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THE EFFECTS OF ATROPINE AND PYRIDOSTIGMINE ON THERMOREGULATION AND WORK TOLERANCE IN THE PATAS MONKEY

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NOTICES

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The animals involved in this study were procured, maintained, and used in accordance with the Animal Welfare Act and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources - National Research Council.

The Office of Public Affairs has reviewed this report, and it is releasable to the National Technical Information Service, where it will be available to the general public, including foreign nationals.

This report has been reviewed and is approved for publication.

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The effects of a single intramuscular atropine injection (0.03 mg/kg) at ambient temperature (Ta) of 25 °C and 35 °C and pyridostigmine treatment (5 doses (0.4 mg/kg)) at Ta of 35 °C on the thermoregulatory capacity and exercise tolerance time of patas monkeys were investigated. A primate treadmill device was developed and used to evaluate the effects of the drugs on the exercise tolerance time. Rectal temperature (Tre) and heart rate (HR) were continuously monitored by a telemetry system while water loss was estimated from weight differences before and after exercise. Atropine effects were more pronounced at Ta of 35 °C as indicated by a significant reduction in water loss (41%) which was associated with an average exercise time of 65 min less than the control value. The final HR and Tre responses in these atropine experiments were significantly elevated above the control values. Pyridostigmine significantly increased water loss (61%) which was associated with an average exercise time of 60 min longer than the control value. The final HR and Tre responses were not significantly affected by the pyridostigmine treatment.

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A continuous flow indirect calorimetry system was developed consisting of a holding cage in which the monkey resided. Calculation of metabolic parameters was done from measurements of O_2, CO_2, P_{H2O}, P_B, F_{out}, and temperature using the algorithms of Brown (3). As an addition to the monkey exercising wheel, an airtight enclosure was designed which enabled the use of the calorimetry system for measurement of metabolic rates during exercise. Typical metabolic rates during daylight hours were 40 to 50 watts per meter square (W/m^2) at rest and 70 to 80 W/m^2 during exercise. It is highly significant that the Respiratory Quotient (RQ) and metabolic rate measured with our new calorimetry system are the same as those we previously reported in chair-restrained animals. This new technology will be very useful as we continue to examine the short- and long-term effects of neuroactive agents on primate thermoregulation, metabolism, and exercise tolerance.

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THE EFFECTS OF ATROPINE AND PYRIDOSTIGMINE ON THERMOREGULATION AND WORK TOLERANCE IN THE PATAS MONKEY

INTRODUCTION

Atropine, the most common antidote for anticholinesterase poisoning (13), suppresses thermoregulatory sweating, and eventually, evaporative heat loss through its anticholinergic activity (2) resulting in increased net heat storage (1, 15), decreased heat tolerance, and reduced exercise performance (4, 6, 7, 9).

Pyridostigmine is used in conjunction with atropine as a prophylactic against anticholinesterase poisoning by reversibly inhibiting cholinesterase. Depending on the degree of enzyme inhibition and state of ordination, these drugs affect thermoregulation and exercise performance in a negative (11) or positive way (12).

In a previous study, the physiological effects of 2 neurogenic drugs, atropine and pyridostigmine, on the thermoregulatory effector system of the patas monkeys were evaluated at rest. It was concluded that this species was an appropriate animal model to study the effects of neuroactive drugs on temperature regulation and thermoregulatory capacity (1, 10). This study expands the previous work by testing the effects of atropine and pyridostigmine on the thermoregulatory capacity of patas monkeys during exercise in the heat. Prolonged exercise in the heat represents a condition where the metabolic and environmental heat load may be considerable and provides the body with maximum strain to challenge the thermoregulatory control system. Since atropine and pyridostigmine interfere with the heat dissipation mechanisms, the testing of these neuroactive agents during prolonged exercise in the heat provides maximum challenge to the thermoregulatory system and gives information about the thermoregulatory capacity of primates, and perhaps, man.

METHODS AND MATERIALS

Design of the Exercise Device

The apparatus used to evaluate the exercise tolerance of the patas monkey was a treadmill wheel (Fig. 1) specifically constructed to exercise nonhuman primates (8) (Appendix). The wheel, consisting of two 122-cm (48 in.) diameter Lucite rings and 120 aluminum bars, forms a circular cage which rotated freely on four bearings. Another ring, affixed to the outside of each Lucite ring, was connected to alternate aluminum bars to provide electrical stimulation for conditioning the animal. The activity

wheel included: 1) a magnetic tachometer pickup to quantitate speed; 2) an automatic control panel interconnected with the tachometer to allow the setting of upper and lower speed limits which the animal had to maintain in order to avoid a sequence of visual or electrical stimuli; 3) a microswitch at the bottom of the control panel which counted each revolution of the wheel and calculated distance traveled; and 4) a brake to stabilize the wheel during the rest periods as well as to prevent the animal from operating the wheel at higher than predetermined rates.

Exercise Program Operation

Five patas monkeys were trained to operate the treadmill wheel until they learned to run at a minimum rate of 2 miles/hour (mph) for 60 min (20).

At the end of a 20-week training period, each animal was capable of completing at least 1 h of exercise while control values of exercising heart rate (HR) and rectal temperature (Tre) were measured every 15 min by a noninvasive telemetry system. The system consisted of an AMF Quantum XL transmitter for measuring the HR and a Mini-Mitter rectal probe transmitter for measuring Tre. HR was recorded by an AMF Quantum digital watch receiver in beats/min (bpm) while Tre was recorded by a President AX52 FM receiver and converted to °C using calibration curves validated in this laboratory. Total distance covered in miles, average speed in miles/hour, and total exercise time were also recorded. Water loss was estimated from weight difference measured before and after the exercise test.

The criteria used to establish the exercise tolerance of the animals and to terminate the standard exercise test were any one of the following: heart rates that approach maximal heart rates for this species, approximately 300 bpm; a Tre higher than 40 °C to protect the animals from heat injury; or going 3 times underspeed (2 mph) in each of 2 consecutive 15-min periods.

The standard exercise tests were then repeated following atropine treatment and 3 months later after pyridostigmine treatment.

Two days after each animal completed a standard exercise test at 25 °C, another exercise test was carried out immediately following a 0.03 mg/kg single intramuscular (i.m.) atropine injection; a dose capable of establishing blood levels of atropine analogous to that produced in humans following an i.m. injection of 2 mg (14, 17). The same procedure was repeated 3 days later at 35 °C.

Pyridostigmine Study

One day after a standard exercise test was carried out at 35 °C, each animal was treated orally with 3 separate doses of

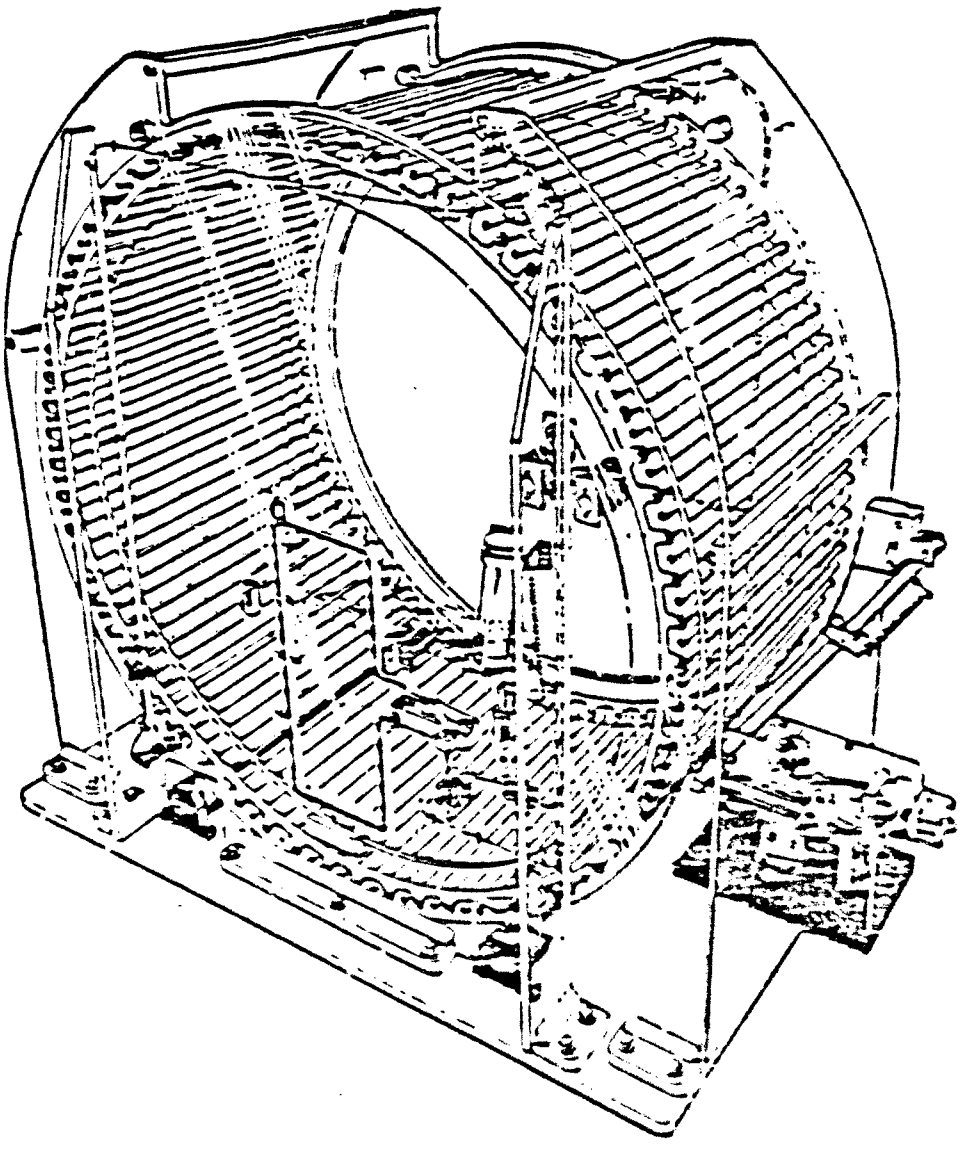

Figure 1. Primate Exercise Wheel (PEW).

solid 0.4 mg/kg pyridostigmine in a piece of banana. The afternoon of the next day, the animal repeated the exercise test after receiving 2 doses of 0.4 mg/kg pyridostigmine: 1 in the morning and 1 an hour prior to exercise, making a total of 5 doses. The 0.4 mg/kg pyridostigmine dosage is capable of reducing cholinesterase plasma levels by 25 to 30% of normal immediately after the second dose and keeps the levels down throughout the treatment period (1).

Treatment of Data

The results are presented as means and standard deviation. They were analyzed by a two-way (condition x time) analysis of variance (ANOVA) with repeated measures on both factors. Turkey's test of critical differences was also used where appropriate. All significant differences are reported at $p < .05$, unless otherwise noted.

RESULTS

The effects of atropine at 25 °C are shown in Table 1 and Figures 2 and 3.

TABLE 1. SUMMARY OF ATROPINE RESULTS DURING EXERCISE AT 25 °C AND 35 °C

	Water loss (g/min)	Time (min)	Distance (mi)	Speed (mph)
Ta = 25 °C				
Control	1.2 ±1.7	177.0 ±39.7	4.8 ±1.2	1.6 ±0.05
Atropine	1.3 ±1.6	146.8* ±30.5	4.0 ±0.9	1.6 ±0.1
Ta = 35 °C				
Control	2.3 ±2.1	149.6 ±37.1	3.6 ±0.8	1.5 ±0.1
Atropine	1.8(†) ±2.3	84.0(†) ±16.9	2.5(†) ±0.5	1.7* ±0.1

* $p < .05$
(†) $p < .08$

Atropine significantly increased fatigue and shortened the exercise tolerance time by approximately 30 min. No significant difference was found in the amount of water loss, distance traveled or the animals' average speed. Figures 2 and 3 show that mean HR

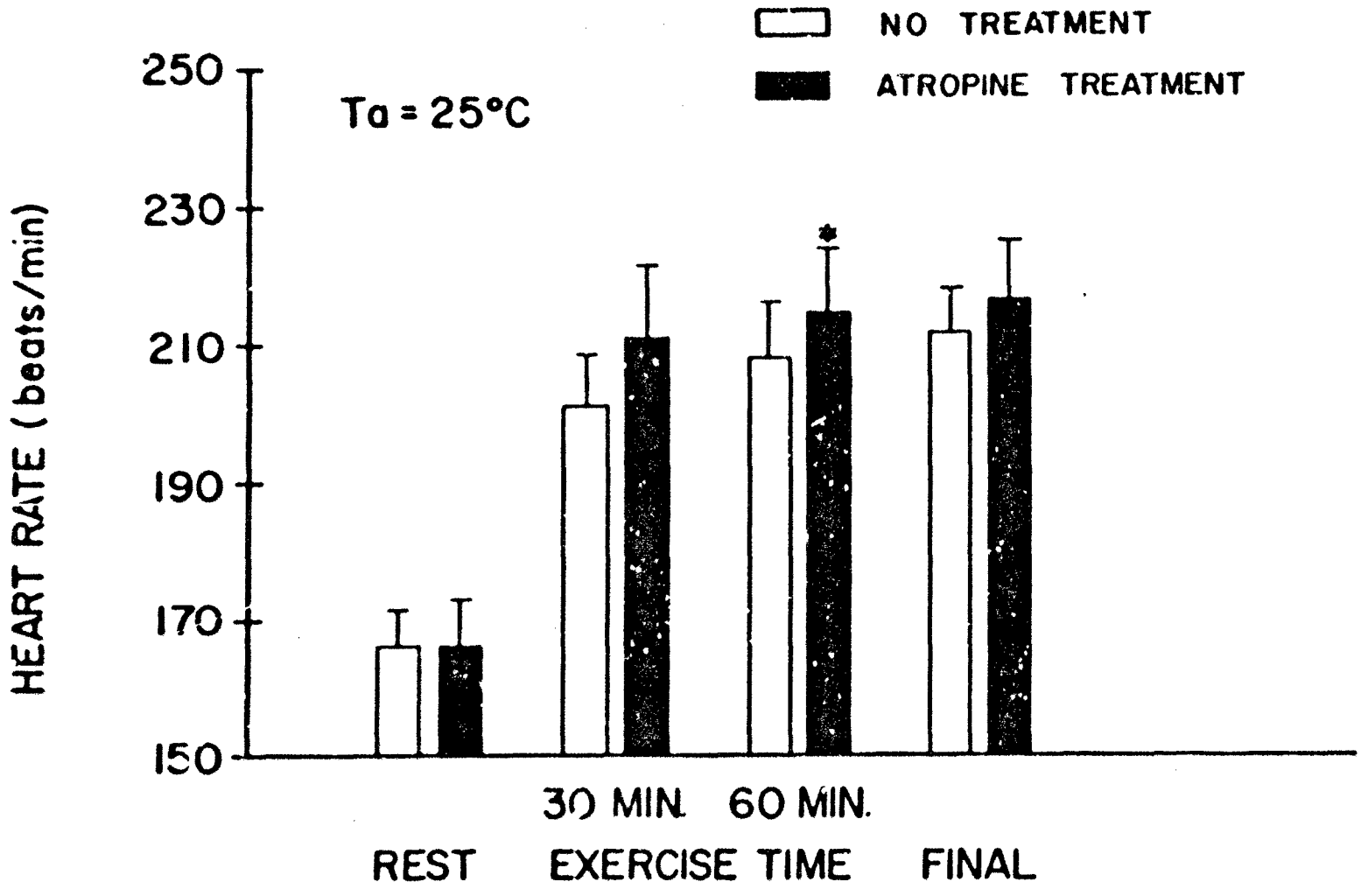

Figure 2. Effects of atropine and exercise on heart rate at Ta of 25 °C. (* $p < 0.05$ compared to no treatment)

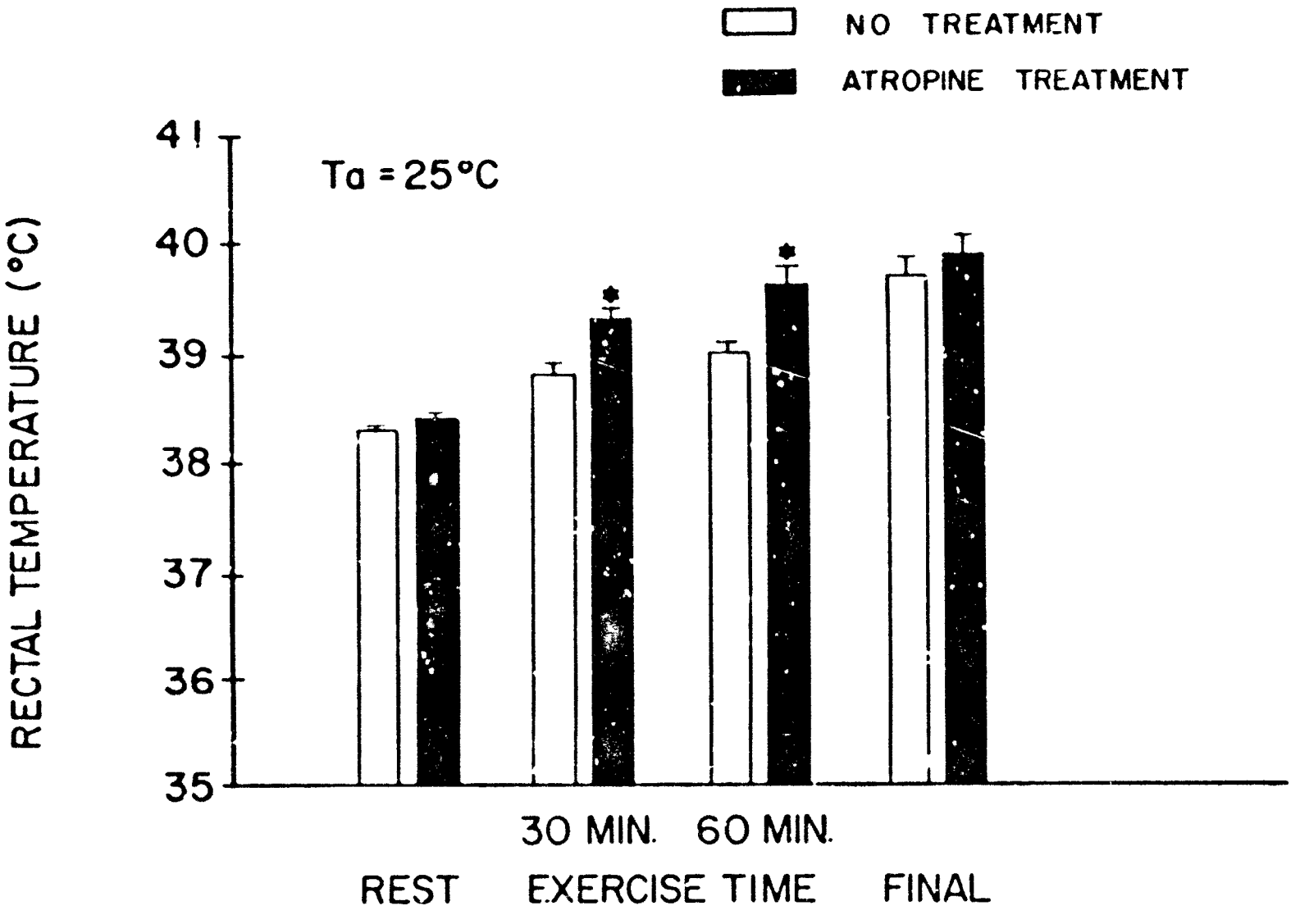

Figure 3. Effects of atropine and exercise on rectal temperature at Ta of 25 °C. (* $p < 0.05$ compared to no treatment)

and Tre responses increased from rest to exercise. While HR during exercise increased slightly over time in the control experiments, atropine administration caused a further increase in HR and was significantly greater at 60 min when compared to the no treatment condition. In addition, atropine was associated with a significant increase in Tre by the end of the first 30 min of exercise and remained 0.5 °C higher at 60 min of exercise, significantly different compared to the respective no treatment period. Mean final HR (F-HR) and Tre(F-Tre) values were not significantly different from the respective values in the control experiments.

The effects of atropine at 35 °C appear in Table 2 and Figures 4 and 5. At this environmental temperature, atropine produced a reduction in water loss rates (22%) and a reduction in total exercise time of 65 min less than the control value. Consequently, the distance covered in miles was also less ($p < .06$). It was also interesting that average speed in mph was slightly but significantly faster in the atropine experiments as compared to the controls. As illustrated in Figure 4, the mean HR response increased from rest to exercise and at the end of exercise. The mean HR response at 60 min of exercise decreased slightly from that at 30 min of exercise due to the fact that 2 animals reached their exercise tolerance before the first hour of exercise and only the mean HR response for 3 animals is shown. The mean HR response in the atropine experiments was higher at 60 min of exercise and before the end of exercise compared to the respective control experimental periods. Figure 5 shows the mean Tre responses in the heat continued to increase throughout the exercise time. However, atropine administration caused further increase in the rate of heat storage, compared to the respective no treatment exercise period.

Table 2 shows pyridostigmine treatment tended to increase water loss (11%) and was associated with an average exercise time of 61 min longer than the control value and consequently longer distance traveled in miles. Average speed in mph was slightly but significantly higher in the pyridostigmine experiments compared to the controls. Final heart rate (F-HR) and final Tre (F-Tre) responses were not significantly different from those in the control experiments.

TABLE 2. SUMMARY OF PYRIDOSTIGMINE EFFECTS DURING EXERCISE AT 35 °C

	R-HR (bpm)	F-HR (bpm)	R-Tre (°C)	F-Tre (°C)	Water Loss (g/min)	Time (min)	Distance (mi)	Speed (mph)
Control	160.4 ±10.9	223.0 ±11.0	37.9 ±0.1	39.3 ±0.2	1.9 ±3.0	115.0 ±29.0	3.0 ±0.8	1.5 ±0.1
Pyrido-stigmine	160.6 ±10.7	214.2 ±11.8	37.7 ±0.2	39.0 ±0.3	2.1 ±3.0	175.0* ±29.0	5.0* ±0.9	1.7* ±0.1

* $p < .05$
R=Resting
F=Final

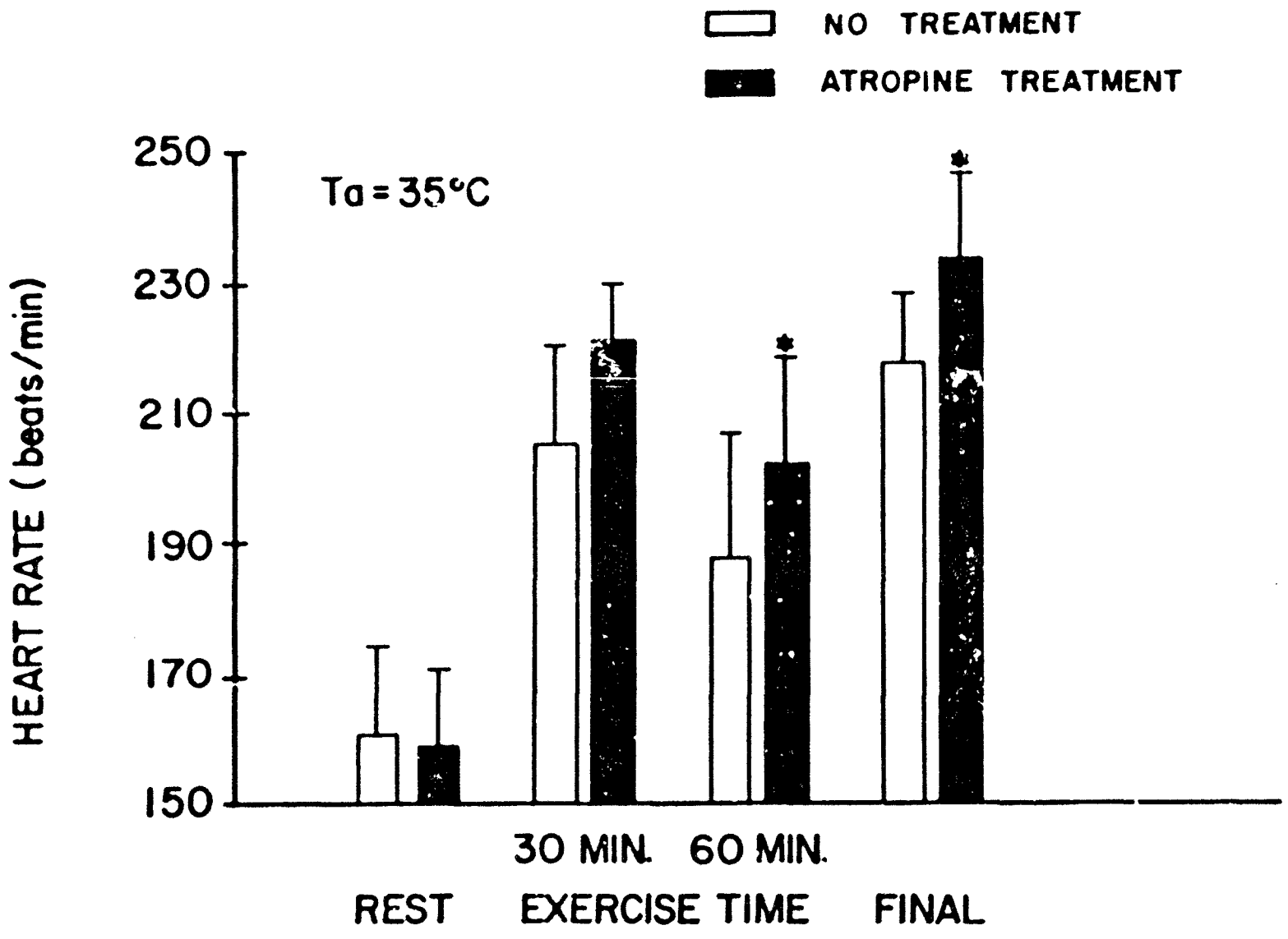

Figure 4. Effects of atropine and exercise on heart rate at Ta of 35 °C. (* $p < 0.05$ compared to no treatment)

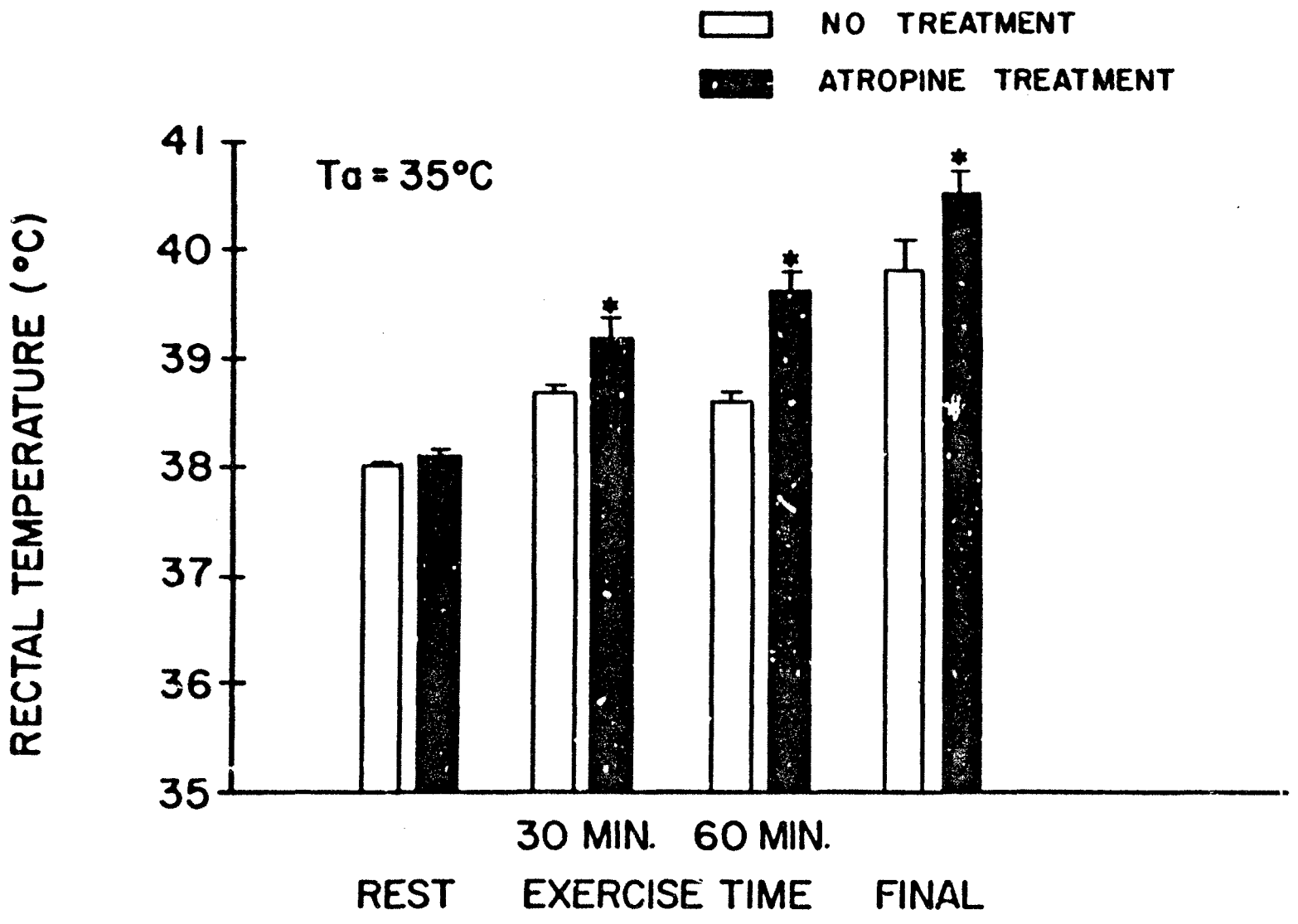

Figure 5. Effects of atropine on rectal temperature during exercise at Ta of 35 °C. (* $p < 0.05$ compared to no treatment)

DISCUSSION

The results of these studies showed that the physiological effects of atropine in exercising patas monkeys were similar to those reported for humans. The suppressed sweating capacity of the atropine significantly affected the heat loss mechanisms of the exercising animals in the heat as indicated by the 43% reduction in water loss. On the contrary, during exercise at thermoneutral environment, the amount of water loss was not significantly different between the atropine and control experiments. During exercise, there is enhanced release of epinephrine by the adrenal medulla which accounts for increased sweating (24); a fact which at neutral environment seems to completely counteract the negative effects of atropine on sweating. The suppressed sweating induced by atropine generally resulted in increased heat storage causing considerable thermal strain on the animals. It is speculated to account for the reduced time that the animals could exercise. In addition, exercise in the heat caused much faster rise in the rate of heat storage on the animal's body with potentially greater performance decrements and increased risks for heat injuries. For instance, exercise in the heat, for all animals but one, was terminated by the investigator when the Tre was in excess of 40 °C. Conversely, at the thermoneutral environment, the animals took longer to reach exercise tolerance. The time that elapsed between the first signs of discomfort and the time they reached the criteria for termination of exercise (see Methods and Materials) was also much longer. At this environmental temperature, all animals but one were stopped from exercising because they fulfilled the criterion concerning the speed limit that should be sustained. Although mean F-Tre response at 25 °C was not significantly different in the control and atropine exercise experiments, these data revealed that animals with low exercise tolerance (exercise time < 2.30 h) demonstrated much higher F-Tre values in the atropine experiments (40.2 °C vs control value of 39.5 °C). This may have to do with the pharmocokinetics of atropine in the plasma (half-life 2.5 h) and the fact that the exercise time of the animals varied between 1.30 and 5.0 hours.

Mahoney (22) investigated the response of a single patas monkey while running in the heat and reported that at any given temperature the onset of exercise caused a threefold increase in conductance regardless of the particular speed. Some of this increase could be associated with increased blood flow to the working muscles, and previous work from this laboratory in resting animals showed that atropine induced peripheral vasodilation as indicated by increased whole-body conductance (1). Similar increases in conductance were also found in exercising human subjects after atropine (9, 19). Therefore, it was speculated that increased blood pooling in the periphery to compensate for the decreased heat dissipation from sweating would have aggravated the problem by compromising blood flow to the exercising muscles and would have reduced their exercise capacity.

Although atropine blood levels were not measured in this study, results show that the time course for the physiological effects of atropine on heart rate and heat loss mechanisms, as indicated by increase in Tre, was between 30 to 60 min post-injection. This finding agrees with the results found by other investigators involving a variety of atropine dosages injected in human subjects (5, 6, 21, 23, 25). Furthermore, Craig (4) reported that 2 mg of atropine, a dose analogous to the one administered in the present study, resulted in nearly maximal vagal inhibition. In this study, mean final heart rate increased by 16 bpm and mean final rectal temperature increased by 0.7 °C under the influence of atropine during exercise in the heat. Various results, concerning the amount of increase in HR and Tre, have been found in human studies (4, 21, 25). Direct comparisons between the studies are tenuous because of differences in environmental conditions, subject variability, exercise mode, and protocols used.

The effects of pyridostigmine treatment have been reported in rats but not in primates. Francesconi et al. (11) reported that in rats, pharmacological acute doses of pyridostigmine greatly affected exercise performance, thermoregulation, and chemical indices of heat/exercise injury following 64% cholinesterase inhibition. In another study, Francesconi et al. (12) reported that moderate cholinesterase inhibition of 23% and 39% attenuated several of the acute responses and had no debilitating effects on physical performance and thermoregulation during exercise in the heat. They reached the conclusion that a rather narrow range of cholinesterase inhibition must be achieved before the physiological and protective effects of pyridostigmine are observed. Their findings agree with the results found in this study. We found that oral administration of 0.4 mg/kg pyridostigmine improved thermoregulatory function and was associated with a 60 min longer average exercise time than the control value.

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APPENDIX

REPORT ON THE MEASUREMENT OF ENERGY EXPENDITURE BY INDIRECT CALORIMETRY IN PATAS MONKEYS AT REST AND DURING EXERCISE

A continuous flow indirect calorimetry system was developed consisting of a metabolic cage in which the monkey resided. Fresh air was pulled through the cage by a fan and the airflow out was measured by a turbine flow-rate meter. Airstream temperature and water vapor pressure were measured before a small aliquot of gas was sampled for oxygen and carbon dioxide content (Fig. A-1). Calculation of metabolic parameters from the measurement of O_2, CO_2, P_{H_2O}, P_B, F_{out}, and temperature was done using the algorithms of Brown (3), which account for the storage (integration) of gas volumes in the metabolic cage. As an addition to the monkey exercising wheel, an airtight enclosure was developed which used the calorimetry system for metabolic rate measurement during exercise.

Five patas monkeys underwent a week of metabolic measurements in the metabolic cage. These same 5 monkeys then underwent a week in the metabolic cage combined with 3 exercise periods of 3 h. Typical metabolic rates during daylight hours were 40 W/m^2 at rest and 70 to 80 W/m^2 during exercise. Table A-1 illustrates the calorimetry data for daily oxygen, carbon dioxide, and metabolic rates for each monkey at rest and with exercise. It should be noted that the W/m^2 are on a per minute basis and are averages for an entire day including the dark period in which metabolic rates may go as low as 16 to 18 W/m^2.

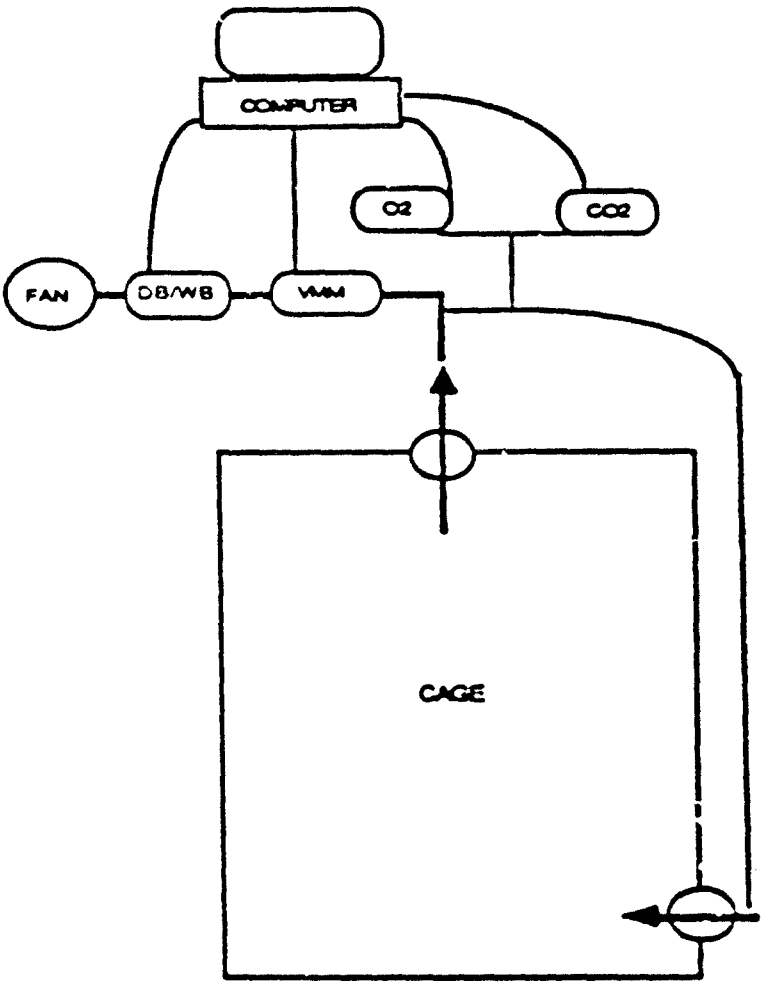

Figure A-1. Monkey indirect calorimetry system.

TABLE A-1. CALORIMETRY DATA AVERAGE DAILY O_2 AND CO_2 AND MINUTE METABOLIC RATE.

MONKEY	VCO_2, L/day	VO_2, L/day	RQ	Watts/m^2
		REST		
F10	64.53	85.67	0.75	36.40
F 9	75.91	76.59	0.99	25.60
M5584	62.67	91.69	0.68	29.26
B333	67.30	73.76	0.91	32.99
M9207	55.85	72.58	0.77	32.70
Total per day	326.26	400.29	0.82	31.40
			Avg/min	31.40
		PLUS EXERCISE		
F10EX	80.27	92.53	0.87	40.46
F 9EX	93.41	93.10	1.00	31.21
M5584 EX	72.30	77.81	0.93	26.42
B333 EX	73.13	74.96	0.98	34.04
M9207 EX	66.46	71.45	0.93	33.51
Total per day	385.59	409.84		
			Avg/min =	33.13

The results of the study using the newly designed continuous flow indirect calorimetry system for quantitation of energy expenditure in unrestrained monkeys is significant in light of ongoing studies of the effects of neuroactive agents on temperature regulation, metabolism, and work tolerance.

This is the first study that reports resting metabolic rate data in unrestrained patas monkeys. It is highly significant that the RQ and metabolic rate during daylight hours measured with our new calorimetry system are of the same order of magnitude as those which we have previously reported (16, 18) in chair-restrained animals. It should also be noted that the RQ's recorded in the exercise experiment are those which one would predict in an exercising animal (Table 1). Furthermore, the metabolic rate quantitates for the first time that, with the exercise wheel, we are inducing metabolic rates that are approximately twice those of the resting level. The metabolic rates during the exercise period were significantly higher than the daylight resting metabolic rates. Finally, it should be noted that in terms of 24 h energy expenditure, 3 exercise periods of 3 h duration during a 24 h period did not result in a significant increase in the metabolic rate when averaged over a 24 h period (Table A-1).

It is clear that the technology that has been developed will be very useful as we continue to examine the short- and long-term effects of neuroactive agents on thermoregulation, metabolism, and exercise tolerance in nonhuman primates.