Hemodynamic Effects of Nicotine in Canine Skeletal Muscle (43210)

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Abstract. **Studies were conducted in 36 artificially ventilated, anesthetized dogs to clarify hemodynamic effects of nicotine in resting gracilis muscle. In Series 1, effects of intravenous nicotine (36 μg/kg/min) were evaluated in (i) intact muscles (Condition 1), (ii) denervated muscles (Condition 2), (iii) denervated muscles following local α-adrenergic blockade (Condition 3), (iv) denervated muscles following combined local α- and β-adrenergic blockade (Condition 4), and (v) intact muscles with aortic pressure maintained constant (Condition 5). In Series 2, nicotine was infused directly into the gracilis artery at a rate of 3.6 μg/kg/min. Muscle blood flow was obtained with an electromagnetic flowmeter and used to calculate vascular resistance and oxygen consumption (Fick equation). Plasma catecholamine levels were determined with a radioenzymatic method. Intravenous nicotine doubled mean aortic pressure under Conditions 1–4. In intact and denervated muscles (Conditions 1 and 2) proportional increases in vascular resistance, reflective of vasoconstriction, held blood flow constant. Muscle oxygen consumption was unchanged. α-Adrenergic blockade with phenoxybenzamine following denervation (Condition 3) converted muscle vasoconstriction to vasodilation during nicotine infusion. Additional β-adrenergic blockade (Condition 4) restored muscle vasoconstriction. Nicotine-induced muscle vasoconstriction was maintained under controlled pressure (Condition 5). Intravenous nicotine significantly increased plasma catecholamine levels. Intra-arterial infusions of nicotine (Series 2) caused no hemodynamic changes in muscle. In conclusion, intravenous nicotine caused vasoconstriction in muscle, which was not due to reduced metabolic demand, pressure-flow autoregulation, or a different effect on vascular smooth muscle, but to stimulation of α-adrenergic receptors. Following denervation, this vasoconstriction was maintained by elevated plasma catecholamines. α-Adrenergic blockade unmasked nicotine-induced vasodilation mediated by β-adrenergic receptors, whereas combined α- and β-adrenergic blockade unmasked nicotine-induced vasoconstriction by a nonadrenergic mechanism.**

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Intravenous infusion of nicotine causes peripheral vasoconstriction, resulting in increased systemic vascular resistance and aortic blood pressure (1). This vasoconstriction is primarily attributable to stimulation of α-adrenergic receptors by norepinephrine released from sympathetic nerve terminals via the action of nicotine on the arterial chemoreceptors, the sympathetic ganglia, and the central nervous system (2–4). Nicotine also activates other vasomotor mechanisms, including vasopressin released from the posterior pituitary gland (5).

In previous studies in anesthetized dogs, we utilized the radioactive microsphere technique to evaluate the contribution of the regional vascular beds to the nicotine-induced increases in systemic vascular resistance (6, 7). The results demonstrated significant vasoconstriction in the kidney and splanchnic beds, but because of limitations relating to the use of the microsphere technique in tissues with low flow, hemodynamic responses in skeletal muscle were not evaluated. Although previous studies have examined hemodynamic effects of nicotine in skeletal muscle, their interpretation is complicated by the use of different protocols, doses, routes of administration, and species (8–10). The contribution of skeletal muscle to the increase systemic vascular resistance caused by nicotine may be significant since skeletal muscle has been shown to be a target

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for reflex vasoconstriction under other conditions, including arterial hypoxemia (11). Furthermore, although blood flow to resting skeletal muscle is low on a per weight basis, muscle constitutes more than 40% of body mass and thus it may play a prominent role in systemic hemodynamic adjustments.

Accordingly, the objective of this study was to evaluate changes in blood flow, vascular resistance, and oxygen consumption in resting canine gracilis muscle during intravenous administration of nicotine and to define mechanisms that may contribute to these changes. The nicotine infusion rate and canine model employed in the present study were similar to those used in our previous studies of nicotine-induced responses in other peripheral organs (6, 7), which facilitated interorgan comparisons.

Materials and Methods

Thirty-six conditioned, heartworm-free mongrel dogs (weight range, 16–30 kg) were anesthetized with sodium pentobarbital, 30 mg/kg iv with supplementations at a rate of 2 mg/kg/hr. After tracheal intubation, the animals were ventilated with room air supplemented with oxygen via a Harvard respirator. Arterial PO_2, PCO_2, and pH were measured with a blood gas analyzer (model ABL-1; Radiometer, Copenhagen, Denmark) and held within the physiologic range (PO_2, 125–150 mm Hg; PCO_2, 33–39 mm Hg; pH, 7.35–7.40). Polyethylene cannulas were inserted into the aorta to measure mean aortic blood pressure (MAP) and to obtain blood samples for analysis, and into the right femoral vein for intravenous infusions. Pancuronium bromide (Pavulon; Organon Inc., West Orange, NJ) in a dose of 0.15 mg/kg was administered for muscle paralysis to facilitate controlled ventilation and to prevent muscle fasciculations. Heparin (350 units/kg) was administered to prevent blood coagulation. A permanent record of hemodynamic parameters was obtained with a multichannel physiologic recorder (model 2800-S; Gould Inc., Cleveland, OH)

The left gracilis muscle was vascularly isolated *in situ*, as modified from the preparation of Renkin and Rosell (12). All blood vessels to the muscle were ligated with the exception of the gracilis artery and vein. Collateral blood flow to the muscle was precluded by tight umbilical tape ligatures placed at its ends. Evans blue dye was injected into the arterial supply of the muscle at the termination of each experiment to verify vascular isolation of the muscle. The obturator nerve, which is a mixed nerve carrying sympathetic vasomotor fibers to the gracilis muscle (13), was carefully isolated for later transection. The muscle was kept moist with isotonic saline under a Saran film. Muscle temperature was maintained with a heat lamp and monitored with a thermometer. Gracilis artery blood flow was measured with a noncannulating electromagnetic flow transducer and flowmeter (model RT-500; Narco, Houston, TX). Muscle venous blood samples were obtained through a narrow (PE-50) catheter threaded into the gracilis vein. When necessary to avoid recirculation of drugs administered directly into the gracilis artery (see below), a wider venous catheter was used which permitted diversion of the entire venous effluent from the muscle. Oxygen content of arterial and venous blood samples was measured with a Lex-O_2-Con (Lexington Inc., Waltham, MA). Muscle oxygen uptake (MVO_2) was calculated using the Fick equation

$$MVO_2 = MBF \times (CaO_2 - CvO_2)/100$$

where MBF = muscle blood flow (ml/min/100 g) and ($CaO_2 - CvO_2$) = muscle arteriovenous oxygen content difference (vol %).

Gracilis muscle vascular resistance was calculated by dividing mean aortic pressure by muscle blood flow. Changes in muscle vascular resistance were normalized by conversion to percentage of change from the (pre-nicotine) control value (Fig. 1).

Experimental Protocols

Series 1. Effects of Intravenous Nicotine. *Condition 1. MAP uncontrolled, intact muscle innervation.* In 33 dogs, control measurements for hemodynamic and metabolic variables in muscles with intact nerve supply were obtained after sufficient time (at least 30 min) for stabilization of experimental preparation. These dogs then received intravenous infusion of nicotine (36 μg/kg/min), and the measurements were repeated at the peak of the pressor response. This occurred 3–5 min after commencing infusion of nicotine.

In five of the dogs participating in Condition 1, arterial samples were collected under control conditions and during the peak nicotine-induced pressor response for measurements of plasma catecholamine concentra-

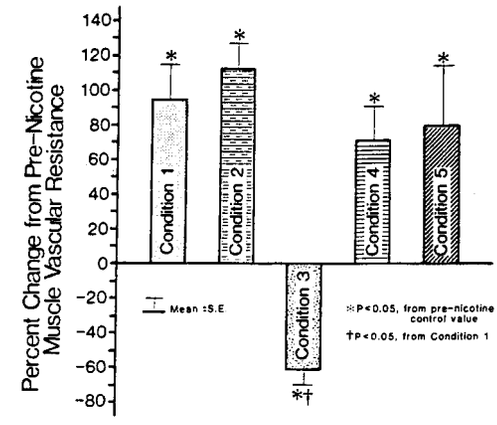

Figure 1. Effect of intravenous infusion of nicotine on muscle vascular resistance under Condition 1 (MAP uncontrolled; intact innervation), Condition 2 (MAP uncontrolled; denervation), Condition 3 (MAP uncontrolled; denervation with α-blockade), Condition 4 (MAP uncontrolled; denervation with combined α- and β-blockade), and Condition 5 (MAP controlled; intact innervation).

tions using a radioenzymatic method (Cat-a-Kit; Upjohn Diagnostics, Kalamazoo, MI) (14). In this method, norepinephrine and epinephrine are simultaneously converted to their corresponding methoxy derivatives by the catalytic action of catechol-*O*-methyltransferase in the presence of a methyl donor ([^{3}H]adenosyl methionine). The resulting catecholamine derivatives, [^{3}H] normetanephrine and [^{3}H]metanephrine are separated by thin-layer chromatography, oxidized to [^{3}H]vanillin, extracted, and quantified by liquid scintillation counting.

Condition 2. MAP uncontrolled, muscle denervated. In 16 dogs, effects of intravenous nicotine were also evaluated following acute transection of the obturator nerve. Muscle blood flow increased immediately following denervation due to acute loss of sympathetic vasomotor tone, although flow returned to predenervation levels within 30 min. At this time, control (prenicotine) measurements were obtained. Infusion of nicotine was begun and at the peak pressor response, the measurements were repeated.

Condition 3. MAP uncontrolled, muscle denervated, α-blockade. The persistence of nicotine-induced vasoconstriction in denervated muscles (Condition 2; Fig. 1) suggested continued stimulation of α-adrenergic receptors by circulating catecholamines. This mechanism was evaluated in six dogs by studying effects of intravenous nicotine in gracilis muscles following acute denervation and subsequent α-adrenergic blockade with phenoxybenzamine HCl (Dibenzaline; Smith Kline & French Laboratories). 200 μg of phenoxybenzamine in 20 ml of isotonic saline was infused into the gracilis artery over 5 min. The total venous effluent was collected and discarded during the period of phenoxybenzamine infusion to prevent systemic recirculation; this blood was replaced by infusing autologous blood collected from the dog just prior to the experiment. Completeness of α-adrenergic blockade was verified by absence of muscle vasoconstrictor responses (manifested by reductions in blood flow) during 40-μg intra-arterial injections of methoxamine (Vasoxyl; Burroughs Wellcome Co.). After control measurements were obtained, nicotine was infused and the measurements repeated at the peak pressor response.

Condition 4. MAP uncontrolled, muscle denervated, combined α- and β-adrenergic blockade. These studies performed in five dogs evaluated the role of muscle β-adrenergic receptors in the nicotine-induced increases in blood flow and oxygen consumption following combined denervation and α-adrenergic blockade (Condition 3). After muscle denervation and α-adrenergic blockade with phenoxybenzamine, propranolol (Inderal; Ayerst Laboratories), 100 μg in 5 ml of saline, was infused into the gracilis artery over 5 min. Propranolol was not permitted to recirculate into the systemic circulation. β-Adrenergic blockade was verified by the absence of a muscle vasodilator response to an intra-arterial 0.05-μg bolus injection of isoproterenol (Iprenol; Vitarine Co.). Measurements were obtained in the gracilis muscle under control conditions and at the peak pressor response during intravenous infusion of nicotine.

Condition 5. MAP controlled, intact muscle innervation. In order to eliminate the contribution of increased aortic pressure to the nicotine-induced changes in muscle vascular resistance, studies were performed in five dogs where aortic pressure was held constant. Aortic pressure was controlled by connecting a 500-ml pressurized reservoir to the left subclavian artery, which was ligated and then cannulated with wide bore tubing. Reservoir pressure was maintained equal to mean aortic pressure with compressed air. During infusion of nicotine, vascular constriction caused blood to be translocated from the dog's circulation to the reservoir, allowing aortic pressure to be maintained within 5 mm Hg of the control pressure. Control measurements were obtained after hemodynamic parameters were stable following surgical preparation. Nicotine infusion was then initiated, and measurements were obtained when reservoir volume reached maximum, thus indicating that pressor mechanisms were maximally activated.

Series 2. Effects of Intra-Arterial Nicotine. In this series comprised of six dogs, nicotine was infused into the gracilis artery at a rate of 3.6 μg/kg/min. Three of the muscles studied were innervated, while three were denervated. Measurements were obtained in the muscle immediately preceding commencement of nicotine infusion, and after 15 min of nicotine infusion had elapsed. The total venous effluent was collected in these studies so that nicotine did not recirculate into the systemic circulation.

Statistical Analyses

Comparisons between values under control conditions and during nicotine infusion were made using the Student's t test for paired samples (15). Comparisons of nicotine-induced changes in muscle vascular resistance under Conditions 1–5 in Series 1 were made using a completely randomized analysis of variance in combination with the Student-Newman-Keuls test (15). A $P < 0.05$ was considered to be significant throughout this study.

Results

Series 1. Effects of Intravenous Nicotine. In studies with uncontrolled aortic pressure (Conditions 1–4), intravenous nicotine increased aortic pressure by approximately 100% (Table I). In innervated muscles (Condition 1), the nicotine-induced pressor response was accompanied by no significant change in muscle blood flow, implying a proportional (2-fold) increase in muscle vascular resistance (Fig. 1). Muscle oxygen con-

Table I. Effect of Intravenous Infusion of Nicotine (N) on Muscle Blood Flow and Oxygen Consumption under Conditions 1–5

	Condition 1		Condition 2		Condition 3		Condition 4		Condition 5	
	C	N	C	N	C	N	C	N	C	N
MBF[a] (ml/min/100 g)	5.1 ± 0.7[b]	5.9 ± 0.6	4.6 ± 0.8	4.8 ± 1.1	7.7 ± 3.8	32.0 ± 7.7[c]	5.1 ± 1.3	5.5 ± 1.3	4.9 ± 1.6	2.7 ± 0.5[c]
MVO_2 (ml/min/100 g)	0.48 ± 0.05	0.44 ± 0.06	0.42 ± 0.08	0.36 ± 0.05	0.37 ± 0.21	0.74 ± 0.25[c]	0.51 ± 0.23	0.47 ± 0.20	0.51 ± 0.20	0.28 ± 0.08[c]
AVO_2 (vol %)	10.1 ± 0.6	8.9 ± 0.7	9.4 ± 1.1	9.5 ± 1.1	5.1 ± 1.9	2.2 ± 0.3[c]	9.1 ± 1.7	8.3 ± 1.3	9.7 ± 1.1	9.8 ± 1.7
MAP (mm Hg)	123 ± 3	235 ± 9[c]	118 ± 6	227 ± 17[c]	118 ± 8	212 ± 19[c]	107 ± 8	193 ± 17[c]	103 ± 4	106 ± 7

[a] MBF, muscle blood flow; MVO_2, muscle oxygen consumption; AVO_2, muscle arteriovenous oxygen difference.
[b] Values are mean ± SE.
[c] $P < 0.05$, from prenicotine control value.

sumption was not affected. Responses to nicotine were similar following denervation (Condition 2). α-Adrenergic blockade following denervation (Condition 3) resulted in an increase in muscle blood flow that was disproportionate to the nicotine-induced increase in mean aortic pressure, reflecting a decrease in vascular resistance. Muscle oxygen consumption doubled. Additional β-adrenergic blockade (Condition 4) restored the changes in muscle hemodynamic parameters during nicotine infusion that were evident under Conditions 1 and 2, i.e., muscle blood flow remained constant in the face of nicotine-induced hypertension because of increased vascular resistance and muscle oxygen consumption was unaffected.

Intravenous nicotine with uncontrolled aortic pressure caused appreciable increases in plasma catecholamine concentrations in all studies in which measurements were obtained (Table II). These increases were variable and showed no correlation to changes in muscle blood flow or vascular resistance.

Nicotine infusion with mean aortic pressure controlled (Condition 5) caused reduction in muscle blood flow due to increased vascular resistance. Muscle oxygen consumption decreased in proportion to the decrease in blood flow, since the arteriovenous oxygen difference was constant.

Series 2. Effects of Intra-Arterial Nicotine. Local intra-arterial infusion of nicotine caused no change in muscle blood flow, vascular resistance, or oxygen consumption.

Discussion

Critique of Methods. The canine gracilis muscle has been used in numerous studies of muscle circulatory control because of its anatomical accessibility and the ease of isolation of its vascular and nerve supply (11–13, 16, 17). To facilitate measurements of muscle blood flow, the conventional gracilis muscle preparation was used which involved ligation of all arteries with the exception of the major artery. Two findings from our previous study (11) suggest that this preparation does not cause regions of ischemia within the muscle. First, blood flow to the upper, middle, and lower thirds of the muscle remained uniform, as demonstrated from the distribution of radioactive microspheres. Second, the muscle retained significant vascular tone as evidenced by vigorous reactive hyperemic responses.

Table II. Effects of Intravenous Infusion of Nicotine on Plasma Catecholamine Concentrations (pg/ml)

	Control	Nicotine
Norepinephrine	415 ± 109[a]	18,665 ± 6,344[b]
Epinephrine	971 ± 244	93,761 ± 27,694[b]

[a] Values are mean ± SE.
[b] $P < 0.05$, from prenicotine control value.

Like previous investigators (11, 16), we assumed that the obturator nerve carried the sympathetic vasoconstrictor fibers to the gracilis muscle and thus that transection of this nerve would eliminate local neuronal release of norepinephrine. This assumption appears valid in light of the previous report that vasoconstrictor responses in the canine gracilis muscle were similar during selective electrical stimulation of the sympathetic chain and the obturator nerve (17).

Previous findings obtained in our laboratory in similarly prepared dogs indicated that mean central venous pressure is low under control conditions (approximately 3 mm Hg) and that intravenous nicotine in a dose of 36 μg/kg/min raised central venous pressure by only 2–3 mm Hg (7). Because the magnitude of these values for central venous pressure (a reflection of muscle venous pressure) was very small compared with those for mean aortic pressure, neglecting back pressure in our calculations of muscle vascular resistance introduced only minor error into these estimates, and would not be expected in any way to alter the conclusions of the present study.

Acute surgical preparation and general anesthesia were required for the canine model used in the present study. These factors were probably responsible for the higher control values for plasma catecholamines compared with those in chronically instrumented, conscious dogs (14), and for the variable increases in plasma catecholamines during nicotine infusion that were observed.

Without an available nicotine assay, it was not possible to match precisely the gracilis arterial concentrations of nicotine during the intra-arterial and intravenous administrations. The infusion rate for nicotine during the intra-arterial administrations was established at one-tenth of that used during the intravenous administration, which took into account the relatively small mass of the gracilis muscle (approximately 60 g), and the tendency for recirculation of nicotine during the intravenous infusions to increase progressively arterial concentrations before the steady state measurements were obtained.

Hemodynamic Effects of Nicotine. Intravenous nicotine caused a pronounced increase in vascular resistance in the intact gracilis muscle, consistent with vasoconstriction, which was sufficient to hold blood flow constant in the face of marked aortic hypertension. The 2-fold increase in muscle vascular resistance was comparable to that observed previously under similar conditions in renal cortex, duodenum, and hepatic artery bed, but it was less than that in pancreas (6, 7). Although all of these tissues make important contributions to the rise in systemic vascular resistance during nicotine infusion, the importance of muscle is heightened by the fact that it constitutes over 40% of the body mass.

A series of studies were performed to define the mechanism(s) underlying nicotine-induced muscle vasoconstriction. The results suggest no role for local factors in this response. First, the constancy of muscle oxygen consumption ruled out vasoconstriction secondary to reduced metabolic demand (18). Second, the persistence of vasoconstriction with aortic pressure controlled suggests that pressure-flow autoregulation, i.e., the natural tendency for vascular smooth muscle to contract when stretched, was not responsible. This is not surprising since previous studies showed that the perfusion pressures caused by intravenous nicotine in the present study (approximately 200 mm Hg) exceeded the autoregulatory range in canine skeletal muscle (19). Finally, absence of effect of inter-arterial infusions of nicotine on muscle blood flow precludes a direct constrictor effect on vascular smooth muscle.

The present findings indicated no effect of acute denervation alone on muscle vasoconstrictor responses during intravenous infusion of nicotine; only when denervation was followed by α-adrenergic blockade with phenoxybenzamine was vasoconstriction converted to vasodilation. Two explanations for these findings may be proposed. One explanation is that the elevated levels of circulating catecholamines were solely responsible for nicotine-induced vasoconstriction in intact muscles. However, the ability of nicotine to cause generalized activation of the sympathoadrenal system (20) and the predominance of neurogenic versus humoral control of muscle blood flow (21) suggest that this explanation is unlikely. A more probable explanation was that both neurogenic and humoral adrenergic mechanisms contributed to nicotine-induced vasoconstriction in intact muscles, and that denervation did not distinguish vasoconstrictor responses because resistance vessels had become more sensitive to blood-borne catecholamines. The phenomenon of denervation hypersensitivity has been described previously (22) and it has been attributed to blunted neuronal uptake of catecholamine in the junctional cleft.

Blockade of α-adrenergic receptors with phenoxybenzamine unmasked increases in muscle oxygen consumption and blood flow, and reductions in muscle vascular resistance during nicotine infusion. Since these responses were prevented with propranolol, they were due to stimulation of muscle β-adrenergic receptors by circulating catecholamines. The ability of blood-borne catecholamines to increase oxygen consumption of canine skeletal muscle is in keeping with previous reports (23). A portion of the nicotine-induced increase in blood flow (and decrease in vascular resistance) in muscles with blocked α-adrenergic receptors was attributable to metabolic autoregulation in response to the increased oxygen consumption (18). The significant decrease in muscle oxygen extraction suggests that a direct stimulation of vascular β_2-adrenergic receptors

by circulating catecholamines may have also contributed to the nicotine-induced vasodilation (17).

It is generally accepted that oxygen consumption in canine skeletal muscle is relatively independent of blood flow (24). This has been attributed to metabolic control mechanisms which modulate open capillary density in accordance with tissue requirements for oxygen extraction. In this study, the reduction in muscle blood flow during nicotine infusion with controlled aortic pressure was accompanied by no compensatory increase in oxygen extraction, and oxygen consumption decreased proportionally. This is consistent with impairment to capillary recruitment by nicotine itself or by a factor released by nicotine. The lack of effect of intra-arterial infusions of nicotine on muscle blood flow or oxygen consumption argues against a direct nicotine mechanism. A more probable mechanism appears to be nicotine-induced release of norepinephrine. This mechanism is supported by the decreased capillary exchange capacity in skeletal muscle, as evaluated by the capillary filtration coefficient, the permeability-surface area product, or oxygen extraction, demonstrated previously during direct sympathetic nerve stimulation or administration of exogenous norepinephrine (12, 25, 26).

The data indicate that intravenous nicotine caused vasoconstriction in completely adrenergically blocked muscles. Such nonadrenergic vasoconstriction is consistent with our previous reports of increases in systemic and regional, i.e., splanchnic organs and kidney, vascular resistances during intravenous infusion of nicotine following combined systemic administration of phenoxybenzamine and propranolol (1, 7). The nonadrenergic mechanism acting in muscle during nicotine infusion is a matter for speculation. One possibility is angiotensin (27). By activating the renal sympathetic nerves, nicotine would be expected to increase secretion of renin from the kidney, resulting in conversion of angiotensinogen into angiotensin. Another possible nonadrenergic vasoconstrictor mechanism is vasopressin, whose plasma concentration increases during nicotine infusion (28). The well-preserved increases in muscle vascular resistance during nicotine infusion in adrenergically blocked muscles (Condition 4) are consistent with the ability of phenoxybenzamine to potentiate vasopressin-induced vasoconstriction (29).

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