Effects of Sodium Pentobarbital Anesthesia on Left Ventricular Function and Distribution of Cardiac Output in Dogs, with Particular Reference to the Mechanism for Tachycardia

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SUMMARY Sodium pentobarbital (PB), 30 mg/kg, iv, was administered to 30 conscious dogs instrumented for measurement of cardiac output and regional blood flow distribution, left ventricular (LV) diameter, LV pressure, dP/dt, and dD/dt, i.e., velocity of myocardial fiber shortening. Ventilation was controlled during anesthesia to maintain arterial blood gases at control values for conscious dogs. The anesthetic produced an initial transient, peripheral vasodilation but the steady state effects 15–30 minutes later were characterized by slight reductions in mesenteric flow and cardiac output and increases in mesenteric and systemic resistances, whereas iliac and renal resistances were not significantly different from control. When heart rate rose, PB increased end-systolic diameter and decreased coronary resistance, LV end-diastolic diameter, dP/dt/P (42%), and shortening velocity (36%). When heart rate was controlled, PB still increased end-systolic diameter and decreased shortening velocity and dP/dt/P, as occurred during spontaneous rhythm, but end-diastolic diameter rose instead of falling and coronary resistance did not change. After recovery from bilateral cervical section of both carotid sinus and aortic nerves, PB failed to elicit tachycardia. Thus, PB affects systemic and regional hemodynamics only slightly, but depresses the myocardium markedly. The tachycardia associated with PB anesthesia in intact, trained dogs appears not to be only vagolytic, as previously thought, but is predominantly mediated through the arterial baroreceptor reflex.

SODIUM PENTOBARBITAL remains one of the most widely used anesthetics for experimental cardiovascular studies. However, the effects of the anesthetic agent are generally disregarded in the interpretation of experimental data from studies in which PB is employed. This is due in part to the fact that the effects of this anesthetic are not completely known. In addition, results from previous studies, which indicated that the anesthetic has little effect on cardiac output and arterial pressure,1,2 have previously been used as justification for disregarding its effects. The primary goal of this study was to provide a comprehensive picture of the effects of sodium pentobarbital (PB) on left ventricular (LV) function, coronary dynamics, distribution of regional blood flow, and regional vascular resistance. A secondary goal was to examine the mechanism for the PB-induced tachycardia, which is currently thought to be due to a vagolytic action.3,4

Methods

Thirty normal mongrel dogs, weighing 20–30 kg, were anesthetized with intravenous (iv) PB, 30 mg/kg. Through a left thoracotomy in the 5th intercostal space, a Doppler ultrasonic flow transducer was implanted around the left circumflex coronary artery, stimulator electrodes were sutured to the left atrium, a miniature pressure transducer (Zepeda) was implanted around the ascending aorta. Through a midline laparotomy, Doppler ultrasonic transducers (10 dogs) or electromagnetic transducers (five dogs) were placed around the mesenteric, renal, and iliac arteries. In all dogs, a heparin-filled Tygon catheter was chronically implanted in the thoracic aorta through a lumbar branch. In an additional seven dogs, under PB anesthesia and through a midline cervical incision, the carotid sinus nerves and aortic nerves were sectioned bilaterally, according to the technique described by Edis and Shepherd.4 Completeness of denervation was confirmed several days after the operation by observing absence of a reflex heart rate response to bolus intravenous injections of nitroglycerin (nitroglycerin U.S.P., Lilly, 48 µg/kg) and methoxamine (Vasoxyl, Burroughs Wellcome, 48 µg/kg). Normally these drugs induced a tachycardia of 97 ± 5 beats/min and a bradycardia of 46 ± 4 beats/min, respectively. After recovery from the operation electromagnetic flow probes were implanted on the ascending aorta at a subsequent operation using PB anesthesia, 30 mg/kg, iv.

Arterial and left atrial pressures were measured with Statham P23Db strain gauge manometers. LV pressure was measured with the implanted miniature gauges; diastolic pressure was calibrated against the measurement obtained with the left atrial catheter and Statham strain gauge. An improved ultrasonic transit time dimension gauge was used...
to measure LV diameter; the details of this technique have been published previously.

Regional blood flow was measured with a Doppler ultrasonic flowmeter (10 dogs), which has been described in detail previously and has an accurate electronic zero reference. In 11 dogs, an electromagnetic flowmeter (Benton) was used to measure blood flow. In these dogs, zero was determined by inflation of an occluding cuff implanted distal to the probe; zero was assumed to occur during late diastole in measurement of aortic blood flow.

The experiments were conducted 2 weeks to 2 months after recovery from operation, when the dogs appeared vigorous and healthy. Continuous recordings of LV pressure, diameters, coronary blood flow, cardiac output, regional blood flow, arterial pressure and heart rate were taken with the dogs lying in the right lateral position for the entire experiment, i.e., while conscious, during induction of anesthesia (PB, 30 mg/kg, iv) and continuously for the following 30 minutes. On induction of anesthesia with PB arterial Po2 fell from 80 ± 3 to 51 ± 4 mm Hg. Accordingly, the dogs were intubated after 2½ minutes and ventilation was controlled to maintain arterial blood gases at control levels for conscious dogs; pH remained at 7.42 and PCO2 at 30 ± 1 mm Hg. Arterial blood gases were measured on a BMS 3 MK 2 blood microsystem (Radiometer) and pH was measured on a PHM 71 MK 2 acid-base Analyzer (Radiometer). In the dogs in which LV and coronary dynamics were studied, heart rate was increased to 150 beats/min during control measurements and returned to this value by electrical stimulation for 1-minute intervals for each data point after anesthesia. To test the integrity of the parasympathetic nervous system, atropine (0.1 mg/kg) was administered intravenously to conscious dogs both while intact and after recovery from denervation and also to these dogs in the anesthetized state. To determine whether the tachycardia induced by the anesthesia was due to a vagolytic action or due to a baroreceptor mechanism activated in response to a reduction in systolic arterial pressure, methoxamine (10–20 μg/kg per min) was administered intravenously to five anesthetized, intact dogs to return systolic arterial pressure to the preanesthetic control level.

The data were recorded on a Brush (Clevite Brush) Mark 200 multichannel tape recorder and played back on a direct-writing oscillograph. A cardiactachometer, triggered by a signal from the pressure pulse, provided instantaneous and continuous records of heart rate. Electronic resistor-capacitor filters with 2-second time constants were used to derive mean arterial blood pressure and mean regional and coronary blood flows, and an 8-second time constant was used to derive mean aortic flow. Mean regional vascular resistances were calculated as quotients of mean arterial pressure and regional blood flow, respectively.

Continuous records of dP/dt and dD/dt were derived from LV pressure and diameter signals using Teledyne Philbrick operational amplifiers connected as differentiators and having frequency responses of 700 and 140 Hz, respectively. However, when used in conjunction with the multichannel oscillographic recorder, frequency response was 60 Hz for both differentiators. A triangular wave signal with a known slope was substituted for pressure and diameter signals to calibrate directly the dP/dt and dD/dt signals. The effects of PB on myocardial force-velocity relationships, dP/dt, and dP/dt/P were assessed as described previously. 10-12 Results were compared with the preanesthetic control by use of the paired t-test, and responses of intact and denervated dogs were compared by the unpaired t-test.

Results

EFFECTS OF PB (INTACT DOGS)

Systemic Effects (n = 9)

Mean arterial pressure fell initially from a control of 91 ± 2 to 85 ± 3 mm Hg at 2½ minutes, returned to control at 7½ to 10 minutes, and then fell slightly below control at 15–25 minutes. Systolic arterial pressure remained significantly depressed for the entire period of measurement (Fig. 1). Cardiac output rose from 2.20 ± 0.16 to 2.73 ± 0.24 liters/min, at 2½ minutes then gradually fell, but was significantly reduced below the control only at 25–30 minutes. Conversely, total peripheral resistance fell significantly below control at 2½ minutes (from 0.038 ± 0.003 to 0.033 ± 0.002 mm Hg/liter/min) and returned to control at 25–30 minutes (from 0.034 ± 0.003 to 0.031 ± 0.003 mm Hg/liter/min) (Fig. 2). Cardiac rate fell from 151 ± 8 to 120 ± 10 beats/min at 2½ minutes and then fell further to 113 ± 9 beats/min at 25–30 minutes (Fig. 3). Total peripheral resistance fell significantly below control at 2½ minutes (from 0.038 ± 0.003 to 0.033 ± 0.002 mm Hg/liter/min) and returned to control at 25–30 minutes (Fig. 2).

The effects of pentobarbital, 30 mg/kg, iv, on mean arterial pressure, systolic arterial pressure, cardiac output, total peripheral resistance, and heart rate of intact dogs (n = 9, solid lines) and denervated dogs (n = 7, dashed lines). Asterisks (*) denote changes that are significantly different from control. Daggers (†) represent responses of denervated dogs that are significantly different from those of intact dogs. The vertical bars represent ± SEM. Intact dogs were able to maintain arterial pressure better than denervated dogs. In both cases systolic arterial pressure fell significantly. The heart rate response in the denervated dogs was qualitatively different from that of the intact, since heart rate failed to rise in the denervated dogs.
0.031 ± 0.002 mm Hg/ml per min, \( P < 0.05 \) rose above control at 15 minutes, and remained significantly elevated. Stroke volume fell from 33 ± 3.0 to 18 ± 2.8 ml, \( P < 0.01 \), and remained significantly depressed. Heart rate rose from 80 ± 3 to 160 ± 4 beats/min at 2½ minutes, then fell gradually to 109 ± 5 beats/min at 30 minutes.

**Left Ventricular Dynamics \( (n = 14) \)**

**Spontaneous Rhythm.** Peak systolic LV pressure fell from 120 ± 3 to 106 ± 4 mm Hg \( (P < 0.01) \) at 2½ minutes and remained depressed. LV end-diastolic pressure rose from a control of 6 ± 1 to 8 ± 1 mm Hg \( (P < 0.05) \) at 2½ minutes and remained significantly above control only until 10 minutes. LV end-diastolic diameter fell from a control value of 36.3 ± 1.3 to 35.4 ± 1.7 mm \( (P < 0.01) \), and remained depressed significantly. In contrast, LV end-systolic diameter increased from a control of 24.7 ± 1.8 to 27.3 ± 1.8 mm at 2½ minutes, then gradually returned toward control but remained significantly elevated \( (P < 0.01) \). Thus, stroke shortening fell substantially and remained significantly reduced. Peak shortening velocity fell from 78 ± 3 to 50 ± 3 mm/sec, and remained depressed significantly. LV dP/dt fell from a control of 3,350 ± 90 to 2,020 ± 150 mm Hg/sec, and remained depressed significantly. LV dP/dt/P fell from a control of 1.63 ± 0.09 to 0.92 ± 0.06 mm Hg/ml per min \( (P < 0.01) \) and remained significantly depressed.

**Heart Rate Controlled \( (150 \text{ beats/min}) \).** When heart rate was controlled peak systolic LV pressure fell, while LV end-diastolic pressure rose significantly from 3 ± 1 to 7 ± 1 mm Hg at 7½ minutes and remained significantly elevated. LV end-diastolic diameter, instead of falling as during spontaneous rhythm, rose slightly but not significantly from 31.4 ± 2.2 to 32.8 ± 2.3 mm \( (P < 0.01) \). LV end-systolic diameter still rose significantly. The responses for peak dP/dt, dP/dt/P, and velocity were all essentially the same as were observed during spontaneous rhythm \( (P < 0.01) \); all values fell and remained significantly depressed, \( P < 0.01 \).

**Coronary Blood Flow and Resistance \( (n = 13) \)**

**Spontaneous Rhythm.** Mean coronary blood flow rose from 44 ± 4 to 65 ± 7 ml/min \( (P < 0.01) \) at 2½ minutes and gradually fell but remained significantly above control \( (P < 0.01) \). At 2½ minutes, late diastolic coronary resistance fell from 1.63 ± 0.09 to 0.92 ± 0.06 mm Hg/ml per min \( (P < 0.05) \) and remained significantly depressed.

**Heart Rate Controlled.** In contrast to results obtained during spontaneous rhythm, when heart rate was controlled, coronary flow decreased instead of rising and remained below control until 15 minutes. Late diastolic coronary resistance, in contrast to results for spontaneous rhythm, did not fall, but remained essentially constant \( (P < 0.01) \). A slight reduction in coronary resistance may have occurred with induction, but heart rate was not controlled prior to 7½ minutes.

**Regional Flows and Resistances \( (n = 15) \)** \( (P < 0.01) \).

Initially mesenteric flow rose slightly but not significantly, then fell and remained significantly below control after 10 minutes. Conversely mesenteric resistance rose significantly after 10 minutes. Changes in renal blood flow and resistance were not significant. Iliac flow rose significantly at 2½ minutes \( (P < 0.01) \) and then remained significantly above the control value only through 10 minutes. Conversely, initially iliac resistance fell sharply and remained significantly below control only until 10 minutes.

**EFFECTS OF PB AFTER SECTION OF ARTERIAL BARORECEPTOR NERVES \( (n = 7) \)**

After the dogs had recovered from section of arterial baroreceptor nerves, responses to PB were significantly different for arterial pressure, heart rate, and cardiac output but not for total peripheral resistance \( (P < 0.01) \). Heart rate rose initially in six of seven dogs studied, but after artificial ventilation had restored arterial \( P_{O_2} \) to control values, heart
rate was actually slightly but not significantly lower than the preanesthetic control level of 107 ± 11 beats/min. This response was significantly different for the entire 30-minute period from that found for intact dogs.

STUDIES ON THE MECHANISM OF TACHYCARDIA INDUCED BY PB (FIG. 6)

Atropine \((n = 4)\)

Administration of atropine, 0.1 mg/kg, to conscious dogs after recovery from denervation increased heart rate from 103 ± 6 to 157 ± 2 beats/min. When atropine was administered 30 minutes after anesthesia, heart rate rose by a similar amount, indicating that release of vagal tone can be induced in conscious and anesthetized dogs without arterial baroreceptor pathways.

Conscious intact dogs responded to atropine by increasing heart rate from 86 ± 6 to 160 ± 4 beats/min, whereas after anesthesia the heart rate rose from 105 ± 13 to 157 ± 2 beats/min.

Methoxamine \((n = 5)\)

When systolic arterial pressure of intact dogs was returned to the control level for conscious dogs by infusion of methoxamine \((10-20 \mu g/kg per min)\) 15-30 minutes after PB anesthesia, heart rate returned to the control level for the conscious dogs (Fig. 6).

Discussion

The majority of studies on PB anesthesia have examined effects on pressure, heart rate, and cardiac output. Although there is universal agreement that the anesthetic induces tachycardia, reports of its effects on arterial pressure and cardiac output are divergent. For instance, arterial pressure has been reported to rise after administration of PB \(^{14}\) and also generally is found to be elevated in studies in which PB is used as an anesthetic. In contrast, mean arterial pressure actually fell slightly as a result of injection of PB, \(^{15}\) a result which is consistent with our findings.

In general, the changes in cardiac output and total peripheral resistance were not striking. PB induced a transient vasodilation in all beds immediately after administration. Renal flow and resistance were not significantly changed from control during the sustained response. Iliac flow and resistance returned to control by 15 minutes and remained there. In contrast, mesenteric flow fell below...
control for 10–30 minutes, while mesenteric resistance rose at this time.

PB anesthesia elicited its most dramatic effect on cardiac dynamics. Myocardial contractility fell significantly as reflected by 30–40% decreases in dP/dt, dP/dt/P, and shortening velocity. Since the reduction in myocardial contractility was similar when heart rate varied and LV end-diastolic size fell or when heart rate was controlled and end-diastolic size rose, the decrease in contractility cannot be attributed to the indirect effect of a decrease in preload. Stroke volume fell significantly with induction of anesthesia and remained significantly depressed for the entire period of observation, as has been reported previously.16–19 However, the manner in which ventricular dimensions change to account for the reductions in stroke volume has not been established. We found that this marked decrease in stroke volume was associated with a smaller LV end-diastolic diameter and a larger end-systolic diameter, resulting in a decrease of approximately 25% in stroke shortening. Rushmer20 and Van Citters et al.31 also found a reduction in LV end-diastolic diameter during anesthesia. This is surprising, since one would expect that a powerful myocardial depressant such as PB would increase LV end-diastolic diameter. However, tachycardia decreases LV end-diastolic size22 and thus could have masked the opposing myocardial depressant effects of the anesthetic on dimensions. This hypothesis was supported by the studies with heart rate controlled, in which we found that LV end-diastolic diameter actually increased slightly.

The fact that LV end-diastolic diameter fell while LV end-diastolic pressure rose with PB in dogs in spontaneous rhythm suggests that there was a change either in ventricular shape or in diastolic compliance of the ventricle. A recent study by Templeton et al.38 also suggested that barbiturates altered diastolic ventricular compliance and supports the latter hypothesis.

With induction of anesthesia we found a transient marked increase in coronary blood flow that was associated with substantial tachycardia and initial hypoxia; there was a reciprocal reduction in late diastolic coronary resistance. Even after 2½ minutes, when the dogs were ventilated and the hypoxia had been corrected, coronary resistance remained reduced. Coronary dilation following PB anesthesia was reported initially by Essex et al.34 for one dog, and subsequently by Ericsson16 for dogs and by Forsyth and Hoffbrand24 for monkeys. However, previous studies did not take into account changes in cardiac function, which would affect myocardial oxygen consumption the primary determinant of coronary flow and resistance. In the present study the effects of tachycardia, which would in itself increase coronary flow and decrease coronary resistance,24 were eliminated by studying dogs with heart rate controlled. In these experiments, no significant change in coronary flow or calculated resistance was observed 7½–30 minutes after administration of PB. However, if under these circumstances myocardial oxygen consumption fell, this could be interpreted to mean that coronary vessels actually dilated.

To determine what role the arterial baroreceptor reflexes play in the maintenance of cardiovascular dynamics, seven dogs were studied after recovery from section of carotid sinus and aortic nerves in the neck. As expected, in denervated dogs arterial pressure fell by a significantly greater amount during PB anesthesia.

The most surprising effect of denervation was the lack of tachycardia after PB anesthesia. It generally has been thought that the tachycardia that occurs during PB anesthesia is due to a vagolytic action of the anesthetic.4–5 If this were the case, then heart rate should have risen and remained elevated in the denervated dogs during anesthesia because the vagi were intact. Since heart rate did not remain elevated during PB anesthesia in denervated dogs, the mechanism for the tachycardia appeared to be mediated by arterial baroreceptor reflexes rather than by a vagolytic effect of PB. To test this hypothesis, we gave atropine (0.1 mg/kg) to conscious and anesthetized denervated dogs and found a substantial increase in heart rate in both cases, indicating that the vagi were not "turned off." Since mean arterial pressure was not significantly different from control in intact dogs and systolic arterial pressure was significantly depressed, it appeared that arterial baroreceptor reflexes were responding to the decreased systolic arterial pressure, or pulse pressure. To return systolic arterial pressure to control levels methoxamine (10–20 μg/kg per min) was infused intravenously. When systolic arterial pressure returned to control levels, heart rate fell to the control value. These experiments further support the hypothesis that the sustained tachycardia of PB anesthesia in intact, trained dogs appears to be due not to a vagolytic mechanism but rather to be mediated predominantly by arterial baroreceptor reflexes. This is not to say that a vagolytic effect will not manifest itself, when (1) untrained or excited animals are studied, (2) in the presence of surgical trauma in addition to the anesthetic, or (3) when larger doses approaching the lethal dose of PB are used. It has been pointed out previously that with larger doses of the anesthetic more impressive vagolytic actions can be elicited.4–5 We chose the dose of 30 mg/kg for this study because it produces a surgical level of anesthesia in the absence of preanesthetic medication.

In conclusion, PB anesthesia elicits relatively minor effects on cardiac output and regional blood flow distribution, while exerting a major myocardial depressant effect. Controlling heart rate prevents the reductions in LV end-diastolic diameter and coronary resistance. Finally, the response to PB anesthesia in the absence of arterial baroreceptor reflexes is different in that mean arterial pressure cannot be maintained as well and the tachycardia induced by this anesthetic is not observed. The latter finding suggests that the mechanism for the sustained tachycardia of PB anesthesia in intact, trained dogs is mediated by the baroreceptor reflex rather than a vagolytic action.

References

Bioassay in Vivo for Circulating Vasoactive Agents after Renal Artery Constriction in Dogs

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SUMMARY We used the gracilis muscle vascular bed to bioassay blood from the two renal veins, vena cava, and aorta continuously for the presence of vasoactive agents before and for 45 minutes after partial occlusion of the left renal artery in dogs. Compared to comparable blood samples from control dogs, left renal venous, vena cava, and aortic blood, but not right renal venous blood, from dogs with renal artery constriction developed vasoconstrictor activity. This was associated with increased renin concentration in plasma from the left renal vein and the vena cava and an increase in systemic arterial pressure. In dogs pretreated with indomethacin, blood from the right renal vein also showed vasoconstrictor activity. Pretreatment with antirenin serum abolished all of the differences between control and experimental dogs. These findings suggest that during acute unilateral renal artery constriction the contralateral kidney releases renin and the contralateral kidney releases prostaglandins in sufficient quantity to produce systemic vascular effects.

DATA FROM a number of investigators indicate that the early development of hypertension following unilateral renal artery constriction is associated with increased release of renin and systemic generation of angiotensin II.

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