Regional Hemodynamic Responses to Nicotine in Conscious and Anesthetized Dogs: Comparative Effects of Pentobarbital and Chloralose (42940)

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Abstract. **This study was conducted in 12 dogs to evaluate regional hemodynamic responses during intravenous infusion of nicotine (36 μg/kg/min) in the conscious state and compare them with those in the same dogs following either pentobarbital (*n* = 6) or chloralose anesthesia (*n* = 6). Values for regional blood flow were obtained with 15-μm radioactive microspheres and used to calculate regional vascular conductance. In the conscious state, nicotine increased aortic pressure (+70%) and caused hyperventilation that reduced arterial PCO_2 (−44%). These systemic effects were associated with decreases in vascular conductance in the renal cortex (−48%), pancreas (−81%), duodenum (−58%), and cerebral cortex (−55%), whereas no significant change in vascular conductance was evident in spleen, liver, or myocardium. Pentobarbital anesthesia blunted the increases in aortic pressure and respiratory activity and the reductions in vascular conductance in the renal cortex, pancreas, duodenum, and cerebral cortex during nicotine infusion. In contrast, chloralose anesthesia accentuated the increase in aortic pressure and the decrease in vascular conductance in the renal cortex during nicotine infusion, while it converted no change in vascular conductance in the spleen into a decrease and no change in vascular conductance in the myocardium into an increase. Chloralose anesthesia blunted nicotine-induced hyperventilation. These findings demonstrate that general anesthetic agents may have markedly different effects on cardiovascular reflex pathways. They emphasize the importance of considering the particular characteristics of the anesthetic agent used in interpreting results from studies of cardiovascular pharmacology and physiology in anesthetized animals.**

[P.S.E.B.M. 1989, Vol 191]

Our previous studies in anesthetized dogs demonstrated that intravenous nicotine infusion causes marked systemic and regional hemodynamic responses (1–4). These responses are attributable largely to activation of the sympathoadrenal system (5) via the action of nicotine on the arterial chemoreceptors, the central nervous system, and the autonomic ganglia, including the adrenal medullae (6–8), although nicotine also activates other diverse vasomotor mechanisms, including vasopressin released from the posterior pituitary gland (9). The hemodynamic effects of nicotine demonstrated significant quantitative differences depending on which of the widely used research anesthetic agents was employed, sodium pentobarbital or α-chloralose (1, 2).

General anesthesia has been shown to modify virtually every aspect of cardiovascular control, including the arterial chemoreceptors (10). Barbiturates such as pentobarbital appear to cause significant depression to neural reflex pathways, whereas chloralose has less marked effects on these pathways (10). Thus, it would not be surprising if nicotine-induced responses under chloralose anesthesia more closely approximated those in the conscious state.

The objective of this study was to test this hypothesis by evaluating for the first time systemic and regional hemodynamic responses during intravenous nicotine infusion in the conscious dog and then comparing

Received July 12, 1988. [P.S.E.B.M. 1989, Vol 191]
Accepted March 22, 1989.

0037-9727/89/1914-0396$2.00/0

these responses with those in the same dog following general anesthesia with sodium pentobarbital or α-chloralose.

Materials and Methods

Preparation of Chronically Instrumented Dog. Twelve mongrel dogs ranging in weight from 20 to 25 kg were anesthetized with sodium pentobarbital (30 mg/kg iv) and chronically instrumented under sterile surgical conditions. After tracheal intubation, the animal was placed on positive-pressure ventilation with a Harvard respirator. Through a left thoracotomy in the sixth left intercostal space, catheters were chronically implanted in the aorta, inferior vena cava, and left atrium. The thoracotomy was closed, air was displaced from the pleural cavity, and the animals were allowed to recover from general anesthesia. The animals were treated for 5 days following surgery with the antibacterial agent, Tribessen (Burroughs Wellcome Co.), 30 mg/kg/day.

The dogs were studied 7–10 days following surgery, when they appeared to be vigorous and healthy and had been conditioned to the laboratory environment. This conditioning involved daily placement of the dog in a sling (Alice King Chatham, Los Angeles, CA) and acclimation to intravenous infusions by flushing of the vascular catheters with heparinized saline.

Determination of Regional Hemodynamic Responses during Nicotine. On the day of experimentation, the animal was placed in the sling. Respiration was not regulated until after general anesthesia oxygen was added to the inspired room air to maintain arterial PO_2. A catheter was inserted percutaneously into the left saphenous vein for intravenous infusions. Aortic and vena caval pressures were measured with Statham model 23Db pressure transducers (Gould, Inc., Oxnard, CA) and recorded with a Hewlett Packard model 7784A recorder. Arterial blood samples were analyzed for PO_2, PCO_2, and pH with an Instrumentation Laboratory model 113 blood gas analyzer (Instrumentation Laboratory, Inc., Boston, MA) and for hematocrit by centrifugation.

Regional blood flow before and during nicotine infusion was determined from tissue content of 15 ± 3-μm microspheres injected into the left atrium. The microspheres were labeled with γ-emitting radionuclides (^{46}Sc, ^{51}Co, ^{85}Sr, ^{113}Sn; New England Nuclear, DuPont, Wilmington, DE and 3M Co., St. Paul, MN). Prior to injection, the microspheres were dispersed by agitation in a ultrasonic bath and with a vortex mixer. Approximately 10^6 microspheres were injected for each blood flow determination. These injections had no detectable effect on monitored hemodynamic parameters. Upon injection of microspheres, a 2-min reference sample of arterial blood was withdrawn from the aorta at a constant rate of 7.5 ml/min, so that blood flows could be computed (11).

After the final dose of microspheres, the dog was killed by intravenous injection of potassium chloride. Transmural samples of myocardium were obtained from the left and right ventricular free walls. After the skull was opened, the brain was removed and samples of tissue were obtained from the cerebral cortex, cerebellum, pons, medulla, and cervical spinal cord. Samples of tissue were also obtained from the renal cortex, pancreas, spleen, liver, and duodenum. These tissue samples and reference arterial blood samples were analyzed for radioactivity in a gamma counter equipped with a multichannel analyzer (Packard Instrument Co., Downers Grove, IL). Isotope separation was accomplished by standard techniques of gamma spectroscopy with the aid of a PDP/8E minicomputer (Digital Equipment Corp., Maynard, MA).

Blood flow is a direct function of perfusion pressure and vascular conductance. To identify regional vasomotor effects of nicotine in the presence of wide variations in perfusion pressure (Table I), vascular conductance for each organ was computed using the equation: Vascular conductance = organ blood flow/(mean aortic pressure − mean central venous pressure). Since mean vena caval pressure rather than portal venous pressure was used to calculate perfusion pressure in pancreas, duodenum, and spleen, vascular conductance values for these organs were slightly underestimated.

The changes in aortic pressure (Table I) and regional blood flow (Table II) caused by the general anesthetics themselves suggested significant alterations in the baseline (prenicotine) vascular conductance in several organs, e.g., pancreas. Accordingly, the nicotine-induced changes in regional vascular conductance were normalized to "percentage of change from control" (Fig. 1) to facilitate statistical comparisons among the experimental groups.

Experimental Protocols. In all 12 dogs, measurements of hemodynamic parameters and regional blood flow were first obtained in the conscious state, before and during intravenous infusion of nicotine, 36 μg/kg/min. The rate of infusion of the nicotine solution was standardized at 1.0 ml/min. A rather high dose of nicotine was selected for use throughout the study, so that hemodynamic effects were pronounced and modification of these effects by general anesthesia was readily detectable. Furthermore, this dose of nicotine was used in our previous studies in anesthetized dogs (1–4), which facilitated comparisons between the present findings and those from those previous studies. Nicotine infusion always caused marked aortic hypertension, and microsphere injections were made at the peak hypertensive response, which occurred 3–3.5 min after the infusion was begun. Nicotine infusion was continued for 2 min after injection of microspheres, during collection of reference blood samples. At least 30 min were provided for recovery from effects of nicotine in the conscious state. Then the dog received, on a randomized basis, a single bolus intravenous injection of either of two general anesthetics, sodium pentobarbital (30 mg/kg) or α-chloralose (100 mg/kg). The doses of anesthesia utilized were equivalent to those reported for previous experimental studies (2, 12, 13). There was no attempt to maintain the animals in a particular stage of anesthesia by administration of supplemental anesthesia. The concentration of sodium pentobarbital was 60 mg/ml (30 g of sodium pentobarbital, 200 ml of propylene glycol, and 50 ml of ethyl alcohol in deionized water to a volume of 500 ml with pH corrected to 9.5). The concentration of α-chloralose was 80 mg/ml (20 g of α-chloralose and 23.44 g of sodium borate in deionized water to a volume of 250 ml). The volume of sodium pentobarbital injected for general anesthesia was 10–12.5 ml, whereas that for α-chloralose was 25–31.5 ml.

Thirty to 45 min after induction of general anesthesia radioactive microspheres were injected to define new, prenicotine values for regional blood flow. Previous studies have demonstrated that this was sufficient time for attainment of steady-state hemodynamic conditions following the substantial transient hemodynamic responses that occur upon induction of anesthesia with either sodium pentobarbital or α-chloralose (12, 13). A second infusion of nicotine was then performed and microspheres were injected at the peak hypertensive response. The lack of tachyphylaxis to repeated infusions of nicotine has been demonstrated (4).

Statistical significance of effects was determined with Student's *t* test (14). Student's *t* test for paired samples was used, when appropriate, to negate the complication of interanimal variation in uncovering experimental effects. Pairing of data would not have been possible if an analysis of variance was chosen to compare findings simultaneously under the three conditions studied (conscious, pentobarbital anesthesia, and chloralose anesthesia), since pentobarbital and chloralose were employed in different dogs and a completely randomized experimental design would have been required. A value of $P < 0.05$ was considered to be significant.

Results

Effects of Nicotine in Conscious Dogs. Intravenous infusion of nicotine in conscious dogs increased aortic pressure (+70%), heart rate (+20%), arterial PO_2 (+10%), pH (+2.3%), hematocrit (+16%), and decreased arterial PCO_2 (−44%) (Table I). The changes in arterial blood gases were secondary to the visually observed marked hyperventilation. These systemic hemodynamic effects of nicotine infusion were accompanied by decreases in blood flow in the renal cortex (−23%), pancreas (−72%), duodenum (−38%), and brain (cerebral cortex, −27%; cerebellum, −25%; pons, −31%; medulla, −33%; spinal cord, −22%) and by increases in blood flow in the spleen (+74%), liver (+131%), and myocardium (left ventricle, +120%; right ventricle, +168%) (Table II).

Figure 1 presents percentage of changes in regional vascular conductance during nicotine infusion. For the sake of simplicity and space, findings in the cerebral cortex and the left ventricular myocardium are presented as examples of vasomotor responses for their respective organs. Nicotine in conscious dogs caused vascular conductance to decrease in the renal cortex (−48%), pancreas (−81%), duodenum (−58%), and cerebral cortex (−55%), whereas it had no significant effect on vascular conductance in other tissues.

Effects of General Anesthetics Themselves. Depression of respiration by both pentobarbital and chloralose anesthesia reduced arterial PO_2 to approximately 60 mm Hg; thus, supplementary oxygen was

Table I. Effect of Nicotine on Systemic Hemodynamic Parameters and Arterial Blood Gases in Conscious State and after General Anesthesia with Either Sodium Pentobarbital or α-Chloralose

	Conscious (n = 12)		Pentobarbital (n = 6)		Chloralose (n = 6)	
	Control	Nicotine	Control	Nicotine	Control	Nicotine
Mean arterial pressure (mm Hg)	102 ± 3[a]	173 ± 9[b]	108 ± 9	154 ± 8[b]	93 ± 3	221 ± 17[b]
Heart rate (beats/min)	102 ± 6	122 ± 10[b]	133 ± 10[c]	105 ± 10	97 ± 10	110 ± 18
Arterial values						
PO_2 (mm Hg)	84 ± 4	92 ± 6[b]	161 ± 17	174 ± 20	141 ± 14[c]	140 ± 12
PCO_2 (mm Hg)	34 ± 1	19 ± 2[b]	39 ± 2	33 ± 2[b]	35 ± 2	23 ± 2[b]
pH	7.44 ± 0.01	7.61 ± 0.03[b]	7.38 ± 0.01	7.45 ± 0.02	7.38 ± 0.01	7.48 ± 0.02[b]
Hematocrit (%)	32 ± 1	37 ± 1[b]	29 ± 1	37 ± 1[b]	30 ± 2	37 ± 1[b]

[a] Values are mean ± SE.
[b] $P < 0.05$ from respective prenicotine control.
[c] $P < 0.05$ from respective conscious control.

Table II. Effect of Nicotine on Regional Blood Flow (ml/min/100g) in Conscious State and after General Anesthesia with Either Sodium Pentobarbital or α-Chloralose

	Conscious (n = 12)		Pentobarbital (n = 6)		Chloralose (n = 6)	
	Control	Nicotine	Control	Nicotine	Control	Nicotine
Renal cortex	630 ± 96[a]	486 ± 66[b]	568 ± 86	526 ± 73	584 ± 32	399 ± 46[b]
Pancreas	213 ± 35	60 ± 10[b]	68 ± 17[c]	37 ± 10[b]	79 ± 12[c]	24 ± 6[b]
Duodenum	107 ± 16	66 ± 8[b]	64 ± 7[c]	66 ± 15	60 ± 2[c]	56 ± 8
Spleen	136 ± 19	237 ± 26[b]	218 ± 52	278 ± 42[b]	136 ± 13	122 ± 25
Liver	16 ± 3	37 ± 6[b]	20 ± 3	35 ± 8	23 ± 10	32 ± 11
Cerebral cortex	85 ± 5	62 ± 3[b]	60 ± 8[c]	55 ± 8[b]	49 ± 5[c]	58 ± 13
Cerebellum	81 ± 6	61 ± 9[b]	60 ± 7[c]	52 ± 7[b]	57 ± 3[c]	50 ± 7
Pons	62 ± 5	43 ± 5[b]	52 ± 4	40 ± 6[b]	46 ± 4	36 ± 5[b]
Medulla	52 ± 4	35 ± 3[b]	49 ± 4	35 ± 2[b]	44 ± 5	36 ± 5[b]
Spinal cord	27 ± 3	21 ± 3[b]	27 ± 3	19 ± 3[b]	24 ± 3	19 ± 1[b]
Myocardium						
Left ventricle	126 ± 14	277 ± 49[b]	109 ± 12	205 ± 50[b]	93 ± 12[c]	539 ± 136[b]
Right ventricle	75 ± 9	201 ± 50[b]	53 ± 6	136 ± 31[b]	47 ± 3[c]	433 ± 149[b]

[a] Values are mean ± SE.
[b] $P < 0.05$ from respective prenicotine control.
[c] $P < 0.05$ from respective conscious control.

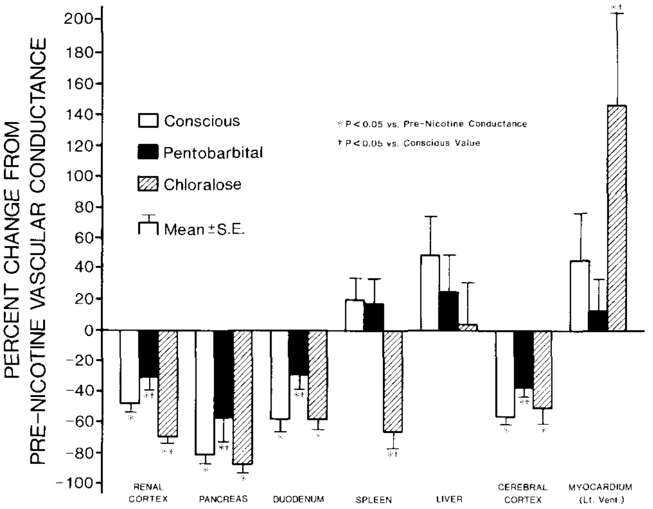

Figure 1. Effect of nicotine on regional vascular conductance in dogs before and after general anesthesia with either pentobarbital or chloralose.

administered to return arterial PO_2 to acceptable levels. Neither anesthetic caused significant changes in hematocrit or in systemic hemodynamic parameters, with the exception that pentobarbital increased heart rate (+30%) (Table I). Pentobarbital caused decreases in blood flow in the pancreas (−68%), duodenum (−40%), cerebral cortex (−29%), and cerebellum (26%) that were not significantly different from those caused by chloralose (Table II). Chloralose alone decreased left and right ventricular myocardial blood flow (−26% and −37%, respectively). Blood flow in other tissues was not affected significantly by either anesthetic.

Effects of Nicotine after General Anesthesia. After pentobarbital anesthesia, intravenous nicotine continued to increase mean aortic pressure and arterial pH and hematocrit, and to decrease arterial PCO_2 secondary to hyperventilation (Table I). These changes were less than those in conscious dogs. After pentobarbital anesthesia, nicotine reduced blood flow in the pancreas (−46%) and the brain (cerebral cortex, −8%; cerebellum, −13%; pons, −23%; medulla, −29%; and spinal cord, −30%), and it increased blood flow in the spleen (+28%) and myocardium (left ventricle, +88%; right ventricle, +157%). Blood flow in other tissues was not affected significantly (Table II). After pentobarbital, nicotine caused decreases in vascular conductance in the renal cortex (−31%), pancreas (−57%), duodenum (−29%), and cerebral cortex (−36%) that were less than those in conscious dogs (Fig. 1). However, the lack of change in vascular conductance in the liver, spleen, and myocardium persisted.

After chloralose anesthesia, nicotine infusion caused changes in systemic hemodynamic parameters and arterial blood gases that were directionally similar to those in the conscious state (Table I). However, the increase in mean aortic pressure was greater than that observed in conscious dogs, whereas the increase in arterial pH and decrease in PCO_2 due to hyperventilation were less. In chloralose-anesthetized dogs, nicotine reduced blood flow in the renal cortex (−32%), pancreas (−70%), and in regions of the brain other than the cerebral cortex and cerebellum (−22%), and it increased blood flow in the left (+480%) and right (+821%) ventricular myocardium. Blood flow to other tissues was not affected significantly (Table II). Chloralose anesthesia accentuated the decrease in vascular conductance during nicotine infusion in the renal cortex and it converted no change in vascular conductance in the spleen into a decrease (−65%) and no change in vascular conductance in the myocardium into an increase (+118%). The nicotine-induced decreases in vascular conductance in the pancreas, duodenum, and cerebral cortex following chloralose anesthesia were similar to those in conscious dogs (Fig. 1).

Discussion

There were three major findings in this study. First, intravenous infusion of nicotine caused marked systemic and regional hemodynamic responses in the conscious, chronically instrumented dog. Second, pentobarbital and chloralose anesthesia both caused significant alterations in these hemodynamic responses during nicotine infusion. These alterations were largely opposite in direction; pentobarbital depressed nicotine-induced responses, whereas chloralose enhanced them. Third, both anesthetics caused themselves changes in baseline blood flow in a number of tissues.

Intravenous nicotine in conscious dogs caused arterial hypertension. This hypertension was associated with vasoconstriction in several organs, namely, the kidney, pancreas, duodenum, and brain. Findings from our extensive series of studies conducted in anesthetized dogs (1-4) point to mechanisms that may have contributed to these regional hemodynamic responses. The major mechanism for vasoconstriction in the renal and splanchnic beds was likely increased release of norepinephrine from local sympathetic nerve terminals because of stimulation of the central nervous system, sympathetic ganglia, and arterial chemoreceptors (6–8). Another factor possibly contributing to vasoconstriction in the abdominal viscera was vasopressin, which undergoes accelerated release from the posterior pituitary gland during nicotine infusion (9). Additional mechanisms with potential influence in these vascular beds derive from the ability of nicotine to stimulate respiratory activity via the arterial chemoreceptors (6). Increased activity of pulmonary stretch receptors causes vasodilation by withdrawal of sympathetic outflow (15). Furthermore, hypocapnic alkalosis accompanying hyperventilation may itself influence regional vasomotor tone. Although hypocapnic alkalosis causes vasoconstriction locally (16), it also reduces activity of arterial chemoreceptors (17), which may blunt sympathetic vasoconstrictor responses to nicotine. The role of the vascular mechanisms relating to increased respiratory activity on hemodynamic responses in the renal and splanchnic beds during nicotine infusion in conscious dogs awaits clarification. However, the local vasoconstrictor effect of hypocapnia secondary to hyperventilation was probably sufficient to account for the observed cerebral vasoconstriction in conscious dogs (18).

The increased myocardial blood flow during nicotine infusion is consistent with an augmented cardiac work demand and oxygen consumption because of increased ventricular afterload and heart rate (3, 19). The exaggerated increases in blood flow in the right ventricular myocardium during nicotine infusion (especially following chloralose anesthesia) likely reflects the lesser capability for pressure-flow autoregulation in the right coronary circulation compared to the left coronary circulation (20).

The ability of pentobarbital to depress cardiovascular control mechanisms is well established (9). Pentobarbital has been demonstrated to blunt pressor reflexes, including those to carotid occlusion and hypotension (21), to electrical stimulation of the medulla, hypothalamous, and sciatic nerve (22), and to selective carotid chemoreceptor stimulation with nicotine (23). Furthermore, pentobarbital has been observed to accentuate pressor responses to exogenous catecholamine infusions which has been interpreted as reflecting depression of baroreceptor reflex pathways (24).

Previous studies of effects of α-chloralose on cardiovascular reflexes have lacked similar unanimity. On the one hand, chloralose has been reported to exaggerate systemic baroreceptor responses (25), to accentuate spinal reflexes and responses to carotid sinus nerve stimulation (26), and to heighten activity of the vasomotor and cardiac control centers in the medulla (27), whereas on the other hand it has been reported to decrease systemic pressor responses to carotid sinus hypotension (21) and to injections of nicotine into the carotid sinus (23), and to magnify systemic pressor responses to exogenous catecholamines (24). These differences in results suggest that, unlike pentobarbital anesthesia which apparently causes generalized depression of neural pathways, chloralose may depress activity of certain neural pathways while enhancing others. This notion is consistent with the present findings that chloralose depressed nicotine-induced hyperventilation but enhanced nicotine-induced arterial hypertension. The enhanced hypertensive response following chloralose anesthesia was associated with more uniform regional vasoconstrictor responses during nicotine infusion (Fig. 1). This was apparent from the ability of chloralose to augment vasoconstrictor activity in the splenic and renal cortical circulations.

Cerebral vasoconstriction during nicotine infusion persisted following general anesthesia, but it was attenuated by pentobarbital anesthesia. The lesser fall in carbon dioxide tension because of blunted chemoreceptor-mediated hyperventilation was apparently sufficient to account for this effect of pentobarbital (18). The well-preserved decreases in cerebral vascular conductance during nicotine infusion following chloralose anesthesia occurred despite a similar attenuation of nicotine-induced hypocapnia. This suggests that chloralose potentiated another cerebral vasoconstrictor mechanism activated by nicotine, perhaps the sympathetic nerves (28). The depressive effect of general anesthesia on chemoreceptor-mediated hyperventilation is in keeping with previous reports (29).

The present findings indicate that although pentobarbital and chloralose anesthesia themselves had little effect on monitored systemic hemodynamic parameters, they caused similar vasomotor changes in the regional circulations. The decrease in vascular conductance in the splanchnic organs was in keeping with previous reports (30) and it has been attributed to baroreceptor-mediated vasoconstriction secondary to reduced cardiac output. Since both pentobarbital and chloralose cause relaxation of vascular smooth muscle directly (31), the observed cerebral vasoconstriction was likely an autoregulatory response to reduced oxygen consumption in the most metabolically active regions of the brain (32). The similar blood flow in cerebral cortex, cerebellum, pons, and medulla following the administration of pentobarbital or chloralose is consistent with the previous study that demonstrated, utilizing a microspectrophotometric technique, homogeneity in regional oxygen consumption in cat brains following general anesthesia (33).

The tendency for pentobarbital and chloralose anesthesia to depress respiration has been described (29). This depression was evident in our preparation so oxygen supplementation was utilized. Oxygen supplementation increased arterial PO_2 to levels modestly greater than that in conscious dogs. However, this higher arterial PO_2 caused only little increase in arterial O_2 content, since the levels of arterial PO_2 and pH prior to anesthesia were adequate for essentially complete saturation of hemoglobin (34), and it was sufficient to increase only negligibly the amount of oxygen dissolved in the plasma (35). Since arterial oxygen content, not arterial PO_2, is a primary determinant of convective tissue oxygen delivery (35), the variation in arterial PO_2 among the experimental conditions was not a significant confounding variable in the present study.

The tachycardia caused by pentobarbital is a well-known phenomenon which has been attributed to both a vagolytic effect (12) and to a baroreceptor-mediated reflex (36).

This study showed that two general anesthetic agents widely used in cardiovascular studies in laboratory animals disturb, albeit differently, the regional vasomotor mechanisms activated by intravenous administration of nicotine. Although these findings apply strictly to nicotine, which is a drug with a unique and complex pharmacologic profile (5), they point out the importance of considering the particular characteristics of the general anesthetic agent employed in interpreting results from any study of cardiovascular pharmacology or physiology performed in anesthetized animals.

This work was supported by the Smokeless Tobacco Research Council, Inc. and the Cardiology Fund.

We are grateful for the technical assistance of Arthur G. Williams and John Anthony.

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