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# INFLUENCE OF CHLORALOSE AND PENTOBARBITONE SODIUM ON ATRIOVENTRICULAR CONDUCTION IN DOGS

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**1** Atrial pacing at progressively increasing frequencies was performed on unanaesthetized dogs through electrodes placed aseptically in the wall of the right atrium and exteriorized in the neck region.

**2** Heart rate and two atrioventricular conduction (AVC) parameters, namely the Wenckebach Point (one or two systole block at the end of expiration) and the maximum atrioventricular conduction frequency (the frequency of pacing for which ventricles do not follow any auricular stimulation) were measured by electrocardiography.

**3** Chloralose (0.08 g/kg i.v.) did not affect either heart rate or AVC but significantly reduced the effect of atropine (0.1 mg/kg i.v.) on all three parameters measured. The effect of isoprenaline ($0.25\ \mu g\ kg^{-1}\ min^{-1}$) remained unchanged.

**4** Pentobarbitone Na (25 mg/kg i.v.) increased heart rate and usually caused the Wenckebach Point to disappear. It reduced the effects of atropine but did not modify those of isoprenaline.

**5** In view of these results we suggest that pentobarbitone Na be avoided as an anaesthetic agent in AVC studies. It is possible to dispense with an anaesthetic agent if the technique described here is used.

## Introduction

Although pentobarbitone Na and chloralose are the two anaesthetics most frequently used in cardiovascular research, certain of their properties are not yet well-understood, particularly their action on atrioventricular conduction (AVC). Experimental difficulty may be partly to blame. Two methods of approach have been tried, both with obvious drawbacks. The first consists of inducing anaesthesia with chloralose (Calderon, Gomes & Friedman, 1974) or pentobarbitone Na (Jaillon, Cheymol & Rozensztajn, 1976) and then looking for AVC effects due to supplemental injections of the same anaesthetics. With the second method, the effects of pentobarbitone Na are studied in animals under a different anaesthetic (phenobarbitone, chloralose or ketamine) (Urthaler, Krames & James, 1974).

A straightforward study of the effects of chloralose and pentobarbitone Na on the P-R duration on the ECG would not by itself be an accurate enough measure of AVC modification. Extrastimulus techniques (Wit, Weiss, Berkowitz, Rosen, Steiner & Damato, 1970; Urthaler *et al.*, 1974; Bissett, Kane, de Soyza & Murphy, 1975) would be preferable or atrial pacing with progressively increasing frequency (Arnould, Duchêne-Marullaz, Boulange & Schaff, 1963; Scherlag, Lau, Helfant, Berkowitz, Stein & Damato, 1969). This last method was chosen here to investigate the effects of chloralose and pentobarbitone Na on AVC and any modifications due to these anaesthetics on the action of atropine and isoprenaline.

## Methods

Twelve mongrel dogs of either sex weighing on average $15 \pm 1$ kg were used. A thoracotomy was performed at the fourth right intercostal space in aseptic conditions under chloralose anaesthesia (0.08 g/kg i.v.). Two surgical electrodes set in stainless steel (laboratoires Bruneau) were implanted in the wall of the atrium. One was placed in the upper part of the atrium near the top of the Keith-Flack node, the other at the same height 2 cm away. The free ends were exteriorized in the neck region via a skin tunnel.

To assess the significance of the modifications on heart rate and AVC induced by chloralose and pentobarbitone Na, the effects of these anaesthetics on blood pressure were examined. In addition, in six dogs, a silastic catheter (Dow Corning 0.40 cm in i.d.) was chronically implanted in the thoracic aorta through the left external carotid and exteriorized at the back of the animal's neck to allow easy monitoring of blood pressure. The blood pressure catheter was regularly rinsed with heparin in saline at least

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once a week. The dogs were then trained to remain quiet on an examination table. Pharmacological tests were begun 10–15 days after implantation. The animals could thereafter be used for several months and be their own controls.

During tests, which were always carried out by the same experimenter for the same dogs, an electrocardiogram was recorded simultaneously in the three standard peripheral leads, or in lead I and lead II when the third track was used to monitor blood pressure, on a Philips Cardiopan 3 instrument. Blood pressure was measured with a Statham P23 dB unit. The two electrodes were connected to a Hugo-Sachs Stimulator type I 7170 A1; pulse duration was 1 ms. The excitation threshold was located and an intensity twice that of the threshold value was used. The values of the intensity were from 5 to 10 mV according to the dogs. The pacing frequency was initially set lower by several systoles/min than the spontaneous heart-rate, and then gradually increased. The following critical values were noted: (1) The pacing frequency at which the first blocked P-wave appeared on the ECG (Wenckebach point). P waves were rhythmically blocked in one or two systoles at the moment of expiration (first stage), (2) The frequency at which the ventricles do not follow any auricular stimulation (maximal atrioventricular frequency, MAVF) second stage. Only few atrial impulses crossed the AV node and caused a ventricular response.

The dogs randomized to one drug were split into groups, generally of six. Injections were made through a slender catheter inserted beforehand into a cephalic vein. Three control recordings were made in each case at 5 min intervals. After injection of the anaesthetic, atrial pacing was applied at regular intervals (see Tables). Individual experiments lasted 75 or 120 min. The animals were completely anaesthetized but they were not artificially ventilated since their chest was intact and closed. Spontaneous heart rates were measured over 30 s periods, and the action of the following compounds on the two above-mentioned parameters was examined: sterile saline solution (0.9% w/v NaCl solution); chloralose (Merck) (0.08 g/kg); pentobarbitone Na (Abott) (25 mg/kg); atropine sulphate (0.1 mg/kg) injected alone, before and after anaesthesia with pentobarbitone Na and chloralose; isoprenaline hydrochloride (Winthrop) perfused (Braun perfusor 0.1 ml/min) (0.25 $\mu g\,kg^{-1}\,min^{-1}$) before and after anaesthesia with pentobarbitone Na and chloralose. At least five days elapsed between successive tests on the same animal.

The statistical significance of the effect of the drugs as a function of time upon heart rate, Wenckebach point and MAVF was evaluated by two factor analysis of variance followed by Student's Fisher *t* test.

## Results

### *Control values*

At the beginning of the study the mean value ± s.e. of spontaneous heart rates was 88 ± 2 beats/min. Atrial pacing performed at a frequency slightly higher than the spontaneous heart rate produced a regular corresponding response in both atrium and ventricle. In six dogs regularly tested over 2 h and 15 min, the mean value ± s.e. of the Wenckebach point was 136 ± 2 beats/min. The Wenckebach point always coincided with the maximum degree of expiratory bradycardia (marked respiratory arrhythmia was present under these experimental conditions). Complete AV block occurred at much higher frequencies. The mean value ± s.e. of MAVF was 317 ± 8 beats/min. Injection of 5 ml of sterile saline solution modified none of the three parameters recorded, which remained stable throughout the 2 h of observation (Figure 1).

However, as the animals became used to the experiments, these values fell somewhat and became less scattered. The lowest control values before the pharmacological tests were 82 ± 4; 92 ± 6 and 203 ± 10 beats/min respectively for heart-rate, Wenckebach point and MAVF.

Average values of the systolic, diastolic and mean arterial pressure measured in individual animals under unrestricted control conditions were: 125 ± 2 mmHg, 88 ± 2 mmHg and 103 ± 2 mmHg.

### *Effects of chloralose* (Figure 2)

Chloralose tended to depress the heart rate, but never significantly. The value ± s.e. of heart rate before and after chloralose was 87 ± 9 and 78 ± 8 beats/min (20th min). The value ± s.e. of the Wenckebach point before and after chloralose was 107 ± 11 and 94 ± 11 beats/min (20th min). This last rose noticeably after the 70th min when the dogs were beginning to recover. The value ± s.e. of the Wenckebach point was 189 ± 43 beats/min at the 100th min. MAVF remained practically unchanged except for the very last value whose elevation can be attributed to the end of anaesthesia.

Mean arterial pressure increased gradually from the control value of 98 ± 3 to 125 ± 5 mmHg at 100 min and thereafter remained well above the control value.

The same effect was observed with systolic and diastolic arterial pressure.

### *Effects of pentobarbitone Na* (Figure 3)

No attempt was made to monitor either respiration, blood gas composition or acid-base balance. Pen-

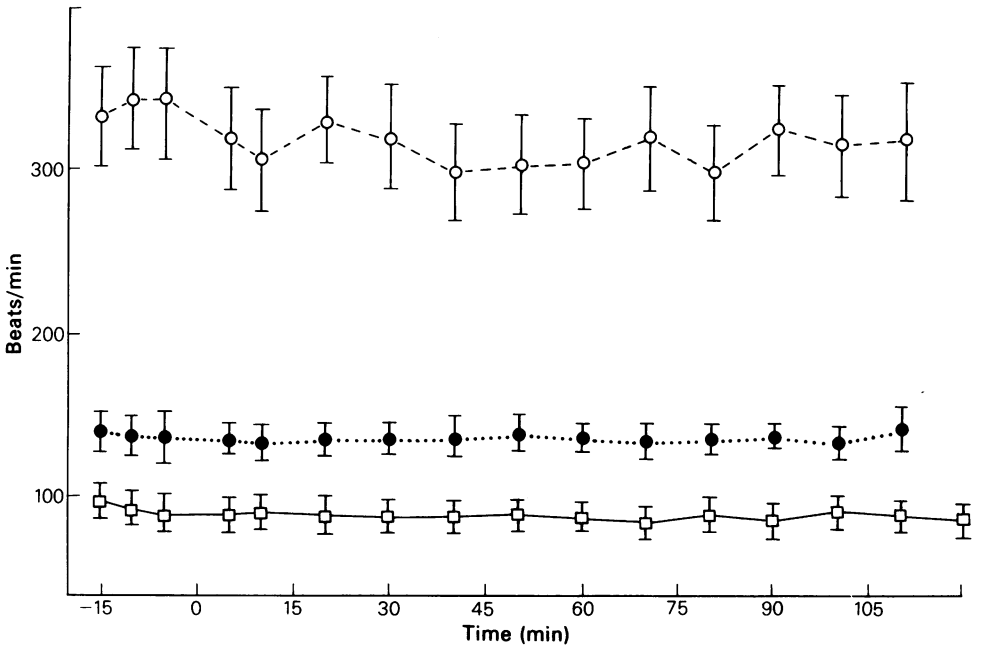


**Figure 1** Effects of an intravenous injection of 5 ml of sterile saline on heart rate (□), Wenckebach point (●) and MAVF (○) in the dog. Data are presented as mean with vertical lines indicating s.e. $n = 6$.

tobarbitone Na is known to produce alterations in these factors. However, it was decided that attempting to compensate for such alterations would be rather difficult because of animal-to-animal variability, and also because of the additional complexity introduced into the interpretation of experimental data. The animal's temperature was maintained at 37.5 ± 0.5°C by a heated pad.

Pentobarbitone Na initially raised the heart-rate from, 91 ± 7 to 161 ± 6 beats/min. This then fell and

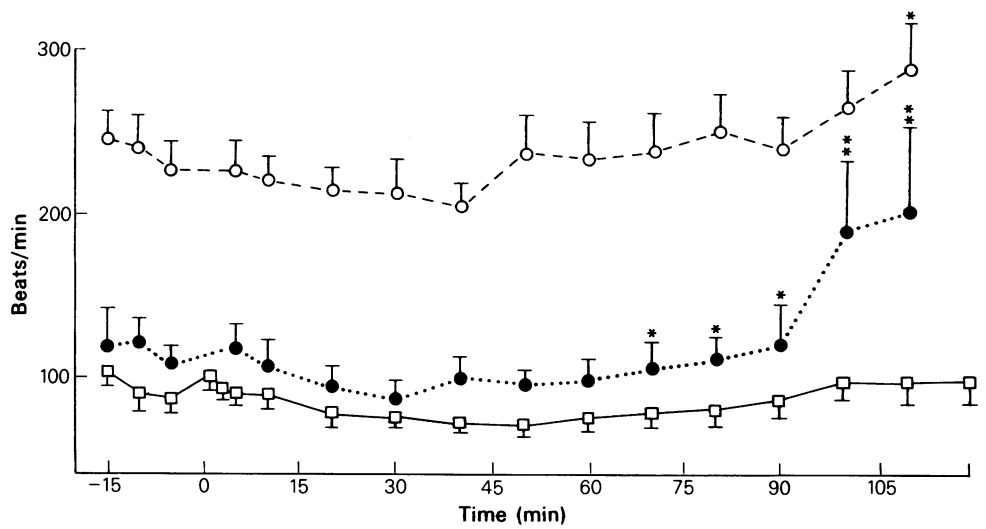


**Figure 2** Influence of chloralose (0.08 g/kg) on heart rate (□) and atrioventricular conduction in the dog. Wenckebach point (●) increased significantly only 70 min and MAVF (○) 115 min after a single dose of chloralose. Data are presented as mean with vertical lines indicating s.e. The significance of difference from the control group is in each case symbolized by: $*P < 0.05$; $**P < 0.01$. $n = 6$.

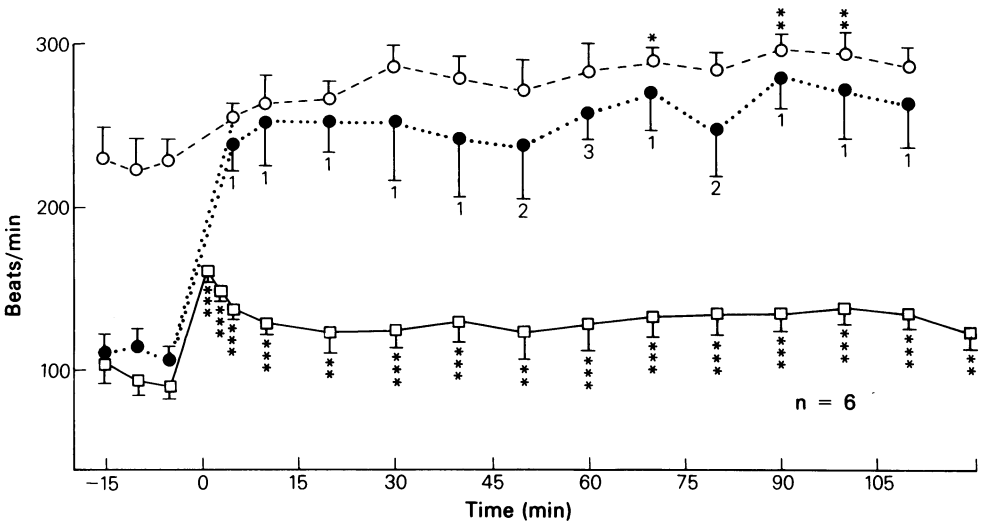


**Figure 3** Influence of pentobarbitone Na (25 mg/kg) on heart rate (□) and atrioventricular conduction. Pentobarbitone Na significantly increased heart rate. The numbers of dogs in which a Wenckebach point (●) could be demonstrated after pentobarbitone Na are indicated in the figure. Data are presented as mean with vertical lines indicating s.e. The significance of difference from the control group is in each case symbolized by: $*P<0.05$; $**P<0.01$; $***P<0.001$.

levelled off at about 130 beats/min by the 20th min. The elevation of heart-rate remained significant throughout the 2 h of observation. The Wenckebach point disappeared in all dogs except one in which it was markedly raised. MAVF increased significantly only for pacing performed at the 70th, 90th and 100th min. The value ± s.e. of MAVF before and after pentobarbitone Na was 227 ± 14 and 289 ± 7 beats/min (70th min), 296 ± 8 beats/min (90th min), 294 ± 12 beats/min (100th min).

Mean arterial pressure fell initially from the control value of 113 ± 12 to 88 ± 3 mmHg at 5 min, returned to the control value at 20 – 30 min and then increased and remained higher than the control value throughout the period of measurement. The value ± s.e. of mean arterial pressure was 138 ± 3 mmHg at the 40th and at the 120th min.

The same effect was observed with systolic and diastolic arterial pressure; for the diastolic arterial pressure, the return to the control value was at 10–20 min.

*Effects of atropine*

Atropine initially raised the heart-rate from 113 ± 12 to 217 ± 15 beats/min (5th min) (Table 1). The effect gradually decreased but still remained significant after 60 min. The Wenckebach point vanished completely in all dogs except for one dog in which it reappeared at a much higher value at the 60th min. MAVF also rose significantly reaching from 224 ± 27 to 345 ± 11 beats/min (5th min). (Table 2).

Administration of atropine (0.1 mg/kg) to four conscious dogs increased mean arterial pressure from the control value of 100 ± 0 to 110 ± 4 mmHg. Systolic arterial pressure was unchanged, only diastolic arterial pressure rose from 84 ± 2 to 102 ± 3 mmHg at 5 min.

*Effects of atropine after chloralose*

After chloralose, atropine raised the heart rate from 74 ± 7 to 191 ± 15 beats/min (5th min) (Table 1) and MAVF from 174 ± 26 to 277 ± 10 beats/min (5th min) (Table 2). Both values are lower ($P<0.01$) than those observed with atropine without chloralose.

Conscious intact dogs responded to atropine by increasing mean arterial pressure and diastolic arterial pressure while after chloralose anaesthesia the mean arterial pressure rose gradually from 100 ± 5 to 120 ± 0 mmHg and the systolic arterial pressure from 123 ± 7 to 135 ± 3 mmHg at 80 min.

*Effects of chloralose after atropine*

Chloralose significantly reduced the atropine-induced tachycardia (36%) (Table 1) and lowered MAVF (21%) (Table 2). The value ± s.e. of the heart rate before and after chloralose in atropinized dogs was 229 ± 18 and 148 ± 27 beats/min (20th min). Those of MAVF were 412 ± 9 and 317 ± 30 beats/min (20th min).

When anaesthesia was induced 15 min after at-

**Table 1** Effects of atropine, chloralose and pentobarbitone sodium on heart rate in the dog

| | | *Control* | 5 | 20 | 40 | 60 min |
|---|---|---|---|---|---|---|
| Atropine | $n=6$ | 113±12 | 217±15*** | 191±14*** | 181±12*** | 181±18*** |
| Atropine after chloralose | $n=6$ | 74±7 | 191±15*** | 155±4 *** | 136±4 ** | 126±6 ** |
| Chloralose after atropine | $n=4$ | 229±18 | 168±23*** | 148±27*** | 147±31*** | 154±32*** |
| Atropine after pentobarbitone Na | $n=6$ | 158±8 | 152±6 | 150±10 | 150±13 | 148±12 |
| Pentobarbitone Na after atropine | $n=4$ | 230±9 | 186±15*** | 169±25*** | 159±25*** | 159±26*** |

Atropine (0.1 mg/kg) significantly increased heart rate in the unanaesthetized dog and in the dog anaesthetized with chloralose (0.08 g/kg). Chloralose (0.08 g/kg) significantly decreased heart rate in the atropinized dog.

Heart rate was not affected by atropine (0.1 mg/kg) in the dog anaesthetized with pentobarbitone Na (25 mg/kg). Pentobarbitone Na (25 mg/kg) significantly decreased heart rate in the atropinized dog. Data are presented as mean±s.e. The significance of difference from the control group is in each case symbolized by: $*P<0.05$; $**P<0.01$; $***P<0.001$.

ropine, mean arterial pressure rose from 118±2 to 165±5 mmHg at 20 min. Systolic and diastolic arterial pressure rose by a similar amount.

*Effects of atropine after pentobarbitone Na*

Heart rate remained essentially constant when atropine was injected 15 min after pentobarbitone Na (Table 1). MAVF rose progressively after injection of atropine (Table 2) from 241±10 to 302±10 beats/min (60th min).

After pentobarbitone Na, anaesthetized intact dogs responded to atropine by a slow increase in mean arterial pressure, systolic and diastolic pressure.

Mean arterial pressure remained unchanged for 10 min, then rose from a control value under pentobarbitone Na of 85±15 to 125±5 mmHg at 70 min and thereafter remained elevated.

Analogous responses to pentobarbitone Na alone were observed. Atropine-induced increases in the mean arterial pressure and diastolic arterial pressure were not observed.

*Effects of pentobarbitone Na after atropine*

Pentobarbitone Na significantly reduced atropine-induced tachycardia (25%) (Table 1) and MAVF (18%) (Table 2). The value±s.e. of the heart rate before and after pentobarbitone Na in atropinized dogs was 230±9 and 169±25 beats/min (20th min). Those of MAVF were 387±14 and 323±3 beats/min (20th min).

When anaesthesia was induced 15 min after at-

**Table 2** Effect of atropine, chloralose and pentobarbitone sodium on maximum atrioventricular frequency (MAVF)

| | | *Control* | 5 | 20 | 40 | 60 min |
|---|---|---|---|---|---|---|
| Atropine | $n=6$ | 244±27 | 345±11*** | 350±16*** | 335±19*** | 341±19*** |
| Atropine after chloralose | $n=6$ | 174±26 | 277±10*** | 292±13*** | 283±18*** | 295±20*** |
| Chloralose after atropine | $n=4$ | 412±9 | 357±15 | 317±30*** | 320±33** | |
| Atropine after pentobarbitone Na | $n=6$ | 241±10 | 256±8 | 279±16** | 324±14*** | 302±10*** |
| Pentobarbitone Na after atropine | $n=4$ | 387±14 | 322±6 *** | 323±3 *** | 317±20*** | |

Atropine (0.1 mg/kg) significantly increased MAVF in the unanaesthetized dog and in the dog anaesthetized with chloralose (0.08 g/kg). Chloralose (0.08 g/kg) significantly decreased MAVF in the atropinized dog.

Atropine (0.1 mg/kg) progressively increased MAVF in the dog anaesthetized with pentobarbitone Na (25 mg/kg). Pentobarbitone Na (25 mg/kg) significantly decreased MAVF in the atropinized dog. Data are presented as mean±s.e. The significance of difference from the control group is in each case symbolized by: $*P<0.05$; $**P<0.01$; $***P<0.001$.

**Table 3** Effects of isoprenaline infusions ($0.25\,\mu g\,kg^{-1}\,min^{-1}$) on heart rate and maximum atrioventricular frequency (MAVF) in the dog

| | | *Heart rate* | *1st stage Wenckebach point* | *2nd stage MAVF* |
|---|---|---|---|---|
| *Control* | $n=7$ | $97\pm4$ | $118\pm4$ | $232\pm4$ |
| Isoprenaline | $n=6$ | $190\pm10$*** | | $344\pm10$*** |
| Pentobarbitone Na | $n=6$ | $130\pm8$ *** | | $264\pm16$*** |
| Isoprenaline after pentobarbitone Na | $n=7$ | $209\pm10$*** | | $357\pm8$ *** |
| Chloralose | $n=6$ | $78\pm8$ | $94\pm12$ | $216\pm12$*** |
| Isoprenaline after chloralose | $n=5$ | $190\pm7$ *** | | $346\pm7$ *** |

Isoprenaline ($0.25\,\mu g\,kg^{-1}\,min^{-1}$) perfused for 5 min significantly increased heart rate and MAVF in the unanaesthetized dog and in the dog anaesthetized with chloralose (0.08 g/kg) or pentobarbitone Na (25 mg/kg). Data are presented as mean ± s.e. ***$P<0.001$.

ropine, mean arterial pressure fell from the control value under atropine of $103\pm1$ to $93\pm3$ mmHg at 5–10 min, returned to the control value at 30 min and then rose slightly above the control value at 40 min.

If control values of mean arterial pressure in atropinized dogs after chloralose and after pentobarbitone Na are compared and if analogous analyses are performed with heart-rate values, it is evident that the increases in mean arterial pressure and the decreases in heart rate are consistently minor after pentobarbitone Na.

*Effects of isoprenaline*

Administration of isoprenaline ($0.25\,\mu g\,kg^{-1}\,min^{-1}$) to conscious dogs abolished the Wenckebach point, significantly raised the heart rate from $97\pm4$ to $190\pm10$ beats/min and decreased systolic arterial pressure from $125\pm0$ to $116\pm2$ mmHg (5th min). Mean arterial pressure and diastolic arterial pressure were all essentially the same as observed in controls.

Anaesthesia with pentobarbitone Na or chloralose did not modify the isoprenaline-induced tachycardia (Table 3). The value ± s.e. of the heart rate was $209\pm10$ beats/min with pentobarbitone Na and $190\pm7$ beats/min with chloralose. The systolic hypotension response to intravenous injection of isoprenaline was not observed under pentobarbitone Na anaesthesia and under chloralose anaesthesia.

Mean arterial pressure in dogs anaesthetized with pentobarbitone Na or chloralose (20 min after anaesthetic injection) was unchanged after administration of isoprenaline.

The value ± s.e. of mean arterial pressure was $128\pm12$ mmHg in dogs anaesthetized with chloralose, $128\pm17$ mmHg with isoprenaline and $108\pm2$ mmHg in dogs anaesthetized with pentobarbitone Na; $113\pm2$ mmHg with isoprenaline.

## Discussion

Two approaches are possible for the study of atrioventricular conduction. The method of extrastimulus (Krayer, Mandoki & Mendez, 1951; Moe, Preston & Burlington, 1956) is the most used especially in functional investigation in man (Wit *et al.*, 1970; Bissett, de Soyza, Kane & Murphy, 1974). The other method consists in carrying out atrial pacing at progressively higher frequencies (Arnould *et al.*, 1963; Damato, Lau, Helfant, Stein, Berkowitz & Cohen, 1969; Scherlag *et al.*, 1969; Rosen, Rahimtoola, Chuguimia, Loeb & Gunnar, 1971). The first technique needs relatively elaborate equipment while the second requires only a pulse generator. Both methods, according to Bissett *et al.* (1975), give quite comparable results in functional investigations in man.

In experiments with dogs, both methods are equally applicable whenever anaesthesia or post-operative shock have suppressed the phasic influence of cardiomoderator innervation. However, in the unanaesthetized dog, where marked respiratory arrhythmia affects sinus rhythm and atrioventricular conduction, the method of extrastimulus is only possible provided the stimuli are applied systematically at the same points in the respiratory cycle. It would further have to be assumed that the phasic effect of the cholinergic innervation remains constant from one respiratory cycle to the next. Thus the values of the effective refractory period of the total AV conducting system in the unanaesthetized dogs when measured with the extrastimulus method are not absolute, and there are wide variations in the intermediate ranges. It is thus apparent that the method of atrial pacing is to be preferred to the method of extrastimulus in the unanaesthetized dog, and this method was accordingly chosen for the present study.

In our experiments, chloralose tended to depress

heart-rate, but never significantly as there were wide variations from one dog to another, in agreement with our previous work (Duchêne-Marullaz, Delort & Vacher, 1964; Cox, 1972b) and neither did it have any noteworthy effect on AVC. Calderon *et al.* (1974) made a study 2 h after induction of anaesthesia with an intravenous bolus of chloralose 80 mg/kg (control), 15 min after an intravenous bolus of chloralose 40 mg/kg and 15 min after another bolus of chloralose 40 mg/kg (30 min after second bolus). The Wenckebach point occurred at lower pacing rates in seven dogs and was unchanged in three after chloralose. The authors concluded that chloralose delays AVC. However, it is possible that 2 h after onset of anaesthesia, certain animals may be beginning to recover and consequently show a relatively facilitated AVC. Such a possibility, which we have indeed encountered in our own experiments, could have been avoided by making further injections of chloralose.

The average values of the systolic, diastolic and mean arterial pressure ($125 \pm 2$, $88 \pm 2$ and $103 \pm 2$ mmHg respectively) are similar to values quoted by most other investigators in the trained, unanaesthetized dog (Horwitz, Bishop, Stone & Stegall, 1969; O'Rourke & Bishop, 1971; Vatner, Higgins, Franklin & Braunwald, 1971). Only a few studies on the acute responses to chloralose or pentobarbitone Na anaesthesia have been performed on chronically instrumented dogs (Van Citters, Franklin & Rushmer, 1964; Cox, 1972a, b). The induction of anaesthesia by chloralose (100 mg/kg) or by pentobarbitone Na (30 mg/kg) is associated with transient hypotension lasting about 5–15 min after the initiation of administration. After 15 min mean arterial pressure remains unchanged up to 60 min and longer (Cox, 1972a, b). For instance, arterial pressure is reportedly elevated in many studies in which chloralose or pentobarbitone Na are used as an anaesthetic (Barlow & Knott, 1964; Goldberg, Linde, Gaal, Momma, Takahashi & Sarna, 1968; Charney, Bass & Buckley, 1970; Arfors, Arturson & Malmberg, 1971). In this study mean arterial pressure was observed to rise gradually as a result of injection of chloralose. We found a transient hypotension during the first 5 min after induction of anaesthesia by pentobarbitone Na, followed by an increase in mean arterial pressure. The arterial pressure response to chloralose could be ascribed to increase in blood volume produced by the chloralose solution injected (10 ml/kg). The anaesthetic dose employed is that usually reported for experimental procedures. It has been reported that arterial pressure rises under pentobarbitone Na with surgical trauma or if the dogs are excited prior to the induction of anaesthesia and in contrast, does not change in trained dogs with low vagal tone indicated by the presence of arrhythmia (Cox, 1972a; Manders & Vatner, 1976). This was not found in this study, where a substantial arrhythmia was present, in our trained dogs prior to the induction of anaesthesia.

As expected (Gautrelet, 1918; Jourdan, Duchêne-Marullaz & Leusen, 1952) chloralose significantly reduced atropine-induced tachycardia whether injection of the anaesthetic was made before or after administering atropine. When atropine was administered after or before anaesthesia by chloralose, intact dogs responded by an increase in mean arterial pressure. In addition, chloralose significantly reduced the AVC-facilitating action of atropine.

The systolic hypotensive response to intravenous injection of isoprenaline ($0.25\ \mu g\ kg^{-1}\ min^{-1}$) was not observed under chloralose anaesthesia. The peak heart-rate increase was found unchanged before and after anaesthesia by chloralose. However, it did not modify the action of isoprenaline on conduction any more than its general haemodynamic properties (Cox, 1972b).

Pentobarbitone Na produced an immediate tachycardia which fell off partially in about 15 min, but remained significant for more than 2 h after injection. This observation is in agreement with all others previously reported (Nash, David & Woodbury, 1956; Barlow & Knott, 1964; Cox, 1972a). It is usually explained in terms of a vagolytic action (Schafer, Underwood & Gaynor, 1930; Olmstead & Page, 1966) but according to Manders & Vatner (1976), may be mainly due to an adaptation of barosensitive reflexes since heart rate did not remain elevated during pentobarbitone Na anaesthesia in denervated dogs. Pentobarbitone Na evidently does have an atropine-like action since the increase in heart-rate is accompanied by the disappearance of the Wenckebach point which depends essentially on vagus innervation. However, the effect of 25 mg/kg of pentobarbitone Na is much less marked than that of 0.1 mg/kg of atropine on heart rate and on MAVF, and even after pentobarbitone Na, atropine still raises both heart rate and MAVF. When pentobarbitone Na is injected after atropine it causes a noticeable decrease in heart-rate and MAVF. Other studies have indicated that the drug blocks ganglionic and peripheral sympathetic endings (Trethewie, 1953; Exley, 1954) and transmission in the nerve fibre (Toman, 1952). Other work reveals a direct effect of pentobarbitone Na on the heart, since a negative chronotropic effect of this anaesthetic has been reported on the isolated atrium of the guinea-pig in concentrations of 0.01 to 0.1 mg/ml (Schaer, 1964) or during perfusion of the artery of the Keith-Flack node (Chiba & Nakajima, 1972) in concentrations of 30 μg to 10 mg/ml. Urthaler *et al.* (1974) in perfusions of both the artery of the SA node and of the artery supplying the Tawara node found pentobar-

bitone Na in a concentration of $10^{-4}$ to $10^{-3}$ μg/ml to possess negative chronotropic and dromotropic effects.

The arterial pressure responses to 0.1 mg/kg of atropine before and after anaesthesia by pentobarbitone Na were comparable with responses obtained before and after anaesthesia by chloralose. However, the peak mean arterial pressure increase and the peak heart-rate decrease were greater before chloralose than before pentobarbitone Na. These results suggest that baroreceptors may be overactive under chloralose anaesthesia (Brown & Hilton, 1956; Armstrong, Porter & Langston, 1961) and underactive under pentobarbitone Na anaesthesia (Cox, 1972a).

Cox (1972a) noticed that pentobarbitone Na reduced the increase in heart rate and output caused by isoprenaline. We have not found any modifications of isoprenaline-induced tachycardia under pentobarbitone Na. This difference may be due to the fact that Cox (1972a) made injections of 1, 2 and 4 μg of isoprenaline whereas we used perfusions of 0.25 $\mu g\,kg^{-1}\,min^{-1}$ over 5 min. As for the influence of chloralose or pentobarbitone Na on the isoprenaline responses, no heart rate response to isoprenaline-induced hypotension could be demonstrated since with chloralose an increase in arterial pressure occurred. With pentobarbitone Na, a reduction in the sensitivity of the peripheral mechano-receptor reflexes could explain this finding.

In summary, if it is not convenient to use pre-instrumented animals, it is possible to use chloralose as an anaesthetic in AVC studies. Stimulation probes can be introduced through the femoral vein into the right atrium for variable-frequency pacing. This method would seem to be the only one possible when marked respiratory arrhythmia is encountered. On the other hand, the use of pentobarbitone Na is best avoided since, depending on conditions, positive chronotropic and dromotropic effects by weakening of vagal tone, and a depressant effect on the SA node and AVC are demonstrable.

## References


ARFORS, K.E., ARTURSON, G. & MALMBERG, P. (1971). Effect of prolonged chloralose anesthesia on acide base balance and cardiovascular functions in dogs. *Acta physiol. scand.*, **81**, 47–53.

ARMSTRONG, C.G., PORTER. H. & LANGSTON, J.B. (1961). Alteration of carotid occlusion response by anesthesia. *Am. J. Physiol.*, **210**, 897–900.

ARNOULD, P., DUCHENE-MARULLAZ, P., BOULANGE, M. & SCHAFF, G. (1963). Le tonus dromotrope des nerfs extrinsèques du coeur chez le chien. *C.R. Soc. Biol.*, **157**, 1069–1071.

BARLOW, G. & KNOTT, D.H. (1964). Hemodynamic alterations after 30 minutes of pentobarbital sodium anesthesia. *Am. J. Physiol.*, **207**, 764–766.

BISSETT, J.K., KANE, J.J., DE SOYZA, N. & MURPHY, M.L. (1975). Electrophysiological significance of rapid atrial pacing as a test of atrioventricular conduction. *Cardiovasc. Res.*, **9**, 593–599.

BISSETT, J.K., DE SOYZA, N., KANE, J.J. & MURPHY, M.L. (1974). Improved intraventricular conduction of premature beats after diphenylhydantoin. *Am. J. Cardiol.*, **33**, 493–497.

BROWN, R.V. & HILTON, J.G. (1956). The effectiveness of the baroreceptor reflexes under different anesthetic. *J. Pharmac. exp. Ther.*, **118**, 198–203.

CALDERON, J., GOMES, J.A.C. & FRIEDMAN, H.S. (1974). Effect of alpha chloralose on the canine conduction system (Abstract). *Clin. Res.*, **22**, 677A.

CHARNEY, A.N., BASS, B.G. & BUCKLEY, N.M. (1970). Cardiovascular effects of chloralose in catecholamine-depleted or receptor blocked dogs. *Archs int. Pharmacodyn.*, **185**, 397–405.

CHIBA, S. & NAKAJIMA, T. (1972). Effect of sodium pentobarbital on the S.A. nodal activity of the dog heart *in vivo*. *Tohoku J. exp. Med.*, **106**, 381–387.

COX, R.H. (1972a). Influence of pentobarbital anesthesia on cardiovascular function in trained dogs. *Am. J. Physiol.*, **223**, 651–659.

COX, R.H. (1972b). Influence of chloralose anesthesia on cardiovascular function in trained dogs. *Am. J. Physiol.*, **223**, 660–667.

DAMATO, A.N., LAU, S.H., HELFANT, R.H., STEIN, E., BERKOWITZ, W.D. COHEN, S.I. (1969). Study of atrioventricular conduction in man using electrode catheter recordings of His bundle activity. *Circulation*, **39**, 287–296.

DUCHENE-MARULLAZ, P., DELORT, P. & VACHER, J. (1964). Chloralose et fréquence cardiaque. *C.R. Soc. Biol.*, **158**, 2354–2356.

EXLEY, K.A. (1954). Depression of autonomic ganglia by barbiturates. *Br. J. Pharmac. Chemother.*, **9**, 170–181.

GAUTRELET, J. (1918). Contribution à l'étude physiologique du chloralose. *C. R. Soc. Biol.*, **131**, 369–371.

GOLDBERG, J.L., LINDE, P., GAAL, P.G., MOMMA, K., TAKAHASHI, M. & SARNA, G. (1968). Effects of barbiturates on pulmonary and systemic hemodynamics, *Cardiovasc. Res.*, **2**, 136–142.

HORWITZ, L.D., BISHOP, V.A., STONE, H.L. & STEGALL, H.F. (1969). Cardiovascular effects of low oxygen atmospheres in conscious and anesthetized dogs. *J. appl. Physiol.*, **27**, 370–373.

JAILLON, P., CHEYMOL, G. & ROZENSZTAJN, L. (1976). Comparaison de l'influence de deux modes d'entretien de l'anesthésie au pentobarbital sur la fréquence cardiaque et la conduction intracardiaque chez le chien. *J. Pharmac.* (Fr.), **7**, 507–516.

JOURDAN, F., DUCHENE-MARULLAZ, P. & LEUSEN, I. (1952). Innervation cardioaccélératrice et chloralose. *C.R.Soc. Biol.*, **146**, 1323–1325.

KRAYER, O., MANDOKI, J. & MENDEZ, C. (1951). Studies

on veratrum alkaloids XVI. The action of epinephrin and of veratramine on the functional refractory period of the auriculo-ventricular transmission in the heart-lung preparation of the dog. *J. Pharmac. exp. Ther.*, **103,** 412–419.

MANDERS, W.T. & VATNER, S.F. (1976). Effects of sodium pentobarbital anesthesia on left ventricular function and distribution of cardiac output in dogs, with particular reference to the mechanism for tachycardia. *Circulation Res.*, **39,** 512–517.

MOE, G.K., PRESTON, J.B. & BURLINGTON, H. (1956). Physiologic evidence for a dual A.V. transmission system. *Circulation Res.*, **4,** 357–375.

NASH, C.B., DAVID, F. & WOODBURY, R.A. (1956). Cardiovascular effects of anesthesia doses of pentobarbital sodium. *Am. J. Physiol.*, **185,** 107–112.

OLMSTEAD, F. & PAGE, I.H. (1966). Hemodynamic changes in dogs caused by sodium pentobarbital anesthesia. *Am. J. Physiol.*, **210,** 817–820.

O'ROURKE, R.A. & BISHOP, V.S. (1971). Cardiovascular hemodynamics in the conscious dog. *Am. Heart. J.*, **81,** 55–60.

ROSEN, K.M., RAHIMTOOLA, S.H., CHUGUIMIA, R., LOEB, H.S. & GUNNAR, R.M. (1971). Electrophysiological significance of first degree atrioventricular block with intraventricular conduction disturbance. *Circulation*, **49,** 491–502.

SCHAER, H. (1964). The action of sodium pentobarbital on the S.A. nodal activity of the mammalian heart. *J. Pharmac. exp. Ther.*, **145,** 267–274.

SCHAFER, G.D., UNDERWOOD, F.J. & GAYNOR, E.P. (1930). The action of amytol in impairing vagus cardiac inhibitory effects and of ether in increasing the respiratory rate after its depression by amytol. *Am. J. Physiol.*, **91,** 461–466.

SCHERLAG, B.J., LAU, S.H., HELFANT, R.H., BERKOWITZ, W..D., STEIN, E. & DAMATO, A.N. (1969). Catheter technique for recording His bundle activity in man. *Circulation*, **39,** 13–18.

TOMAN, J.E.P. (1952). Neuropharmacology of peripheral nerve. *Pharmac. Rev.*, **4,** 108–218.

TRETHEWIE, E.R. (1953). The influence of barbiturate on the sympathetic nervous system. *Med. J. Australia*, **40,** 100–104.

URTHALER, F., KRAMES, B.L. & JAMES, T.N. (1974). Selective effects of pentobarbital on automaticity and conduction in the intact canine heart. *Cardiovasc. Res.*, **8,** 46–57.

VAN CITTERS, R.L., FRANKLIN, D.L. & RUSHMER, R.F. (1964). Left ventricular dynamics in dogs during anesthesia with alpha-chloralose and sodium pentobarbital. *Am. J. Cardiol.*, **13,** 349–354.

VATNER, S.F., HIGGINS, C.B., FRANKLIN, D. & BRAUNWALD, E. (1971). Effects of a digitalis glycoside on coronary and systemic dynamics in conscious dogs. *Circulation Res.*, **28,** 470–479.

WIT, A.L., WEISS, M.B., BERKOWITZ, W.D., ROSEN, K.M., STEINER, C. & DAMATO, A.N. (1970). Pattern of atrioventricular conduction in the human heart. *Circulation*, **27,** 345–359.

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