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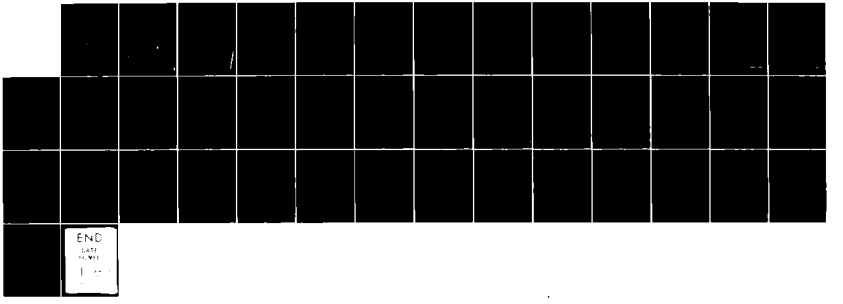

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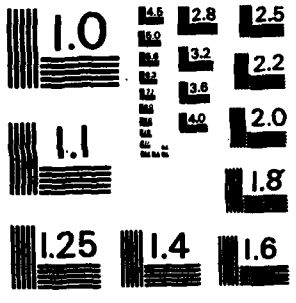

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The effects of bilateral denervations of the lumbar sympathetic chain, vagus nerves, and sacral ventral roots on peripheral circulatory and thermal responses during local cold exposure of a cat hindlimb were determined. Cold exposure apparently produced a peripheral vasocinstriction mediated by a somatosympathetic reflex and local mechanisms. Interruption of the L_3 sympathetic chain ipsilateral as well as contralateral to the cold-exposed hindlimb produced a marked reduction in vascular resistance, a femoral arterial
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hyperemia, and a warming of the foodpad and increased heat loss from the footpad. These responses were acute suggesting that local mechanisms can predominate in the absence of neurogenic mechanisms to restore peripheral vasoconstriction. Interruption of the vagus nerves and sacral ventral roots had little effect on the peripheral vasoconstriction. Interruption of the vagus nerves and sacral ventral roots had little effect on the peripheral circulatory and thermal responses to cold. This study identified the primary autonomic pathway mediating peripheral vasoconstriction during cold exposure as the efferent sympathetic nerves.

AUTONOMIC INFLUENCES ON PERIPHERAL CIRCULATORY AND THERMAL RESPONSES TO COLD

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Running Title: Autonomic Regulation of Cold-Induced Vasoconstriction

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ABSTRACT

The effects of bilateral denervations of the lumbar sympathetic chain, vagus nerves, and sacral ventral roots on peripheral circulatory and thermal responses during local cold exposure of a cat hindlimb were determined. Cold exposure apparently produced a peripheral vasoconstriction mediated by a somatosympathetic reflex and local mechanisms. Interruption of the L_3 sympathetic chain ipsilateral as well as contralateral to the cold-exposed hindlimb produced a marked reduction in vascular resistance, a femoral arterial hyperemia, and a warming of the footpad and increased heat loss from the footpad. These responses were acute suggesting that local mechanisms can predominate in the absence of neurogenic mechanisms to restore peripheral vasoconstriction. Interruption of the vagus nerves and sacral ventral roots had little effect on the peripheral circulatory and thermal responses to cold. This study identified the primary autonomic pathway mediating peripheral vasoconstriction during cold exposure as the efferent sympathetic nerves.

Key Words:

cold vasoconstriction; efferent sympathetic nerves; sacral parasympathetic nerves; vagus nerves; cold-induced vasodilation; anesthetized cat

INTRODUCTION

During cold exposure, peripheral vasoconstriction redistributes blood flow to the body core and thus minimizes peripheral heat loss (2,10). Although neural reflexes presumably mediate the peripheral vasoconstrictor responses to cold (28), there are apparently no published data demonstrating that this actually occurs.

The purpose of this study was to determine which autonomic nerves provide tonic vasomotor influences to a locally cold-exposed hindlimb. This was accomplished by determining the effects on peripheral circulatory and thermal responses of selectively denervating the sympathetic and parasympathetic nerves ipsilateral and contralateral to a cold-exposed hindlimb.

METHODS

General preparation. Experiments were performed on cats which were initially anesthetized with ketamine. In the hindlimb not being studied, the femoral vein was cannulated in order to induce anesthesia with α-chloralose (50 mg/kg iv) and for fluid replacement with lactated Ringer's solution. The femoral artery was cannulated with the catheter tip retrogradely positioned in the abdominal aorta for the continual monitoring of mean and pulsatile arterial pressure. After insertion of an endotracheal tube, breathing was assisted with a positive-pressure respirator and ventilation was adjusted to maintain end-expiratory CO_2 between 4 and 5%. A rectal thermistor was inserted for the continual monitoring of body temperature and auxiliary heat was provided with a heating pad and an infrared lamp. ECG was monitored with standard limb leads and heart rate was derived by triggering a ratemeter. Ambient temperature was monitored with a thermocouple exposed to room air or immersed in a cold bath.

In the hindlimb being studied, an electromagnetic flow transducer was placed around the femoral artery for the continual monitoring of mean and pulsatile blood flow. Skin temperature and heat flow were monitored with a thermocouple and heat flow disc taped to the metatarsal pad.

Surgical preparation. The effects of vagotomy and sympathectomy were studied in twenty cats. The cervical segment of both vagus nerves was isolated and a ligature was looped around them for later sectioning. The lumbar sympathetic chain ipsilateral to the hindlimb being studied was exposed with a flank incision and ligatures were looped around the nerves caudal to the L_3 ganglion. Sympathectomy was accomplished by pulling the ligatures free. In ten cats, bilateral vagotomy preceded ipsilateral sympathectomy. Sympathectomy preceded vagotomy in the other ten cats.

Whether there is laterality of the sympathetic influences ipsilateral to a hindlimb or whether there are also influences crossing-over from the contralateral sympathetics was determined by bilateral lumbar sympathectomies. In ten cats, both lumbar sympathetic chains were exposed with flank incisions and ligatures were looped around the branches caudal to the L_3 ganglion. Contralateral sympathectomy preceded ipsilateral sympathectomy in this experiment.

Sacral parasympathetic influences were studied by performing S_{1-3} ventral rhizotomies in eleven cats. The sacral spinal cord was exposed with a dorsal laminectomy. After identifying the dorsal root ganglion, the S_1, S_2 and S_3 ventral roots were carefully dissected free and looped with ligatures. In this experiment, the contralateral S_{1-3} ventral roots were sectioned before the ipsilateral sacral ventral rhizotomies.

Experimental procedure. All instruments used in this study were calibrated prior to each experiment. After anesthesia and surgical preparation of the cat, the parameters simultaneously and continuously monitored were mean and pulsatile femoral arterial blood flow, footpad temperature and heat loss, mean and pulsatile arterial pressure, ECG, heart rate, rectal temperature and ambient temperature. Transducer signals were simultaneously amplified and displayed on 4- and 8-channel chart recorders, recorded on magnetic tape, stored on-line with a computer, and displayed on a visual display terminal. Femoral arterial vascular resistance was instantaneously calculated as the quotient of mean arterial pressure divided by mean arterial blood flow.

In all experiments, control data were recorded for five minutes with the hindlimb exposed to room air prior to cold exposure. The hindlimb was then inserted into a surgical glove and the entire gloved foot was immersed in a cold bath to the level of the heel. The bath was cooled with an external refrigerated

circulating bath which was adjusted to lower footpad temperature between 0° and 5°C in the neurally intact cat. Skin temperature and heat flow declined exponentially until asymptotic levels were attained after a half hour. The data obtained during the dynamic period have been removed in order to report only the equilibrium data obtained during the final hour of the ninety minute immersion period in the neurally intact cat. The hindlimb was continually immersed during subsequent denervation phases. In one group of cats, the cervical vagi were sectioned and data were recorded for one hour. Then the ipsilateral lumbar sympathetic chain was denervated and data were recorded for the next hour. In another group of cats, ipsilateral lumbar sympathectomy preceded bilateral cervical vagotomy with the recording of data for one hour after each denervation. In a third group of cats, the lumbar sympathetics contralateral to the hindlimb being studied were denervated prior to ipsilateral lumbar sympathectomy and data were recorded for one hour after each denervation. In a fourth group of cats, the S_{1-3} ventral roots contralateral to the hindlimb being studied were denervated prior to the ipsilateral sacral ventral rhizotomies and data were recorded for an hour after each denervation. After both bilateral lumbar sympathectomies and bilateral sacral ventral rhizotomies, the cold bath and glove were removed in order to record data from the denervated cats during re-exposure of the hindlimb to room air for one hour.

Statistical analysis. All data from individual cats in each experimental group were averaged by a computer to obtain a mean value for each separate one-hour phase of the experiment. Whether the mean of each variable varied significantly during different phases of the experiment was determined by a one-way analysis of variance for repeated measurements of the same variable. When the analysis indicated that the variances differed significantly, Tukey's test was used to compare the critical differences between the means. A value of $P < 0.05$

was considered to be statistically significant. All data are expressed as means ± standard error.

Previously recorded data from individual cats in each experimental group were recalled by the computer in order to calculate and chronologically plot the mean values of all variables at 15 second intervals during each one hour phase.

RESULTS

Effects of cold exposure. There was evidence of peripheral vasoconstriction in the locally cold-exposed hindlimb. The following differences were observed when data obtained after cold exposure (-1.2 ± 1.2°C) were compared to control values obtained during room air exposure (21.9 ± 1.4°C): femoral arterial vascular resistance increased 35% from 20.4 ± 3.8 to 27.5 ± 4.9 mm Hg • $(ml/min)^{-1}$; mean femoral arterial blood flow decreased 20% from 6.8 ± 1.2 to 5.4 ± 0.9 ml/min; footpad skin temperature significantly decreased 86% ($P < 0.05$) from 27.1 ± 2.2 to 3.6 ± 1.2°C; heat flow increased 96% from 78 ± 21 to 154 ± 30 W/m^2; mean arterial pressure increased 8% from 108 ± 13 to 116 ± 14 mm Hg; heart rate decreased 6% from 206 ± 14 to 194 ± 23 beats/min; and rectal temperature decreased 1% from 36.9 ± 0.2 to 36.6 ± 0.1°C (combined data from Tables 1,2,3 and 4).

Effects of bilateral cervical vagotomy followed by ipsilateral lumbar sympathectomy. No significant differences in all parameters were observed when data obtained after vagotomy were compared to data obtained in the previously neurally intact period (Table 1). However, several acute cardiovascular changes occurred during the initial 4 minutes after vagotomy: vascular resistance decreased 23%, blood flow increased 156% (Fig. 1), blood pressure increased 27%, and heart rate increased 4%. This was accompanied by a delayed (8.5 minutes after vagotomy) and momentary (3.5 minutes duration) peak in both skin temperature (14% increase; Fig. 2) and heat flow (43% increase).

FIGURES 1 and 2 ABOUT HERE

Fig. 2

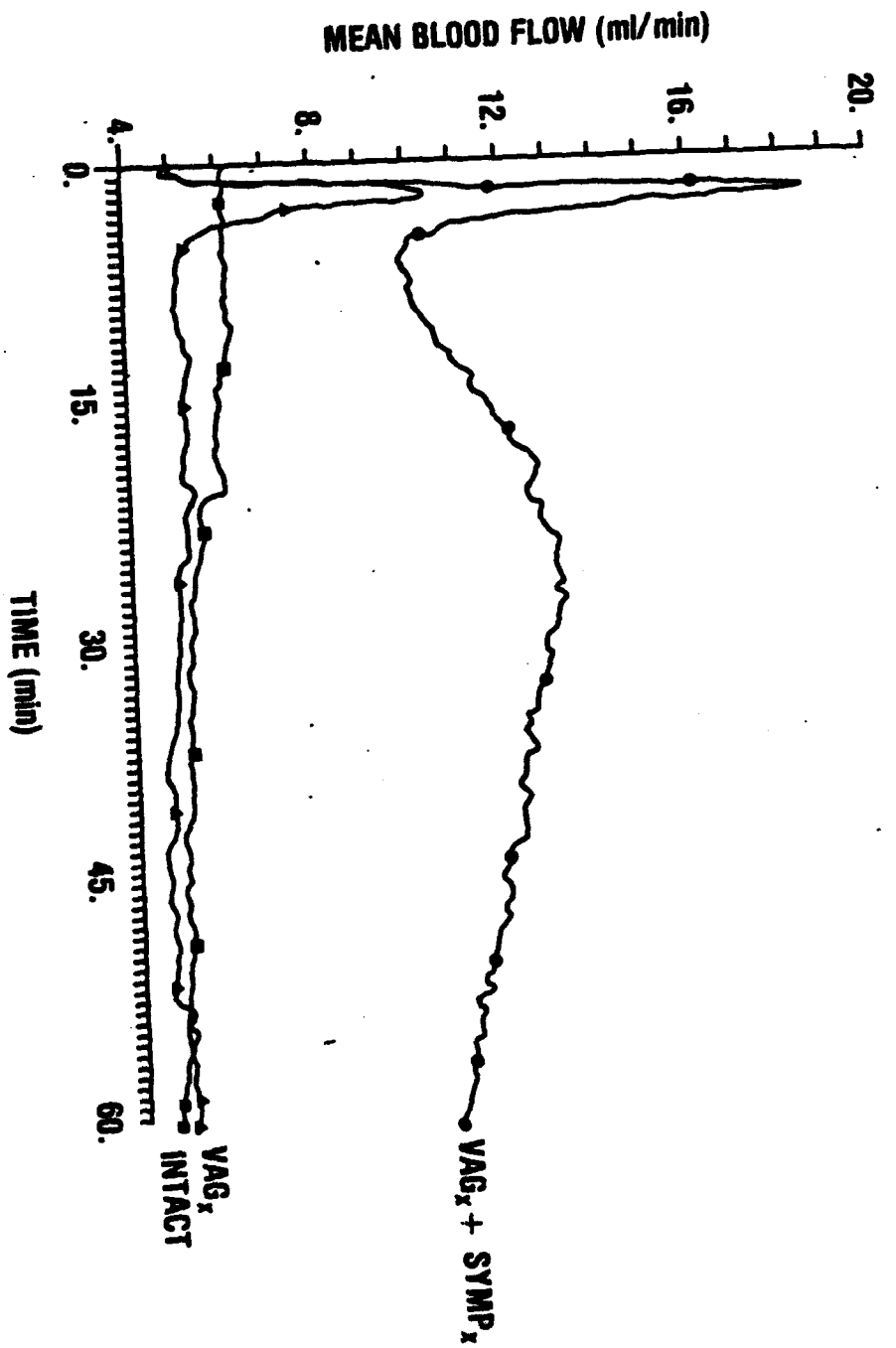
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Fig. 3

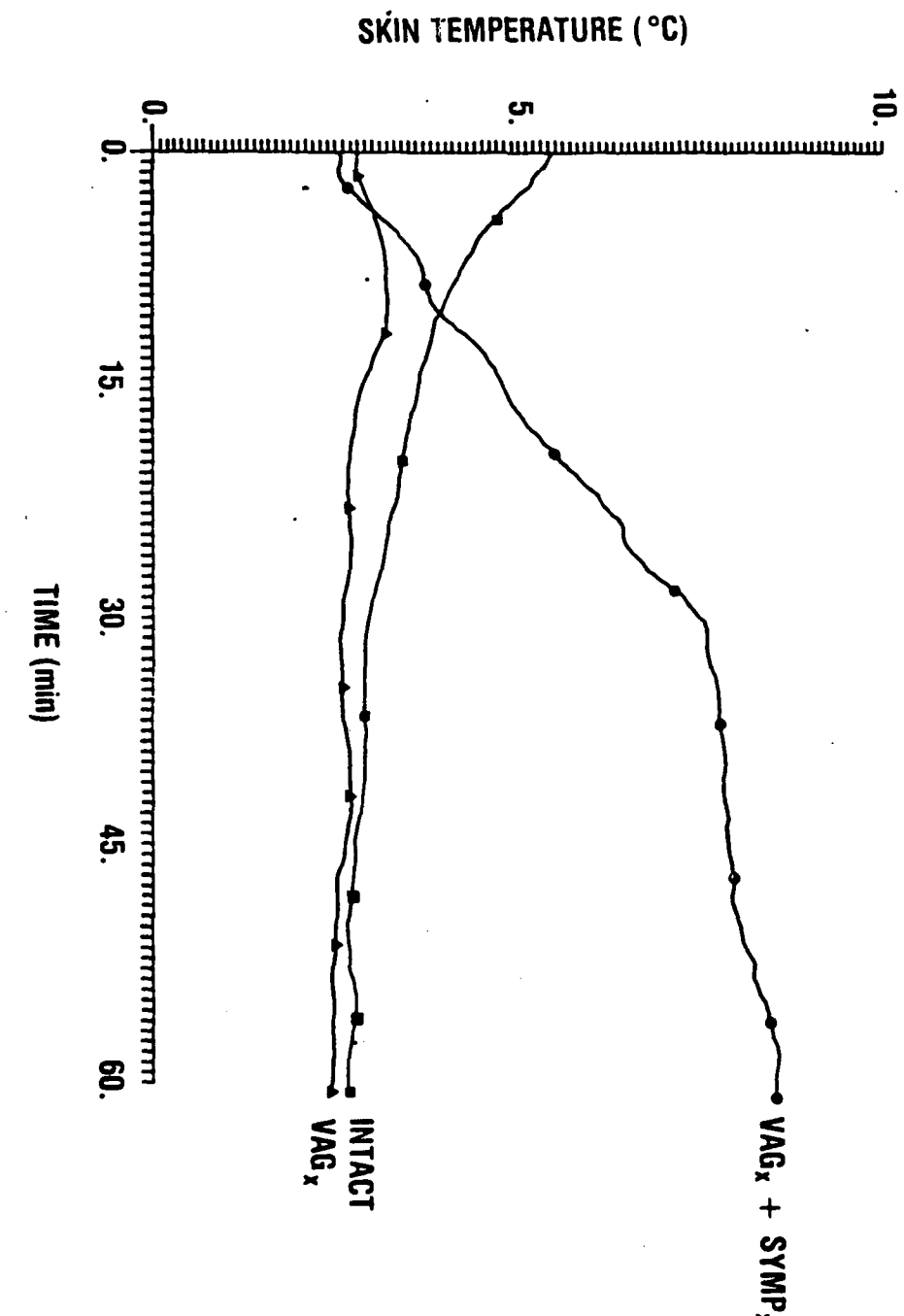
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TABLE 1. Effects of bilateral cervical vagotomy and subsequent ipsilateral lumbar sympathectomy on hindlimb circulatory and thermal function during cold exposure

	Vascular resistance, $mmHg \cdot (ml/min)^{-1}$	Mean blood flow, ml/min	Skin temperature, °C	Heat flow, W/m^2	Mean arterial pressure, *mm* Hg	Heart rate, beats/min	Rectal temperature, °C	Ambient temperature, °C
Control	18.4 ± 3.7	7.1 ± 1.4	26.7 ± 0.7	100 ± 17	114 ± 8	224 ± 8	36.9 ± 0.3	21.8 ± 0.4
Intact	21.5 ± 2.8	5.5 ± 0.9	2.9 ± 0.5	154 ± 28	124 ± 8	213 ± 9	36.5 ± 0.3	-0.1 ± 0.6
Vag_x	26.4 ± 2.8	4.7 ± 0.8	2.7 ± 0.4	181 ± 31	130 ± 6	212 ± 10	36.0 ± 0.3	-0.9 ± 0.6
$Vag_x + Symp_x$	14.2 ± 2.0	12.1 ± 1.6	7.7 ± 1.8	684 ± 167	129 ± 4	207 ± 10	35.3 ± 0.4	-1.5 ± 0.6

Values are means ± SE in 10 cats.

Sympathectomy caused a significant peripheral vasodilation (46% decrease in vascular resistance; $P < 0.05$), hyperemia (158% increase in mean blood flow; $P < 0.05$), warming (185% increase in footpad temperature; $P < 0.05$), heat dissipation (278% increase in footpad heat flow; $P < 0.001$), and hypothermia (2% decrease in rectal temperature, $P < 0.05$) without significant changes in heart rate and mean arterial pressure (Table 1). There were two phases of peripheral hyperemia after sympathectomy (Fig. 1). An initial hyperemia was of short duration (7 minutes) and large amplitude (358% increase in mean blood flow), and occurred in association with a 61% decrease in vascular resistance, 25% increase in blood pressure, and 6% increase in heart rate. A secondary hyperemia was more prolonged (53 minutes duration) and of smaller amplitude (34% increase in blood flow), and was associated with a 14% decrease in vascular resistance but without blood pressure or heart rate changes. Skin temperature (Fig. 2) and heat flow increased 200% and 292%, respectively, during the initial half hour after sympathectomy, and thereafter were maintained at high levels.

TABLE 1 ABOUT HERE

Effects of ipsilateral lumbar sympathectomy followed by bilateral cervical vagotomy. After ipsilateral lumbar sympathectomy, there was a marked vasodilation (50% decrease in vascular resistance, $P < 0.01$), hyperemia (123% increase in blood flow, $P < 0.05$), warming (56% increase in footpad temperature, $P < 0.05$), and heat dissipation (117% increase in footpad heat flow) without significant changes in heart rate or mean arterial pressure (Table 2). The 2% decrease in rectal temperature was double the expected rate of body cooling. Several acute changes were observed during the 6 minutes immediately after sympathectomy: vascular resistance decreased 62%, blood flow increased 282%

(Fig. 3), and mean arterial pressure increased 25%. There was a tendency towards a small amplitude and prolonged secondary hyperemia and pressor response. Skin temperature (Fig. 4) and heat flow increased, initially rapidly and later more gradually, until maximal levels of 5.6°C (133% increase) and 304 W/m^2 (161% increase) were attained after 30 minutes; thereafter both parameters gradually decreased.

Figures 3 and 4 ABOUT HERE

After bilateral vagotomy, vascular resistance increased 45%, blood flow decreased 21%, skin temperature decreased 7%, and heat flow decreased 15% (Table 2). However, these changes were not statistically significant and wre not attributed to the direct effects of vagotomy. Instead, these changes appeared to be attributed to the progressive attenuation of the sympathectomy induced hyperemia and warming by cold. Several acute changes were observed during the 7 minutes immediately after vagotomy: vascular resistance decreased 20%, blood flow increased 37% (Fig. 3), blood pressure increased 23%, and heart rate increased 6%. Skin temperature initially increased 16% to a peak value of 6.3°C, 11 minutes after vagotomy, and thereafter decreased 30% to a minimum of 4.4°C at the end of one hour (Fig. 4). Similarly, heat flow initially increased 16% to a peak value of 292 W/m^2, 8 minutes after vagotomy, and thereafter decreased 46% to a minimum of 158 W/m at the end of one hour. Rectal temperature decreased 1% from 35.4 to 35.2°C during the hour after vagotomy; this rate of body cooling was similar to when the cat was neurally intact (1% decrease from 36.7 to 36.5°C) but less than that observed after sympathectomy.

TABLE 2 ABOUT HERE

Fig. 3

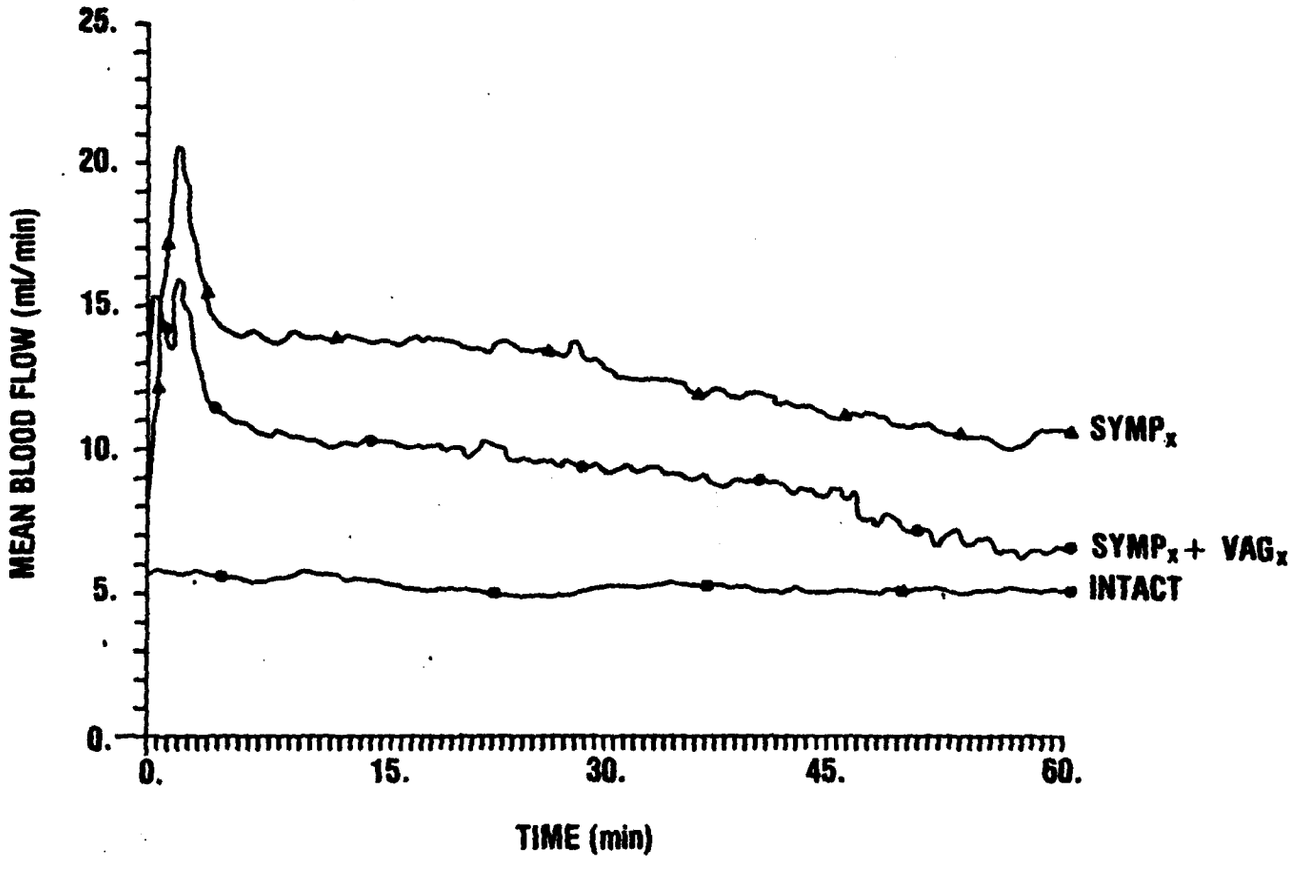
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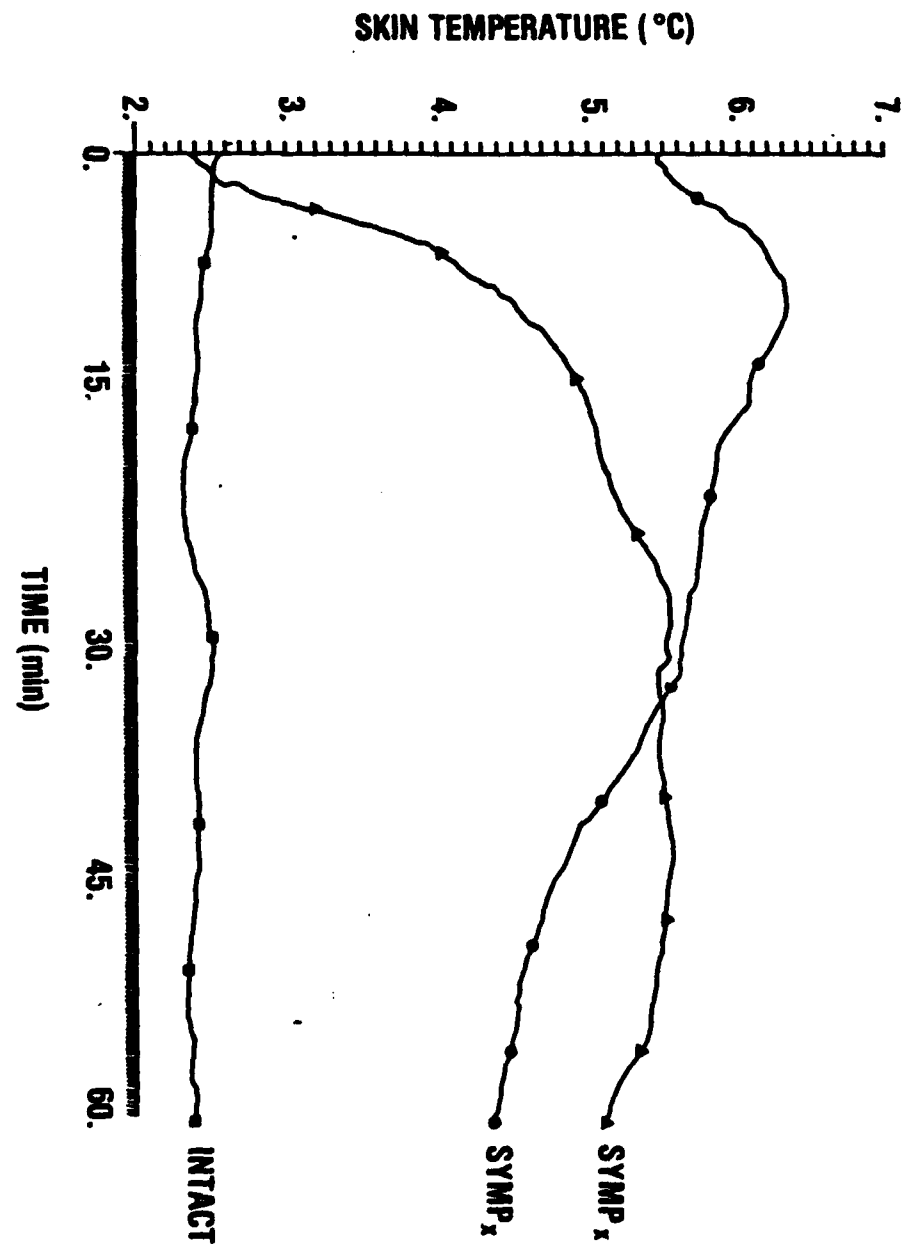
Fig. 4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SYMP$_x$ + VAG$_x$
SYMP$_x$

TABLE 2. Effects of ipsilateral lumbar sympathectomy and subsequent bilateral cervical vagotomy on hindlimb circulatory and thermal function during cold exposure

	Vascular resistance, $mmHg \cdot (ml/min)^{-1}$	Mean blood flow, ml/min	Skin temperature, °C	Heat flow, W/m^2	Mean arterial pressure, mm Hg	Heart rate, beats/min	Rectal temperature, °C	Ambient temperature, °C
Control	23.6 ± 4.2	6.2 ± 0.8	24.2 ± 1.1	52 ± 26	122 ± 10	211 ± 13	37.0 ± 0.4	20.1 ± 0.8
Intact	33.3 ± 6.0	5.3 ± 0.8	2.4 ± 0.6	126 ± 31	133 ± 9	204 ± 13	36.6 ± 0.4	-1.6 ± 1.1
$Symp_x$	16.6 ± 3.1	11.8 ± 2.5	5.5 ± 1.1	273 ± 71	136 ± 10	193 ± 13	35.9 ± 0.6	-0.9 ± 1.1
$Symp_x + Vag_x$	24.1 ± 6.1	9.3 ± 2.1	5.1 ± 0.9	231 ± 43	143 ± 12	193 ± 17	35.6 ± 0.7	-0.2 ± 1.0

Values are means ± SE in 10 cats.

Effects of contralateral and subsequent ipsilateral lumbar sympathectomy. After interrupting the contralateral lumbar sympathetics, vascular resistance decreased 17%, blood flow increased 33%, skin temperature increased 54%, and heat flow increased 39% (Table 3). These changes were statistically insignificant, but demonstrated a trend towards peripheral hyperemia and warming after denervating the lumbar sympathetics contralateral to the cold-exposed hindlimb. Several acute changes were observed during the 5 minutes immediately after contralateral sympathectomy: vascular resistance decreased 35%, blood flow increased 167% (Fig. 5), and mean arterial pressure increased 37%. Skin temperature (Fig. 6) and heat flow increased during the 25 minutes after contralateral sympathectomy, and thereafter were maintained at maximal levels. Rectal temperature declined continually from 36.4° to 35.8°C during the hour after contralateral sympathectomy.

FIGURES 5 and 6 ABOUT HERE

The levels of peripheral circulation and warming were exacerbated after interruption of the ipsilateral lumbar sympathetics: vascular resistance decreased 16%, blood flow increased 14%, footpad temperature increased 38%, and footpad heat loss increased 79% (Table 3). The peripheral hyperemia, warming, heat dissipation, and hypothermia after bilateral lumbar sympathectomy were significantly different ($P < 0.05$) from when the cats were neurally intact. Several acute changes were observed during the 7 minutes immediately after ipsilateral sympathectomy: vascular resistance decreased 60%, blood flow increased 89% (Fig. 5), and mean arterial pressure increased 28%. Skin temperature (Fig. 6) and heat loss increased rapidly during the 18 minutes after ipsilateral sympathectomy, and thereafter were maintained at maximal levels. Rectal temperature declined continually from 35.8° to 35.4°C.

Fig. 5

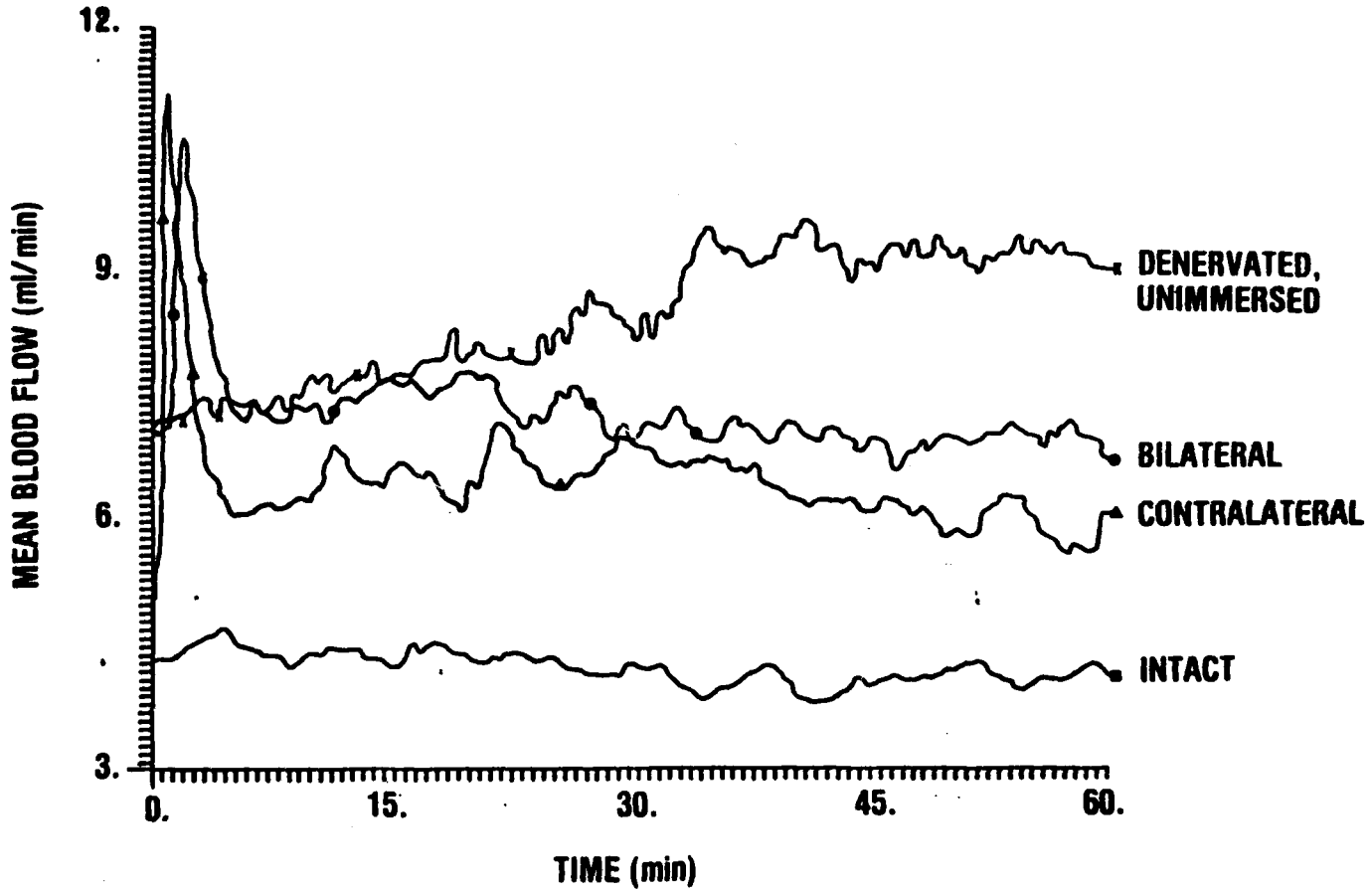
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Fig 6H

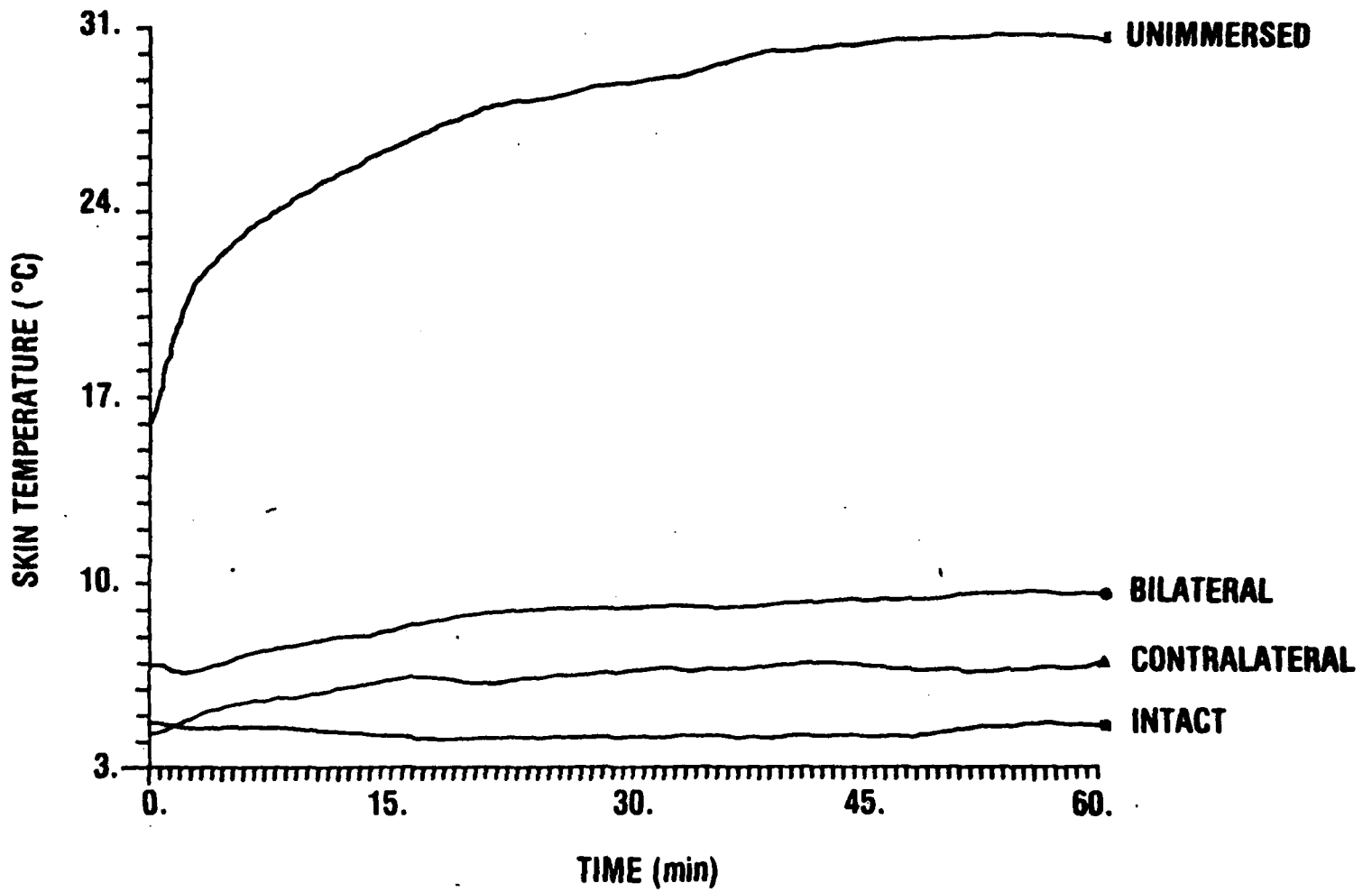
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TABLE 3. Effects of contralateral and subsequent ipsilateral lumbar sympathectomy on hindlimb circulatory and thermal function during cold exposure

	Vascular resistance, $mmHg \cdot (ml/min)^{-1}$	Mean blood flow, ml/min	Skin temperature, °C	Heat flow, W/m^2	Mean arterial pressure, mm Hg	Heart rate, beats/min	Rectal temperature, °C	Ambient temperature, °C
Control	21.6 ± 7.8	5.4 ± 0.8	29.3 ± 0.6	72 ± 11	100 ± 8	190 ± 8	37.1 ± 0.6	22.4 ± 0.6
Intact	27.6 ± 3.3	4.2 ± 0.5	4.3 ± 0.5	140 ± 30	104 ± 7	160 ± 8	36.5 ± 0.7	-2.7 ± 0.5
Contralateral	22.8 ± 4.8	6.3 ± 1.6	6.6 ± 1.7	194 ± 38	109 ± 7	158 ± 8	35.9 ± 0.6	-2.8 ± 0.5
Bilateral	19.1 ± 4.3	7.2 ± 1.3	9.1 ± 2.1	348 ± 112	108 ± 6	153 ± 8	35.5 ± 0.6	-3.0 ± 0.7
Unimmersed	15.4 ± 2.9	8.8 ± 1.0	30.3 ± 1.0	63 ± 24	110 ± 7	152 ± 9	35.4 ± 0.6	23.2 ± 0.3

Values are means ± SE in 10 cats.

TABLE 3 ABOUT HERE

Effects of contralateral and subsequent ipsilateral sacral ventral rhizotomies. No significant differences in any of the variables were observed after interrupting the $S_1 - S_3$ ventral roots contralateral to the cold-exposed hindlimb (Table 4). Blood flow increased 17% during the 5 minutes immediately after the contralateral sacral ventral thizotomies (Fig. 7), but this small hyperemia did not affect footpad temperature (Fig. 8), heat loss, or rectal temperature.

FIGURE 7 and 8 ABOUT HERE

No significant differences in any of the parameters monitored were observed when the ipsilateral sacral ventral roots were subsequently interrupted. Blood flow acutely increased 23% during the 4.5 minutes after sacral ventral rhizotomies (Fig. 7), but there were no secondary effects on footpad temperature (Fig. 8), heat loss, or rectal temperature.

TABLE 4 ABOUT HERE

Effects of re-exposure to room air. There was evidence of peripheral vasodilation and rewarming when the hindlimb was re-exposed to room air after bilateral lumbar sympathectomy and after bilateral sacral ventral rhizotomies. A 42% reduction in vascular resistance allowed a 41% increase in femoral arterial blood flow during the initial 35 minutes of re-exposure to room air (Figs. 5 and 7). This was accompanied by significant increases in footpad

Fig. 7A

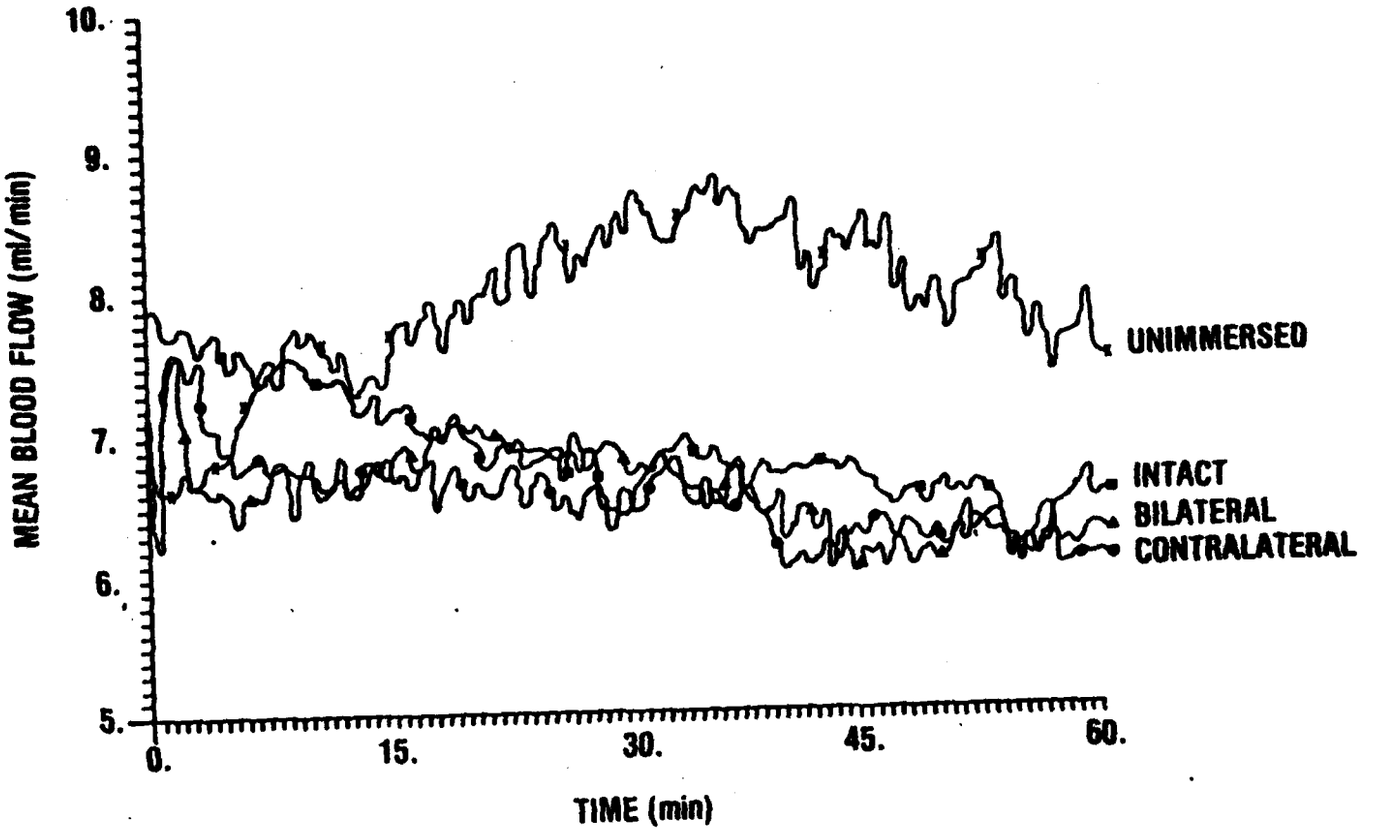
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Fig. 8

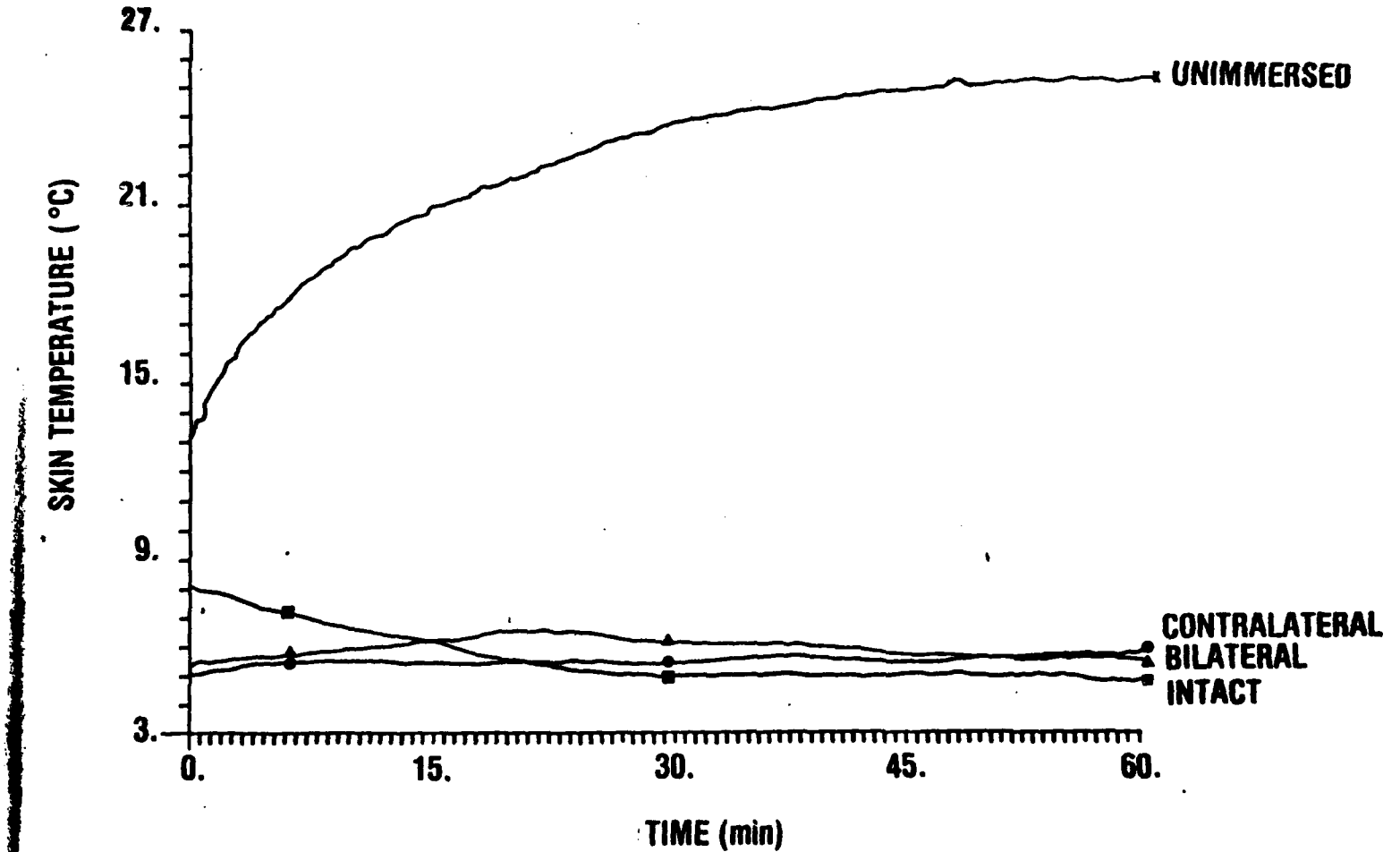
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TABLE 4. Effects of contralateral and subsequent ipsilateral sacral parasympathectomy on hindlimb circulatory and thermal function during cold exposure

	Vascular resistance, mmHg • (ml/min)$^{-1}$	Mean blood flow, ml/min	Skin temperature, °C	Heat flow, W/m^2	Mean arterial pressure, mm Hg	Heart rate, beats/min	Rectal temperature, °C	Ambient temperature, °C
Control	16.0 ± 4.0	8.3 ± 1.1	28.2 ± 0.4	90 ± 10	94 ± 8	201 ± 7	36.7 ± 0.4	23.4 ± 0.8
Intact	26.4 ± 9.0	6.5 ± 1.1	5.0 ± 0.7	196 ± 54	105 ± 8	197 ± 6	36.6 ± 0.4	-0.2 ± 1.0
Contralateral	32.8 ± 11.3	6.4 ± 1.2	5.5 ± 0.8	171 ± 66	109 ± 7	190 ± 9	36.3 ± 0.5	-0.1 ± 1.0
Bilateral	33.5 ± 10.9	6.5 ± 1.6	5.9 ± 1.1	175 ± 67	109 ± 8	188 ± 9	36.2 ± 0.5	1.5 ± 0.9
Unimmersed	27.1 ± 8.7	8.1 ± 1.4	24.6 ± 1.2	-2 ± 25	112 ± 7	188 ± 10	36.1 ± 0.6	24.3 ± 0.5

Values are means ± SE in 11 cats.

temperature (Figs. 6 and 8) and heat loss ($P < 0.05$). Rectal temperature, mean arterial pressure and heart rate were relatively unchanged during re-exposure of the hindlimb to room air.

DISCUSSION

This study demonstrates that there are primarily two mechanisms mediating peripheral vasoconstriction during local cold exposure. A neurogenic vasoconstriction was mediated by sympathetic efferent fibers. This is presumably reflexly elicited by the thermal activation of cold and/or pain sensory receptors in the hindlimb. There was evidence that local mechanisms, principally the direct vasoconstrictor effects of cold, also contribute to cold-induced peripheral vasoconstriction. A predominance of local vasoconstriction in the absence of neurogenic vasoconstriction after sympathectomy resulted in a diminution of the peripheral hyperemia and warming. Others (33) have also demonstrated a synergistic effect between neural and local mechanisms producing cold-induced vasoconstriction.

The increase in sympathetic vasoconstrictor activity is probably reflexly elicited by cold nociceptors. Local exposure to cold below 18°C produces pain sensations and pressor responses (3,8). The excitation of cold nociceptors in this study presumably activated a somatosympathetic reflex mediating peripheral vasoconstriction. The cold-induced reflex peripheral vasoconstriction depends on supraspinal integration since patients with spinal lesions are unable to produce the reflex vasoconstriction during local cold exposure (4). Noxious heat can also reflexly excite lumbar sympathetic preganglionic fibers mediating both muscular and cutaneous vasoconstriction (20). Cold and warm thermoreceptors can also reflexly affect efferent sympathetic activity. Cooling the trigeminal nerve receptive field in the nose and lips of rabbits resulted in a reflex increase in efferent upper cervical sympathetic activity and a cooling of the pinna; warming the receptive area resulted in a decrease in sympathetic activity and a warming of the ear (25). It appears the somatosympathetic reflex mediating peripheral vasoconstriction is activated by cold and heat nociceptors and cold thermoreceptors, and inhibited by warm thermoreceptors.

Claude Bernard (7) demonstrated that sympathetic nerves mediate neurogenic vasoconstriction. The present study extends earlier observations by providing evidence that the efferent sympathetic nerves mediate peripheral vasoconstriction during cold exposure. There is an inverse relationship between sympathetic nerve activity and skin termperature (19). This suggests that cutaneous blood flow and temperatures are regulated by the level of efferent sympathetic vasoconstrictor tone. An enhanced sympathetic vasoconstrictor tone is expected during cold exposure to reduce peripheral blood flow and conserve body heat.

The mediation of peripheral vasoconstriction by the efferent sympathetic nerves was demonstrated by interrupting the lumbar sympathetic chains both ipsilateral and contralateral to the cold-exposed hindlimb. Sympathectomy, whether ipsiolateral or contralateral, produced two phases of vasodilation. The initial vasodilation occurred immediately after sympathectomy and was attributed to the activation of afferent sympathetic fibers causing a reflex pressor response which resulted in a baroreceptor mediated reflex inhibition of alternate descending sympathetic vasoconstrictor pathways. The secondary vasodilation was more prolonged and, since it occurred in the absence of a simultaneous pressor response, was attributed to the interruption of efferent sympathetic vasoconstrictor tone. Consequently, the effect of sympathectomy was a release of sympathetic vasoconstrictor tone which resulted in a decrease in femoral arterial vascular resistance, an increase in femoral arterial blood flow, a warming of the footpad, and increased heat loss from the footpad. It is uncertain which specific vascular beds supplying the various hindlimb tissues were dilated after sympathectomy, although the marked warming of the footpads after sympathectomy indicates the role of the sympathetic nerves in maintaining vasoconstriction of the vasculature in the skin. A relatively larger vasodilation

occurs in the vasculature of the paw rather than in skeletal muscle due to the greater responsiveness of the former vascular bed to catecholamines (24). The marked skin warming is attributed to the opening of arteriovenous anastomoses which hemodynamically accommodates the superficial hyperemia (12).

This study demonstrates that the vasculature in either hindlimb can receive a double innervation from both sympathetic chains. Sympathetic preganglionic fibers subserving peripheral vasoconstriction depart from both sides of the spinal cord to synapse with postganglionic neurons in the sympathetic ganglia. The descending sympathetic postganglionic fibers join peripheral nerves and enter the lumbar plexus where they are believed to descend primarily to the ipsilateral hindlimb, but can also cross-over to contribute to the innervation of the vasculature in the contralateral hindlimb. The largest peripheral hyperemia occurred after interrupting the ipsilateral lumbar sympathetic chain indicating a greater lateral sympathetic vasoconstrictor distribution. This study provides evidence that the vasculature from one hindlimb can receive innervation originating from the contralateral sympathetic chain suggesting that there is no true laterality in efferent sympathetic vasoconstrictor pathways. However, the lesser vasoconstrictor influence originating from the contralateral sympathetic chain resulted in a statistically insignificant hyperemia after contralateral sympathectomy as compared to the significant hyperemia following ipsilateral sympathectomy.

There are discrete differences in the function of different efferent sympathetic fibers. Sonnenschein and Weissman (34) demonstrated separate sympathetic pathways mediating adrenergic vasoconstriction and cholinergic vasodilation of the vasculature in feline hindlimb skeletal muscles. Preganglionic fibers mediating vasoconstriciton depart the spinal cord mainly in the $L_1 - L_3$ ventral roots to enter the respective sympathetic ganglia whereas

preganglionic fibers mediating vasodilation depart primarily in the L_4 ventral root. This corresponds with Sheehan and Marazzi's (31) obervation that the greatest contribution of sympathetic vasoconstrictor fibers to the sciatic nerve originate from the $T_{13} - L_3$ ventral roots. The present study confirms previous observations by demonstrating that bilateral interruption of the L_3 sympathetic chain reverses the cold-induced vasoconstriction. This study extends previous observations by demonstrating that sympathetic vasoconstrictor fibers also affect the paw vasculature resulting in a marked warming when interrupted, and also demonstrates convergent vasoconstrictor fibers originating from the contralateral sympathetic chain.

A neurogenic peripheral vasodilation may occur by either the inhibition of sympathetic vasoconstriction or by active sympathetic vasodilation. There is evidence that vasodilation in the human hand is mediated primarily by an inhibition of sympathetic vasoconstrictor tone (5,29,32,36). A sympathetically mediated active vasodilation of the vasculature in human skin is reflexly elicited by heating other areas of the body (30). This mechanism of enhanced heat loss during hyperthermia is presumably non-functional during cold stress. Sympathetic vasodilator fibers are more numerous in the $L_4 - L_7$ ganglia (34). Since these ganglia were uninterrupted in this study, it is possible that they may have mediated the hyperemia after L_3 sympathectomy. If there is dual innervation of the peripheral vasculature, the elimination of the vasoconstrictor component may result in a predominance of the neurogenically mediated vasodilator component. There is evidence of a neurogenic cholinergic vasodilation in the cold-exposed feet of the giant fulmar (21). Consequently, the differential activation or inactivation of discrete efferent neural pathways can modulate responses in various vascular beds (1).

There are important implications on the effects of sympathectomy in terms of the neural regulation of cold-induced vasodilation. Cold-induced vasodilation is a warming of the periphery during exposure (22). During cold-induced vasodilation, there is a marked hyperemia through arteriovenous anastomoses in the skin (15,16). Cold-induced vasodilation may be viewed as a transient vascular escape mechanism during continued cold exposure which enables the warming of peripheral tissues and prevents cold injuries. It appears that sympathetically mediated peripheral vasoconstriction is a fundamental prerequisite for cold-induced vasodilation. A reduction in sympathetic vasoconstrictor tone, i.e. after sympathectomy, resulted in a marked peripheral hyperemia and warming. Cold-induced vasodilation of lesser amplitude were observed in neurally intact cats generally in association with concomitant pressor responses. This suggests the involvement of baroreceptor-mediated inhibition of efferent sympathetic vasoconstrictor activity as the mechanism of eliciting cold-induced vasodilation. However, others (14,23) argue a more prominent influence of local mechanisms mediating cold-induced vasodilation since they were able to demonstrate the occurrence of cold-induced vasodilation after sympathectomy. It is uncertain if their sympathectomy was extensive enough to interrupt all efferent neural activity to peripheral vessels. Paraplegics with complete spinal lesions were unable to produce cold-induced vasodilation (8). Alternatively, there is evidence that active sympathetic cholinergic mechanisms may also mediate cold-induced vasodilation (21).

It is apparent that complete surgical sympathectomy is difficult to achieve due to the existence of multiple efferent vasoconstrictor pathways. Sympathectomy has been used therapeutically in the treatment of Raynaud's disease, hyperhidrosis, and after frostbite and other cold injuries. Some investigators (3,6) report a prolonged peripheral hyperemia and warming after

sympathectomy while others (26,37) do not. In the present study, there was the possibility of functional residual uninterrupted sympathetic vasoconstrictor pathways occurring rostral or caudal to the L_3 denervation in both the ipsilateral and contralateral sympathetic chains. Compensatory activity in these alternative efferent sympathetic pathways may have enabled vasomotor recovery resulting in only an acute, rather than sustained, peripheral hyperemia and warming after L_3 sympathectomy.

Instead, the attenuation of peripheral hyperemia and warming presumably was evidence of local non-neural mechanisms mediating peripheral vasoconstriction during cold exposure. Since the marked hyperemia occurred after sympathectomy, it appears that there is a more prominent role of neurally mediated rather than locally mediated peripheral vasoconstriction during cold exposure. However, the lack of a sustained peripheral vasodilation and warming after sympathectomy suggests that compensation by local mechanisms can predominate to produce vasoconstriction in the absence of neurogenic constrictor tone. The metabolism of the skin is so low that changes in tissue O_2, CO_2, and lactic acid should be minimal. Consequently, the direct constrictor effects of cold on the peripheral vasculature should be the major local influence. A local automaticity of peripheral vasculature is observed even after lumbar sympathectomy (17,23,24).

There are apparently no studies demonstrating neuroanatomical connections or physiological effects of sacral or vagal parasympathetic fibers on the vasculature of the hindlimb. The sacral parasympathetic preganglionic axons provide the major excitatory input to the urinary bladder and large intestine, whereas the caudal sympathetic chain provides the primary vasomotor innervation of the hindlimb vasculature (11). Electrical stimulation of the parasympathetic pelvic nerve produces a transient vasodilation in the cat colon

(13). The results of this study demonstrate a lack of influence by both the ipsilateral and contralateral $S_1 - S_3$ ventral roots in the maintenance of peripheral vascular tone during cold exposure. Bilateral vagotomy also had little effect on peripheral vascular resistance, femoral arterial blood flow, and footpad temperature and heat loss. It is interesting to note that immediately after all parasympathetic denervations, there was an acute pressor response, minor tachycardia, reduction in vascular resistance, femoral arterial hyperemia, and a small warming and increased heat loss from the footpad. The amplitude of these acute responses were comparatively greater after vagotomy rather than after sacral ventral rhizotomy. It is presumed that the process of denervating parasympathetic nerves resulted in an activation of afferent pathways which elicited the acute cardiovascular reflex responses. Thereafter, the level of each parameter monitored did not differ significantly from the previous neurally intact period.

The physiological significance of the sympathetically mediated peripheral vasoconstriction during local cold exposure is in the conservation of body heat. This study demonstrates that during local cold exposure, there was a peripheral vasoconstriction in the affected hindlimb associated with an increase in vascular resistance, reduction in peripheral blood flow, and cooling of the foot. However, these responses were unable to prevent a continual loss of heat from the foot to the cold bath which resulted in a progressive hypothermia. The rate of footpad heat loss increased as much as three-fold after ipsilateral sympathectomy which resulted in a doubling of the rate of hypothermia. Thus, the efferent sympathetic nerves play an important role in restricting peripheral heat loss in order to conserve body temperature by redistributing warm blood away from the locally cold exposed hindlimb. Similar observations have been made in humans (3,9,28), wolves (35), dogs (18,27), and cats (27). Normothermia was maintained

only after the hindlimb was re-exposed to room air suggesting that there was minimal anesthetic depression of central thermoregulatory capabilities. Since the cat's metabolic heat production was relatively unchanged because shivering was not observed and breathing was regulated with a respirator, variations in peripheral vasomotor tone were presumably the main mechanism of temperature regulation. The skin is especially suitable for this purpose since it requires a minimal blood flow of 0.8 ml/min/100 cc of skin tissue for viability, yet digital blood flow may increase 100-fold during full vasodilation for the rapid dissipation of heat (10). Consequently, the sympathetic regulation of peripheral blood flow can greatly influence both heat conservation and dissipation. This study demonstrates an interrelationship between sympathetic neural function, peripheral circulation, and the regulation of body temperature during adjustments to local cold exposure.

In conclusion, the specific autonomic nerves mediating peripheral vasoconstriction during local cold exposure were identified in this study. The neural mechanism mediating cold-induced vasoconstriction presumably involves a supraspinal somatosympathetic reflex. The afferent limb of the reflex depends on the cold stimulus activating nociceptors and/or cold thermoreceptors having afferent fibers in somatic nerves. Potential sites of supraspinal integration of cold vasoconstriction are the brainstem cardiovascular nuclei and hypothalamic thermoregulatory and circulatory centers. The efferent pathway descends in spinal sympathetic pathways, depart from upper lumbar spinal cord, and the efferent sympathetic vasoconstrictor fibers descend primarily to the ipsilateral hindlimb vasculature, but can also cross-over to innervate the contralateral hindlimb vasculature. The efferent sympathetic nerves were important in increasing femoral arterial vascular resistance, reducing femoral arterial blood flow, and reducing footpad temperature and heat loss during local hindlimb cold

exposure. Interruption of the neurogenic vasoconstrictor tone by sympathectomy resulted in a peripheral hyperemia and warming. Since the hyperemia was acute, local mechanisms such as the direct constrictor effects of cold predominated in restoring peripheral vasoconstriction in the absence of neurogenic vasoconstriction. There was no evidence of tonic parasympathetic regulation of peripheral blood flow or temperature during cold exposure.

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Figure 1. Average changes in mean femoral arterial blood flow in the continually cold-exposed hindlimb of ten cats when neurally intact (INTACT), after bilateral cervical vagotomy (VAG_x), and after interrupting the L_3 sympathetic chain ipsilateral to the hindlimb ($VAG_x + SYMP_x$).

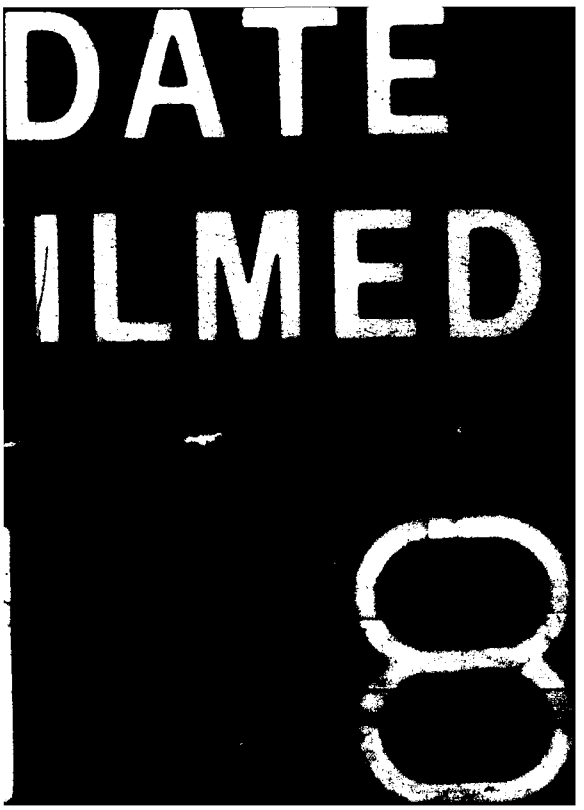
Figure 2. Average changes in footpad temperature in the continually cold-exposed hindlimb of ten cats when neurally intact (INTACT), after bilateral cervical vagotomy (VAG_x), and after interrupting the L_3 sympathetic chain ipsilateral to the hindlimb ($VAG_x + SYMP_x$).

Figure 3. Average changes in mean femoral arterial blood flow in the continually cold-exposed hindlimb of ten cats when neurally intact (INTACT), after interrupting the L_3 sympathetic chain ipsilateral to the hindlimb ($SYMP_x$), and after bilateral cervical vagotomy ($SYMP_x + VAG_x$).

Figure 4. Average changes in footpad temperature in the continually cold-exposed hindlimb of ten cats when neurally intact (INTACT), after interrupting the L_3 sympathetic chain ipsilateral to the hindlimb ($SYMP_x$), and after bilateral cervical vagotomy ($SYMP_x + VAG_x$).

Figure 5. Average changes in mean femoral arterial blood flow in the continually cold-exposed hindlimb of ten cats when neurally intact (INTACT), after interrupting the sympathetic chain contralateral to the hindlimb (CONTRALATERAL), after interrupting the sympathetic chain ipsilateral to the hindlimb (BILATERAL), and after re-exposure of the hindlimb to room air (DENERVATED, UNIMMERSED).

Figure 6. Average changes in footpad temperature in the continually cold-exposed hindlimb of ten cats when neurally intact (INTACT), after interrupting the L_3 sympathetic chain contralateral to the hindlimb (CONTRALATERAL), after interrupting the L_3 sympathetic chain ipsilateral to the hindlimb (BILATERAL), and after re-exposure of the hindlimb to room air (UNIMMERSED).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