Effects of anesthesia and sleep on circulatory response to carotid sinus nerve stimulation

STEPHEN F. VATNER, DEAN FRANKLIN, AND EUGENE BRAUNWALD
Department of Medicine, University of California, San Diego, School of Medicine and Scripps Clinic and Research Foundation, La Jolla, California 92037

The effects of electrical stimulation of the carotid sinus nerves on arterial pressure, heart rate, and peripheral blood flows were studied in healthy dogs while conscious, asleep, after general anesthesia with Na pentobarbital, and after autonomic blockade. In the resting conscious dog, 30-sec periods of carotid sinus nerve stimulation resulted in average decreases in heart rate of 12%, arterial pressure 27%, coronary flow 5%, mesenteric flow 9%, and renal flow 8%, while iliac flow increased by 112%. In sleeping dogs, the decrease in heart rate (22%) was greater than when awake. In anesthetized dogs, the decreases in resistance in all beds with electrical stimulation were not as great as in conscious dogs and the periods following stimulation were prolonged. The bradycardia was necessary for arterial pressure and heart rate to return to control stimulation were minimal. A radiofrequency pacemaker (Medtronic) generating a .3-μsec rectangular wave form was used to stimulate the carotid sinus nerves (25). The frequency was set at 50 pulses/sec and the amplitude (2.5-7.0 v) was adjusted at the beginning of the experiment to obtain a maximal decrease in aortic pressure without the dog showing any evidence of discomfort while awake. Identical stimulation parameters were utilized in the same animals under all conditions.

Stimulation periods of 30 sec were always used, since it was observed that the maximum decrease in aortic pressure occurred during this period. The effects of carotid sinus nerve stimulation were studied in all eight dogs while resting and awake, in seven of them while asleep but unanesthetized; all eight dogs were studied 1 hr after general anesthesia had been induced by Na pentobarbital 30 mg/kg iv. These studies were carried out on the same day that observations in the waking state had been made. The effects of carotid sinus nerve stimulation on heart rate were studied after propranolol 1.0-2.0 mg/kg and atropine 0.2-0.3 mg/kg in five dogs, both in the conscious and anesthetized states.

The pulsed ultrasonic flowmeter (6) was used in two dogs and the Doppler ultrasonic flowmeter (7, 30) in six dogs. When using the pulsed ultrasonic flowmeter, zero flow was approximated during asystole induced with rapid intravenous acetylcholine (0.5 mg/kg) and confirmed during terminal calibration. When using the ultrasonic Doppler flowmeter, zero flow was determined electrically and confirmed after the animal was sacrificed. Velocity, as measured by the ultrasonic flowmeters, is linearly related to volume flow as long as the cross-sectional area within the transducer does not vary. At autopsy in these animals the vessels were found to be fixed to the transducer shells, thus minimizing changes in vessel diameter. Furthermore, volume calibrations of graded flow rates by timed collections were carried out in three representative animals and verified the accuracy and linearity of the flowmeters. Aortic pressure was measured with miniature solid-state gauges (29) chroni-
cally implanted in the thoracic aorta and calibrated in vivo against a Statham P23 Db strain-gauge manometer.

Mean aortic pressure and mean blood flow were derived by electronic filters with a 2-sec time constant. A carotid tachometer (Beckman type 9857 B), triggered by the electrical signal from the aortic pressure pulse provided instantaneous and continuous records of heart rate. Data were recorded on a multichannel oscillograph and magnetic tape recorder. Vascular resistances were calculated as the quotient of mean aortic blood pressure and mean coronary, mesenteric, renal, or iliac arterial blood flows.

RESULTS

Arterial blood pressure. In the resting conscious dog a 30-sec period of carotid sinus nerve stimulation produced an average maximum decrease in mean aortic pressure of 27 ± 4% SEM from control (from 102 to 74 mm Hg). Pressure began to decrease within the first 5 sec of stimulation and reached a minimum level at 20 sec, began to return toward control levels during the latter 10 sec of stimulation and reached control by an average of 15 ± 9 sec after stimulation was discontinued (Fig. 1). Stimulation during sleep produced similar results and the average maximum decrease in aortic pressure was 29 ± 4% (from 98 to 69 mm Hg); this level was also reached at 20 sec of stimulation, and pressure returned to control by 20 ± 12 sec after stimulation was discontinued. After pentobarbital anesthesia, carotid sinus nerve stimulation produced an average maximum decrease in aortic pressure of 24 ± 6% (from 117 to 89 mm Hg). As in the conscious and sleeping animals, this level was also reached at 20 sec of stimulation; but, in contrast to these states, in the anesthetized state the tendency to recovery during the last 10 sec of stimulation was considerably attenuated. Also, recovery was prolonged and required an average of 32 ± 17 sec following discontinuation of stimulation (Fig. 1). The delayed recovery was even more dramatic in three animals. In two of these animals arterial pressure failed to return toward control and continued to decrease following cessation of stimulation and the animals expired after a single period of carotid sinus nerve stimulation which they had tolerated well while awake or asleep (Fig. 2); the third animal had a similar prolonged hypotensive reaction but recovered after 10 min.

Heart rate. In the resting conscious dog, a 30-sec period of carotid sinus nerve stimulation promptly produced a bradycardia. Heart rate decreased to a minimum level 12 ± 2% from control (from 72 to 63 beats/min) within the first 10 sec of stimulation. Heart rate rapidly recovered and returned to control levels between the 10th and 20th sec of stimulation while pressure was still decreasing. Heart rate rose to an average of 9 ± 2% above control at 30 sec, just prior to the discontinuation of stimulation (Fig. 1). In seven animals studied while asleep, the general pattern of heart rate changes were similar, i.e., the prompt bradycardia, the recovery during stimulation and the rebound tachycardia, but in four of these animals the bradycardia was much more marked (Fig. 3). In the sleeping animals, heart rate slowed to a greater extent, by an average of 22 ± 4% (from 69 to 54 beats/min) as compared to 12 ± 2% in the resting awake dogs (P < .01). In the anesthetized state, carotid sinus nerve stimulation produced an average decrease in heart rate of 14 ± 2% (from 135 to 133 beats/min). In contrast to the waking and sleeping states, return of heart rate to control levels was prolonged and required an average of 13 ± 6 sec after discontinuation of stimulation (Fig. 1). In these cases the rebound tachycardia observed in conscious animals was not apparent.

Autonomic components of heart rate response. The administration of atropine (0.2–0.4 mg/kg) to conscious dogs caused the heart rate to increase from an average of 74 to 152 beats/min. Carotid sinus nerve stimulation after atropine in these animals decreased heart rate by an average of only 3 ± 1%
CONSCIOUS AND ANESTHETIZED CAROTID SINUS CONTROL

FIG. 3. Response to a 30-sec period of carotid sinus nerve stimulation (black bar) in a sleeping dog. Responses of mean arterial pressure, phasic and mean mesenteric, renal, and iliac flows, are shown. Note periods of intense bradycardia.

(from 152 to 148 beats/min). On a separate day these dogs were anesthetized with pentobarbital. Atropine (0.2–0.4 mg/kg) caused heart rate to increase only from an average of 136 to 164 beats/min. Carotid sinus nerve stimulation then produced a decrease in heart rate of 12 ± 3% (from 164 to 144 beats/min).

Propranolol (1.0–2.0 mg/kg) in conscious dogs caused the heart rate to decrease from an average of 76 to 66 beats/min. Carotid sinus nerve stimulation in these animals then decreased heart rate further, by 9 ± 2% (from 66 to 60 beats/min). When the anesthetized animals were given propranolol, heart rate decreased from an average of 160 to 138 beats/min. Carotid sinus nerve stimulation produced no further reduction in heart rate (from 138 to 138 beats/min) in all five dogs so studied.

Regional blood flow and resistance. In resting conscious animals, when aortic pressure was at a minimum level during carotid sinus nerve stimulation, left circumflex coronary blood flow showed little change, decreasing on the average by 5 ± 2% (from 42 to 40 ml/min). Similarly, renal flow decreased slightly by 8 ± 3%, from an average of 344 to 316 ml/min, and mesenteric blood flow fell 9 ± 2%, from an average of 315 to 286 ml/min. Iliac blood flow increased 112 ± 13%, from an average of 220 to 466 ml/min. The decreases in calculated resistances averaged 24 ± 3% in the left circumflex coronary bed, 22 ± 3% in the renal bed, 20 ± 3% in the mesenteric bed, and 66 ± 5% in the iliac bed (Fig. 4).

Pentobarbital, 30 mg/kg, increased calculated resistance in the mesenteric (19 ± 5%) and renal (20 ± 5%) beds, and decreased resistance in the iliac (8 ± 3%) and coronary (5 ± 2%) beds. In the anesthetized state, carotid sinus nerve stimulation then resulted in average decreases of coronary flow of 28 ± 3% (from an average of 50 to 36 ml/min), renal flow 7 ± 2% (from 328 to 304 ml/min), mesenteric flow 8 ± 2% (from 304 to 285 ml/min), and increases in iliac flow of 6 ± 5% (from 273 to 295 ml/min). Resistance increased in the coronary bed by an average of 6 ± 3% and decreased in the renal bed by 17 ± 3%, in the mesenteric bed by 15 ± 3%, and in the iliac bed by 30 ± 4% (Fig. 4).

DISCUSSION

Carotid sinus nerve stimulation in the conscious dog resulted in reductions in arterial pressure, heart rate, and resistance of the coronary, mesenteric, renal and iliac beds. In sleeping, unanesthetized dogs the circulatory changes were similar. After pentobarbital anesthesia an identical intensity and duration of carotid sinus nerve stimulation in the same dogs resulted in similar degrees of arterial hypotension and bradycardia, but the recovery of heart rate and arterial pressure were prolonged.

General anesthesia is known to alter cardiac output, heart rate, arterial pressure, and peripheral vasoactivity (9, 20). Barbiturates in particular are known to exert a vagolytic
effect (20, 26) and at higher doses to depress central reflexes including the carotid sinus reflex (3, 4, 18). The levels of anesthesia in this study did not significantly depress the response to carotid sinus nerve stimulation since the resultant arterial hypotension and bradycardia were quantitatively similar in both awake and anesthetized states. However, the time required for recovery of heart rate and arterial pressure became markedly prolonged (Fig. 1). This was evident in all animals studied but was most dramatically seen in the dogs that failed to recover from stimulation. One of these animals recovered 10 min after discontinuation of stimulation. In the other two animals in which this type of reaction was observed, recovery did not occur and these animals expired. In one of these two animals, coronary blood flow and arterial pressure were recorded (Fig. 2); the hypotensive state was accompanied by a marked reduction in coronary blood flow.

Protracted recovery from perturbations in the cardiovascular system has been noted previously with general anesthesia (17, 21). The prolonged hypotension with carotid sinus nerve stimulation observed in anesthetized animals could be due to a supramedullary effect blocking the normal integration of information from other sensors in the cardiovascular system, such as the aortic receptors, that should respond to and buffer the bradycardia and hypotension induced by carotid sinus nerve stimulation. Thus, in the conscious state, heart rate recovered during stimulation and recovery tachycardia occurred, whereas in the anesthetized state this did not occur. However, it is also possible that facilitatory and inhibitory pathways involved with the carotid sinus reflex are blocked with general anesthesia, resulting in a more prolonged response. There is considerable evidence for supramedullary control of the cardiovascular system (1, 22) and, more specifically, for supramedullary modulation of the carotid sinus reflex (8, 12, 13, 15, 23, 27, 33). These studies have shown that the carotid sinus reflex may be facilitated or depressed by electrical stimulation of arcs of the brain above the medulla. Thus, general anesthesia could not only delay integration of information in the brain but might also alter the facilitation and inhibition of the reflex that exists in the conscious state. An increase in facilitation or a decrease in inhibition of the effects of carotid sinus nerve stimulation could explain the protracted response seen in anesthetized animals.

It is important to note that carotid sinus nerve stimulation which is well tolerated in the conscious state can, under general anesthesia, lead to circulatory collapse and death. This observation may be of clinical importance since implantation of carotid sinus nerve stimulating electrodes is being carried out with greater frequency in the management of intractable angina pectoris, paroxysmal atrial tachycardia, and of hypertension. The responsiveness of the nerves to the stimulus is tested while the patient is under general anesthesia. Obviously, this must be done very cautiously, in order to avoid the type of response which we observed experimentally. This caution should be extended to other surgical procedures involving neck dissection, since mechanical traction of the carotid sinus or the carotid sinus nerves might invoke a similar response.

Another striking difference in the response seen in the conscious state as opposed to the anesthetized one, was in the response of the regional beds to carotid sinus nerve stimulation. Anesthesia did not affect the responses of the renal or mesenteric beds significantly. However, the responses of the coronary and iliac beds were markedly altered (Figs. 5 and 6). In the coronary bed of conscious dogs there was a reduction of resting sympathetic vasoconstrictor tone with carotid sinus nerve stimulation (31), i.e., carotid sinus nerve stimulation had little effect on coronary blood flow in the conscious or sleeping dog while calculated coronary resistance decreased by 74%. Stimulation after anesthesia reduced coronary flow by 28%, while coronary resistance actually increased slightly (6%). Iliac blood flow doubled and resistance decreased by 66% in conscious dogs, while iliac flow increased by an average of only 8% and resistance decreased by only 30% with carotid sinus nerve stimulation in the anesthetized state. The effects observed in the conscious and anesthetized states in the iliac and coronary beds may be partially explained on the basis of different levels of vascular resistance prior to stimulation. Anesthesia reduced the steady-state iliac resistance by an average of 8% and coronary resistance by an average of 5% from the control unanesthetized levels. The decrease in coronary resistance by anesthesia could be partially explained by the decreased heart rate after anesthesia, since coronary vascular resistance has been shown to decline with increasing heart rate (19).

On the other hand, since the bradycardia was more sustained with stimulation in the anesthetized state this could partially account for the greater decrease in coronary blood flow and lack of decline of coronary vascular resistance. It is also possible that general anesthesia reduced tonic sympathetic coronary vasoconstriction (31), and that the latter could then not be reduced further by carotid sinus nerve stimulation. Since the control values for resistance in the mesenteric and renal beds were higher in the anesthetized state, the observed attenuated decreases in resistance in these beds with stimulation could not be explained on the basis of an already dilated bed. The differences seen in vasoactivity in the regional beds may be due to a central depressant effect of pentobarbital on the medullary vasomotor center, or to a peripheral depressant effect on the resistance blood vessels (10), or to a combination of these effects.

There is some evidence that during sleep there is an increased baroreceptor sensitivity as compared to the waking state. In the present study, carotid sinus nerve stimulation resulted in a greater cardiac slowing in the sleeping than in the waking state. These data are consistent with those of Smyth and associates (28) who tested baroreceptor sensitivity by measuring reflex cardiac slowing during the transient hypotension resulting from intravenous injections of angiotensin in waking and sleeping subjects and found that baroreflex sensitivity increased during sleep in 7 of 10 subjects (28). Our findings may be due to a resetting of the baroreceptors during sleep, as proposed by Smyth and associates (28), which in turn may be due to an increase in facilitation or a decrease in inhibition of the carotid sinus reflex.

The results of our studies help to clarify the controversy regarding the relative contributions of the sympathetic and parasympathetic nervous systems in the heart rate response to baroreceptor stimulation. The bradycardia observed with
carotid sinus nerve stimulation might result either from an increase in vagal activity or a reduction in cardiac sympathetic activity. We had observed, in conscious dogs, that the bradycardia associated with carotid sinus nerve stimulation is mediated predominantly by the vagus nerves since it can be prevented by cholinergic blockade and is affected only slightly by beta-adrenergic blockade (31, 32); but many earlier studies, such as those of Berkowitz, et al. (2), who

**FIG. 5.** Responses to 30-sec periods of carotid sinus nerve stimulation in same dog on same day, asleep, without anesthesia (left panel) and in the anesthetized state (right panel). Response of mean arterial pressure, phasic and mean coronary blood flow, and calculated mean coronary resistance are shown.

**FIG. 6.** Responses to 30-sec periods of carotid sinus nerve stimulation in same dog on same day, conscious (left panel) and in anesthetized state (right panel). Response of mean arterial blood pressure, iliac blood flow, and heart rate are shown. Differences in paper speed between these 2 responses is indicated at bottom. Note higher level of iliac blood flow and much more reduced degree of vasodilation in this bed during carotid sinus nerve stimulation in anesthetized, as compared to conscious state. In conscious state heart rate declined abruptly during stimulation but returned to control levels and overshot with continued stimulation. In this example, control anesthetized iliac flow was slightly greater than average, while control conscious iliac flow was less than average.
electrically stimulated the carotid sinus nerves in anesthetized dogs, concluded that the bradycardia associated with carotid sinus nerve stimulation was due to sympathetic withdrawal. To resolve these differences in this study, we analyzed the autonomic components of the bradycardia after general anesthesia. We found that in the anesthetized state the bradycardia produced by carotid sinus nerve stimulation appears to be due almost entirely to sympathetic withdrawal, since propranolol blocked the effects of carotid sinus nerve stimulation on heart rate while atropine did not diminish them. The reason for the different response under general anesthesia may be due to the vagolytic effects of anesthesia (9, 20, 26). This hypothesis and our findings are also supported by the study of Scher and Young (24) which also indicated that the bradycardia observed after arterial pressure was elevated mechanically in conscious dogs was predominantly vagal. Thus, in conscious animals, the primary mechanism involved with carotid sinus slowing of the heart appears to be an augmentation of vagal tone, while, in animals anesthetized with pentobarbital, another mechanism, i.e., withdrawal of sympathetic tone, appears to be responsible for the carotid sinus mediated bradycardia.

In the interpretation of the findings of this investigation it should be noted that the pattern of activation of the sinus nerves employed differed from that which occurs normally. In this study, the electrical stimulus was at constant frequency for the entire 30-sec period, whereas the normal impulse traffic in the carotid sinus nerves is rhythmic, being intensified during ejection and reduced during diastole. Thus, the mode of stimulation employed herein resembles that resulting from constant, rather than phasic distention of the carotid sinuses. Although it has been shown that phasic stimulation of the carotid sinus results in qualitatively different responses compared to static stimulation (5), the qualitative effects are identical. It should be noted, however, that most previous investigations on the carotid sinus reflex utilize preparations such as the one described by Moisseyeff (16) which employs a nonpulsatile pressure stimulator and electrodes from Medtronic, Incorporated. We also are grateful for technical assistance from N. C. Benjamin and D. P. McKown and wish to acknowledge the carotid sinus nerve stimulator and electrodes from Medtronic, Incorporated. We also thank Dr. Robert L. Van Citters for his encouragement and advice. This investigation was supported by Public Health Service Grant HE-12973.

Received for publication 1 September 1970.

REFERENCES


17. Morrison, J. L., H. A. Walker, and A. P. Richardson. The effect of pentobarbital on the response of the cardiovascular sys-
CONSCIOUS AND ANESTHETIZED CAROTID SINUS CONTROL


