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Barbiturate Depression of Neurally Mediated Reflexes to Coronary Artery Occlusion[1] (40435)

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Bradycardia has been observed quite frequently in patients who have recently (within hours) suffered a myocardial infarction. This is especially true for posterior wall infarction. In most cases this bradycardia was reversed by atropine (1, 2). A similar finding of vagally mediated bradycardia during coronary artery occlusion has also been reported in the cat (3).

The deleterious effects of this increased vagal tone on the heart may include reduced perfusion of the remaining viable myocardium (4). Beneficial effects may include a reduction in the size of the infarcted region (5) and a reduced incidence of ventricular fibrillation (6). After atropine administration these latter effects cannot be expressed. This as well as adverse clinical experiences after atropine administration in post-MI patients have led several investigators to recommend that vagal blockade by atropine be avoided whenever possible (6).

The role of the autonomic nervous system in the responses to myocardial infarction continues to be an area attracting a great deal of research interest. Numerous experimental studies employing various animal models have been conducted to evaluate the various neurally mediated changes in heart rate, rhythm, and function that occur during and after coronary artery occlusion. A review of the literature reveals that integration of the existing data in animal models is complicated by the different anesthetics used in these studies.

The barbiturate pentobarbital (PBTL) has been used quite frequently in these studies of experimental coronary artery occlusion. This is surprising because it is well known that barbiturates depress cardiac vagal tone, cardiac responses to vagal stimulation, and baroreceptor reflexes (7, 8). Recently, Franciosa *et al.* (9) reported that pentobarbital anesthesia resulted in a bradycardia response whereas morphine-sedated but conscious dogs showed a tachycardia response to coronary artery occlusion. To our knowledge, however, the effect of barbiturates on reflexes activated by coronary artery occlusion has not been previously investigated. Accordingly, this study was undertaken to study the effect of PBTL on one of the neurally mediated cardiac responses to experimental coronary artery occlusion in the cat—i.e., occlusion-induced bradycardia.

Methods. Adult cats were anesthetized with 75 mg/kg of α-chloralose. They were prepared for recording aortic blood pressure via a femoral artery catheter, a lead-II electrocardiogram via subcutaneous needle electrodes, and instantaneous heart rate via a cardiotachometer (which calculated rate from the interval between successive systolic blood pressure peaks). Left ventricular pressure and maximal rate of systolic pressure change (LVdp/dt) were also recorded in several animals via a catheter passed retrograde down the right carotid artery. These cats were artificially respired with the rate and tidal volume of the respirator adjusted to maintain arterial blood gases and pH within normal limits.

To provide access to the coronary arteries, a transsternal thoracotomy was performed and the heart was stabilized in a pericardial cradle. Using a dissecting microscope, the bifurcation of the main left coronary artery was exposed to permit transient occlusion of either the left anterior descending (LAD) or the circumflex coronary artery. A modified Heifetz aneurysm clip was applied to one of these arteries for up to 1 min to study the chronotropic responses that were induced by blockade of blood flow to a major portion of ventricular myocardium. This duration of oc-

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clusion (1 min) was selected because pilot studies revealed that occlusion-induced bradycardia usually reached its maximum within the first minute after the onset of occlusion. In addition, by limiting occlusions to 1 min, the incidence of ventricular fibrillation was reduced.

Occlusions were repeated after an interval of at least 4 min, during which time heart rate and blood pressure returned to preocclusion values. Baseline chronotropic responses to coronary artery occlusion were obtained from a minimum of four occlusions. To evaluate the effect of barbiturates, PBTL was then infused into the femoral vein at a rate of 0.25 mg/kg/min, and coronary artery occlusions were repeated every 4 min. Infusions were continued until the occlusion-induced chronotropic responses were reduced to less than 10% of control values. To insure that the magnitude of the reduction in response was not due to damage to pericoronary nerves during repeated occlusions, 3–9 mg/kg of Mikedimide (Methetharimide), an analeptic agent (10), was administered to reverse the depressant effects of PBTL. Atropine (0.5 mg/kg) and propranolol (1.0 mg/kg) were also administered in several animals to demonstrate that this occlusion-induced bradycardia was indeed dependent on neural reflexes.

Results are reported as mean values ± SE of the mean. Significance between preocclusion data groups was calculated by Student's t test and was considered significant when $p < 0.05$. Significance between occlusion-induced changes in cardiovascular function was determined by the nonparametric Wilcoxon signed-ranks test and was considered significant when $p < 0.05$.

Results. In this study chloralose-anesthetized cats had a baseline heart rate of 222 ± 7 beats per min (BPM) and an aortic pressure of 170 ± 7/126 ± 5 mm Hg. Coronary artery occlusion (CAO) led to marked decreases in heart rate and aortic pressure. Figure 1A is an example of the cardiovascular responses obtained from one animal during the course of an experiment. These responses are qualitatively similar to those obtained in this group. In this cat, circumflex occlusion resulted in a fall in left ventricular pressure, left ventricular dP/dt, and aortic pressure, all having a latency of 3 sec. Heart rate began to fall 9 sec after onset of CAO and reached its minimum value within 22 sec. Near the end of this occlusion period, a short period of arrhythmia is evident in the aortic pressure and heart rate traces. After removal of the occlusion clip, these cardiovascular parameters returned to preocclusion values within 1 min.

Table I summarizes the results obtained from CAO occlusions in 13 animals. Occlusion of either the left anterior descending (LAD) or circumflex (CIRC) arteries led to

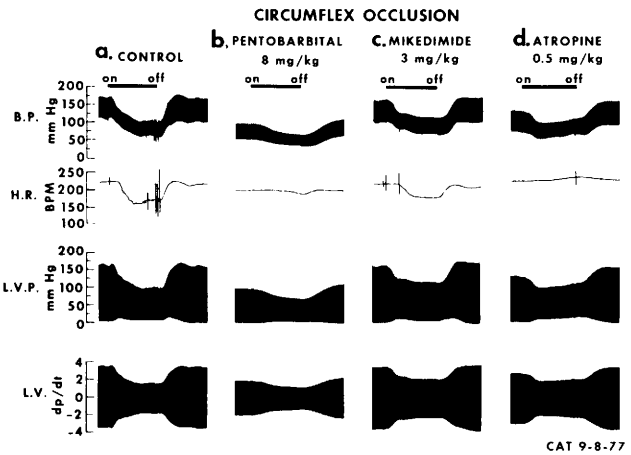

FIG. 1. Effect of a 45-sec circumflex coronary artery occlusion on heart rate, arterial pressure, and left ventricular dynamics. a: control response; b: after infusion of 8 mg/kg pentobarbital; c: after 3 mg/kg of Mikedimide; d: after atropine (0.5 mg/kg). BP, arterial blood pressure; HR, heart rate in beats per min (BPM); LVP, left ventricular pressure; LVPdp/dt, rate of change of LVP.

TABLE I. EFFECT OF PENTOBARBITAL ON CARDIOCARDIAC REFLEX TO CORONARY ARTERY OCCLUSION.

	N	Heart rate (BPM)[a]		Aortic pressure (mm Hg)	
		Control	Change	Control	Change
Coronary Artery Occlusion (CAO)	13	222 ± 7	−56 ± 5	170 ± 7/126 ± 5	−40 ± 6/−34 ± 5
CAO After 1 mg/kg Pentobarb.	13	221 ± 6	−34 ± 5*	164 ± 7/123 ± 6	−35 ± 4/−30 ± 4
CAO After 2 mg/kg Pentobarb.	13	217 ± 6	−23 ± 5*	153 ± 7*/114 ± 7	−30 ± 5/−27 ± 4
CAO After 4 ± 1 mg/kg Pentobarb.	13	207 ± 6*	−4 ± 1*	135 ± 7*/96 ± 6*	−26 ± 3*/−23 ± 3*
CAO After 30 min recovery	13	213 ± 6	−13 ± 4*	152 ± 7*/111 ± 6*	−28 ± 4*/−22 ± 4*
CAO After Dextran	6	201 ± 8*	−14 ± 5*	170 ± 9/126 ± 6	−33 ± 5/−26 ± 3*
CAO After Mikedimide	11	213 ± 6	−40 ± 5*	190 ± 8/144 ± 6**	−38 ± 4/−30 ± 4

[a] BPM = beats per min. Dextran administered = 16 ± 2 ml. Mikedimide administered = 6 ± 1 mg/kg.
* Significantly less than values recorded before pentobarbital ($p < 0.05$).
** Significantly greater than values recorded prior to pentobarbital ($p < 0.05$).

similar changes in cardiovascular function; therefore, results of both occlusions were pooled. Magnitude of the bradycardia during CAO was 56 ± 5 BPM with an average response latency of 16 ± 1 sec and a time to minimum value of 31 ± 3 sec. The concomitant hypotensive response had a latency of 14 ± 2 sec but a slightly longer time to minimum value of 37 ± 2 sec.

To evaluate the effect of low doses of barbiturates on this cardiocardiac reflex, PBTL was infused at a rate of 0.25 mg/kg/min. After receiving a total of 1 mg/kg, the negative chronotropic response (−34 ± 5 BPM) was significantly less than that recorded before PBTL. In contrast, preocclusion heart rate, arterial pressure, and occlusion-induced changes in arterial pressure were not affected by 1.0 mg/kg of PBTL. After a total of 2 mg/kg, both the occlusion-induced changes in heart rate and the preocclusion systolic blood pressure were significantly less than those recorded prior to PBTL.

PBTL infusions were continued until the occlusion-induced change in heart rate was eliminated or reduced to less than 10% of the preinfusion values. An example of the cardiovascular responses to CAO after PBTL are shown in Fig. 1B. It can be seen that 8 mg/kg of PBTL reduced this response to less than 10% of the control magnitude but failed to totally eliminate the response. A further increase in the PBTL dose may have blocked it, but blood pressure was down significantly, and it was felt that these doses of PBTL may have directly compromised cardiovascular function.

Summarizing the data (Table I) for the animals used in this study, blockade of the negative chronotropic response to CAO was considered to be complete after a PBTL infusion of 4 ± 1 mg/kg when the magnitude of the occlusion-induced change in heart rate was reduced to only 4 ± 1 BPM. The other cardiovascular parameters were also significantly less than those recorded before PBTL (Table I). PBTL also appeared to prolong both the latency (26 ± 3 sec) and the time to minimum value (42 ± 3 sec) for the last measurable negative chronotropic response prior to blockade. As can be seen in Fig. 1B, the onset of the bradycardia response was 25 sec, as compared to an 8-sec latency prior to PBTL. In contrast, neither the latency (11 ± 3 sec) nor the time to minimum value (37 ± 4 sec) for the occlusion-induced change in arterial pressure was altered by PBTL. After infusions were discontinued, a 30-min recovery period permitted examination of the persistence of the PBTL effect. At the end of this period, baseline values recovered somewhat (Table I) while the occlusion-induced change in heart rate was only −13 ± 4 BPM.

To evaluate the possibility that arterial pressure levels were important to this response, arterial pressure was restored to preinfusion values (see Table I) in six animals by administration of dextran (16 ± 2 ml). This increase in arterial pressure resulted in a reflex decline in heart rate but failed to significantly alter the magnitude of the occlusion-induced change in heart rate. The latency of this chronotropic response (26 ± 3 sec) was also still prolonged when compared to the preinfusion value.

To demonstrate that this depression of the cardiocardiac reflex was due to PBTL and was not the result of other experimental variables (injury to pericoronary nerves, experiment duration, etc.), Mikedimide (6 ± 1

mg/kg) was then administered to 11 animals. This led to a striking (75%) recovery of the negative chronotropic response to CAO. This recovery is exemplified in Figure 1C by the occlusion-induced change in heart rate (40 BPM) restored to 75% of its preinfusion value by 3 mg/kg of Mikedimide. As can be seen in Table I, Mikedimide also resulted in a significant elevation in arterial pressure above its preinfusion value; however, the occlusion-induced change in arterial pressure was not significantly different from its preinfusion value. It should also be noted that, after Mikedimide, both the onset latency (19 ± 2 sec) and time to minimum value (36 ± 4 sec) for the occlusion-induced change in heart rate recovered to near preinfusion values.

To determine if depression of this cardiocardiac reflex to CAO is specific to barbiturates and not just the additive effect of chloralose plus PBTL, four cats were prepared in a similar manner except that they received injections of chloralose rather than PBTL. Chloralose doses of 10 mg/kg, which is approximately one-seventh the initial anesthetizing dose, were selected. In these cats, baseline aortic pressure and changes in pressure during CAO were similar to those for the group that received PBTL, whereas baseline heart rates (245 ± 13 BPM) and negative chronotropic responses to CAO (−90 ± 12 BPM) were somewhat higher. These values were not significantly affected by 10 mg/kg of chloralose (ΔHR − 75 ± 20 BPM); however, a second chloralose injection at this dose level did significantly ($p < 0.05$) depress the reflex (−54 ± 3 BPM).

Atropine (0.5 mg/kg) was then administered to six animals that had a −51 ± 8 BPM negative chronotropic response to CAO after Mikedimide. After atropine, the response to either LAD or circumflex occlusion was essentially blocked (−1 ± 5 BPM). In two of these animals, CAO (after atropine) led to a small tachycardia. An example of this finding is seen in Fig. 1D. This response was subsequently eliminated by β-adrenergic receptor blockade (propranolol, 0.5 mg/kg), indicating that this response was dependent on cardiac sympathetic efferent pathways.

In one animal, however, it was somewhat surprising that a small negative chronotropic response (−10%) to circumflex artery occlusion persisted after administration of both atropine (0.5 mg/kg) and propranolol (1.0 mg/kg). This persistent response did not appear to be mediated by the autonomic nervous system. An alternative hypothesis is that the bradycardia was dependent on pacemaker ischemia; i.e., occlusion of the circumflex artery may have blocked blood flow to an arterial branch (sinus node artery) which perfused the pacemaker region of the right atrium. To investigate this possibility, six cats underwent a similar experimental procedure wherein the major coronary arteries were exposed and each was transiently occluded to elicit an occlusion-induced bradycardia reflex. An example of results obtained in one of these cats is shown in Fig. 2. Occlusion of the proximal circumflex artery elicited a marked decline in heart rate (−55 BPM) and arterial blood pressure. Occlusion of this circumflex at a point just before it passes under the ascending interventricular vein (distal circumflex) also elicited a bradycardia, but the magnitude of the chronotropic response was less (−27 BPM). Occlusion of a small circumflex branch (sinus node artery) between these two sites also resulted in a bradycardia. After propranolol (1.0 mg/kg) administration, baseline heart rate and blood pressure were reduced, but all three occlusion sites still elic-

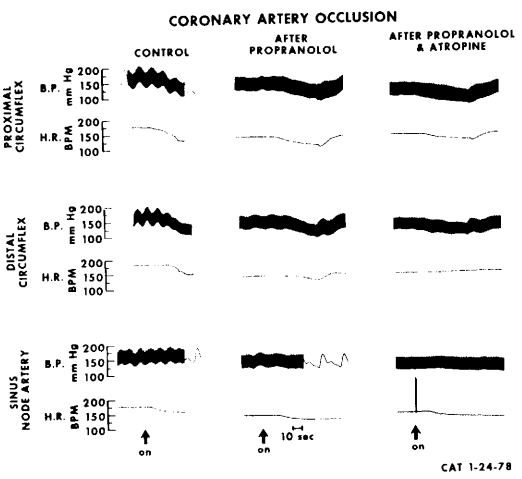

FIG. 2. Effect of coronary artery occlusion on heart rate (HR) and arterial pressure (BP). Occlusion sites included the proximal circumflex, sinus node artery, and a site on the circumflex distal to the sinus node artery. Propranolol (1.0 mg/kg) and atropine (0.5 mg/kg) failed to eliminate the negative chronotropic response due to pacemaker ischemia.

ited bradycardia. To determine the role of efferent vagal pathways, atropine (0.5 mg/kg) was then administered. This resulted in an elimination of the negative chronotropic response to distal circumflex artery occlusion, whereas proximal circumflex and sinus node artery occlusions still elicited a bradycardia. Qualitatively similar results were obtained in three other cats. A fourth cat showed a bradycardia response to right coronary artery occlusion that was not eliminated by autonomic blockade. This was also found to be dependent on occlusion of a small proximal branch. In all cases, these arteries were injected with India ink, which indicated that this artery had perfused the sinus node region near the junction of the right atrial appendage and the superior vena cava.

Discussion. Occlusion of either the anterior descending or circumflex branches of the left coronary artery resulted in a significant bradycardia in the cat. Neural pathways involved in this response include ventricular mechanoreceptors with both afferent and efferent information carried in the vagus nerve (11). In the present study, occlusion of these coronary arteries led to negative chronotropic responses of similar magnitude. That these responses were dependent on vagal efferent pathways was made evident by the finding that these responses were virtually eliminated by atropine (except when the circumflex was the origin of the sinus node artery).

Results obtained in this study indicate that this neurally mediated negative chronotropic response to CAO was inhibited by very small doses of PBTL (1 mg/kg), and the response was essentially eliminated by 4 ± 1 mg/kg of PBTL. These values are lower than those reported as being effective in depressing baroreceptor reflexes (12). That this depressant effect is due to PBTL specifically and not a combination of PBTL in combination with chloralose is exemplified by the lack of any effect on this response by 10 mg/kg of chloralose added in place of PBTL. No depression was observed until a total of 20 mg/kg of additional chloralose was administered. Based on these results, we suggest that not only chronotropic responses but other neurally mediated cardiac responses to CAO may also be inhibited by using PBTL as the anesthetic. This indeed may explain why some investigators have reported compensatory changes in nonischemic muscle function during experimental coronary artery occlusion (13, 14), whereas others have failed to observe any change in mechanical activity in those regions remote from the area of ischemia (15, 16).

An alternate explanation for decrease in the magnitude of the chronotropic response to CAO is that repeated applications of the occlusion clip damaged pericoronary nerves that may carry afferent fibers from the ventricular mechanoreceptors implicated as being the sensors in this reflex (16). However, this was shown not to be the case because Mikedimide administration restored the negative chronotropic response to CAO.

Demonstration of a negative chronotropic response to CAO after autonomic blockade was somewhat surprising. Previous studies of the negative chronotropic responses to CAO in the cat have reported that atropine or bilateral vagotomy eliminated this response (3). In the rhesus, however, the occurrence of a significant negative chronotropic response during circumflex artery occlusion was also observed. This response also persisted after autonomic blockade and was found to be dependent on sinus node ischemia (18). It is possible that earlier investigators failed to observe this ischemia-induced decrease in pacemaker rate because coronary artery flow was interrupted distal to the origin of the sinus node artery. In the present study, occlusion sites were located within 2 or 3 mm of the coronary artery origin and, therefore, occasionally interrupted flow to the sinus node artery.

As is evident in Fig. 2, the bradycardia that occurred during proximal circumflex artery occlusion was due to both a vagally mediated reflex and also sinus node ischemia. The two mechanisms were clearly delineated by occluding the sinus node artery separately, which elicited a bradycardia response after autonomic blockade. In contrast, occlusion of the circumflex distal to this branch elicited a bradycardia that was eliminated by atropine. It is this latter response that is presumably sensitive to low doses of PBTL.

We conclude that sinus node artery occlusion will initiate a decline in sinus rate that is not mediated by any apparent neural reflexes

but instead appears to be dependent on pacemaker ischemia. Further studies are warranted to determine if more prolonged sinus node ischemia will lead to significant sinoatrial dysfunction. Positive results would then indicate that the cat can serve as a suitable model for the study of sick sinus syndrome (19). The sick sinus syndrome is a significant clinical problem in which patients experience a marked bradycardia accompanied by symptoms of dizziness, syncope, and sometimes atrial arrhythmias. The cat may be useful for studies directed towards determining the underlying mechanisms responsible for pacemaker dysfunction.

Summary. This study was undertaken to evaluate the effects of low doses of PBTL on the negative chronotropic responses to coronary artery occlusion (CAO) in the cat. One-minute CAO near the origins of either the left anterior descending or circumflex (CIRC) coronary anteries resulted in a marked bradycardia (-56 ± 5 BPM) and hypotension. Intravenous infusion of only 4 ± 1 mg/kg of PBTL virtually abolished this response. That this negative chronotropic response to CAO was indeed dependent on vagal reflexes was demonstrated by its elimination after atropine (0.5 mg/kg). A PBTL-resistant bradycardia response to CAO was also observed in this study. This bradycardia was found to occur only during CIRC occlusion and was dependent on blockade of blood flow through the sinus node artery. Based on these results it is concluded that study of neural reflexes to CAO in animal models can be markedly impaired by even low doses of barbiturates. In addition, it appears that the cat will serve as an adequate model to investigate development of the sick sinus syndrome, which may be dependent on both neural and ischemic factors.

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