthesia, and the closed squares represent data from responses after anesthesia. The responses are given as percent of control in each experiment. The vertical bars represent standard errors. The existence of statistically significant differences (P < .05) between the two conditions is indicated by asterisks above the data points. The differences, where present, are generally scattered throughout the time course of the response.

Isoproterenol responses. Examples of the analog responses to a 1 µg intravenous injection of isoproterenol are shown in Fig. 6. The tracings on the left are the responses before anesthesia, and those on the right, after anesthesia. Again, the high-speed tracings are responses before injection and during the peak inotropic and chronotropic responses. An intermittent contact in one channel of the tape-recorder electronics caused the strange response of the venous pressure before chloralose. It is apparent that the responses before and after anesthesia are very similar.

The peak responses averaged over all the experiments and represented as a percentage of control are summarized in Fig. 7. The open circles are average data before and the closed squares after anesthesia. The only significant differences that occurred were in the left ventricular pressure-derivative responses.

Figure 8 shows a summary of the transient responses to 2 µg of isoproterenol as previously described. Significant differences, indicated by the asterisks, existed in both the aortic flow derivative and left ventricular pressure derivative. Mean arterial pressure was higher for a short time.
FIG. 7. Peak percentage responses to isoproterenol averaged from all experiments. Open circles represent values before, and closed squares after, chloralose anesthesia. Vertical lines show SEM. Any significant differences are indicated by relevant P value given above isoproterenol dose level. Arrows indicate time of injection.

Other scattered differences also were found as indicated. During anesthesia after the peak response had occurred.

DISCUSSION

Effects of chloralose. Despite the widespread use of chloralose as an anesthetic agent in experimental investigations, its hemodynamic effects have not been extensively studied. Much more is known of its effects on the central nervous system and on reflex mechanisms (3). Most of the work documenting the hemodynamic effects of chloralose was performed without preanesthesia control data (e.g., 1, 3, 14). Only one study of the hemodynamic effects of chloralose has involved measurements in chronically instrumented animals (16). This study, however, was only descriptive in nature and included no quantitative results. We have utilized methods herein that were described previously and applied to the study of pentobarbital anesthesia (7). These methods involving chronically instru-
mented animals allow not only the determination of the acute hemodynamic effects of anesthesia, but also its effects on integrated control mechanisms.

The control unanesthetized values of the hemodynamic variables summarized in Table 1 are similar to data published by other investigators using similar methods. The variability of these data, both between animals and in the same animal, is readily apparent. The latter variability is primarily due to the existence of respiratory-related sinus arrhythmias, which is often used as a measure of the unexcited animal. The induction of anesthesia by chloralose (100 mg/kg) is associated with substantial transient hemodynamic changes which last about 5-15 min after the initiation of administration. The principal transient effects are a peripheral vasodilation, a loss of arrhythmia and resulting tachycardia, myocardial depression, and central venous pooling. Most of these transient changes are quickly reversed, and 15 min after induction they have generally returned to control values. As shown in Table 2, 60 min after induction none of these hemodynamic variables are significantly different from control, pre-anesthesia values. These transient and acute effects of chloralose are summarized in the average results shown in Fig. 2.

It is difficult to compare the acute hemodynamic effects of chloralose found in this study to data in the literature. In the hemodynamic data under anesthesia, the values given here for mean arterial pressure and heart rate are consistently lower than values given by others (1, 4, 6, 14). It is, in fact, often stated that tachycardia is a characteristic of chloralose anesthesia (4, 9). This was not a finding in these experiments.

It has been reported that chloralose converts irregular rhythms to regular ones (8, 16). This was found in this study, but only transiently. After ca. 10 min of anesthesia arrhythmias begin to occur. At ca. 15 min (Fig. 1), a substantial arrhythmia exists which usually shows a different pattern from the control. It has been suggested that chloralose inhibits the parasympathetic nervous system (9). If this were true, it would be unlikely that the low heart rates or the arrhythmias found in this study under chloralose anesthesia would exist.

In experimental applications, chloralose anesthesia is usually performed with some preanesthetic agent, usually morphine. However, morphine itself produces direct and reflex changes which may exaggerate or counteract the effects of chloralose per se (8, 11). It was the objective of these experiments to study the effects of only chloralose; therefore, no other drug was given to these animals.

Norepinephrine responses. A comparison of the hemodynamic responses to norepinephrine before and after chloralose permits an indirect assessment of cardiovascular reflexes and responsiveness. There were only minor differences in the norepinephrine responses summarized in Figs. 4 and 5. No significant differences were observed at the lower dose level, while the peak heart period and stroke volume were higher after chloralose anesthesia. The heart-period response to norepinephrine is the sum of the positive chronotropic action of the drug, which reduces the heart period, and the effects of hypertension on the mechanoreceptors, which would increase the heart period. Under unanesthetized conditions, these two effects offset each other and no net change results. Under chloralose, however, the heart period increases significantly. It has been reported that baroreceptors are overactive under chloralose anesthesia (2, 5). This could explain the observed increase in heart period under chloralose which occurs in response to the same increase in mean arterial pressure. This results in an increased stroke volume probably due to the prolonged diastolic filling time. The cardiac output does not increase but, in fact, decreases because the heart period increase exceeds the stroke volume increase.

Hyperresponsive mechanoreceptor mechanisms would be expected to cause exaggerated reflex changes in peripheral resistance as well as in heart period. It could be expected, therefore, that a smaller increase in peripheral resistance would occur under chloralose. This, in fact, was not observed—no significant differences existed at either dose level. The significance of this cannot be assessed from the data given herein.

Isoproterenol responses. The norepinephrine responses demonstrate that chloralose causes only minimal alterations in the cardiovascular system. This conclusion is supported by the isoproterenol responses which are summarized in Figs. 7 and 8. The isoproterenol responses are virtually unaltered by chloralose. The only variables affected are the left ventricular pressure derivative and the aortic flow derivative, both of which are increased. Both of these variables were also elevated by chloralose in response to norepinephrine. These quantities have been used as indices of myocardial contractile force (10, 12). These results could be interpreted to indicate that chloralose enhances myocardial contractile force. However, in fact, just the opposite effect has been shown to exist. Chloralose causes direct myocardial depression (13). It is to be anticipated, however, that sympathetic outflow to the heart would increase as a compensatory mechanism to depression (13), and chloralose has been shown to increase the excitability of the sympathetic nervous system (3). Therefore, the increase in these indices is possibly due to the increase in sympathetic nerve activity.

In summary, we have shown that acute anesthesia with \(\alpha\)-chloralose (100 mg/kg) produces no change in systemic hemodynamics except for a brief, transient phase immediately after injection which lasts about 15 min. The cardiovascular responses to intravenous injection of norepinephrine and isoproterenol indicate that the heart rate response to hypotension and hypoxia are exaggerated under chloralose anesthesia. No direct action of chloralose on vascular smooth muscle responsiveness could be demonstrated.

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