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PYRIDOSTIGMINE AND WARM WATER DIVING PROTOCOL 90-05:

II THERMAL BALANCE

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TECHNICAL REVIEW AND APPROVAL

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The experiments reported herein were conducted according to the principles set forth in the current edition of the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This technical report has been reviewed by the NMRI scientific and public affairs staff and is approved for publication. It is releasable to the National Technical Information Service where it will be available to the general public, including foreign nations.

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A study was conducted to evaluate whether pretreatment with pyridostigmine affected the thermal balance of divers in warm water conditions. Ten U.S. Navy divers participated in three separate 7-hour exposures. Each test involved a 4-hour exposure in 37.8 °C air (100 °F) at the surface, followed by a 3-hour immersion in 34.4 °C (94 °F) water at a depth of 20 fsw (1.6 ATA). The first two immersed exposures were conducted while breathing 100% oxygen at depth; once after ingesting pyridostigmine bromide (one 30 mg tablet every 8 h for two days prior to testing), and once after ingesting placebo in the same pattern. The third exposure was conducted with no drug and while breathing air at depth. The subjects performed leg exercise on a cycle ergometer in a semi-recumbent position during the immersion phase. During the first 2 h of immersion, the subjects repeated a cycle of 30 min of light work ($V_{O_2} \sim 1.0$ ℓ/min), followed by 10 min of rest. The last hour consisted

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of cycles of 5 min of light work, 10 min of moderate work (V_{O_2} ~ 2.0 ℓ/min), and 5 min of rest. Prior to their first test exposure subjects were heat-acclimated for 5 days. The interval between exposures was 5 days, with heat acclimation continued on alternate days between exposures. Subjects ate MRE rations for 2 days prior to each test. Camouflage utilities were worn by each subject throughout the 7-hour exposure. During both the dry and the wet phases thermal balance was assessed by measurement of 8 regional heat fluxes, 8 regional skin temperatures, rectal temperature, and oxygen consumption as a measure of heat production. During the dry phase, resting heart rate was reduced 7 ± 4 beats/min, skin temperature was 0.1-0.2 °C lower, and rectal temperature was generally 0.1 °C lower after pyridostigmine pretreatment. There were, however, no significant effects on thermal balance (heat production vs. heat loss) between pyridostigmine vs. placebo during this phase. During immersion neither drug vs. placebo nor breathing air vs. 100% oxygen significantly affected thermal balance: heat flux was unchanged across experimental conditions, skin temperatures increased an average of 0.5 °C, and oxygen uptake was unchanged by either drug or breathing gas conditions. Rectal temperature was unchanged as a result of drug administration during immersion. Breathing air resulted in a significantly lower rectal temperature during the lighter workloads (25 W), but not at 1 W/kg, when compared to breathing 100% oxygen. This difference can only be explained as an effect of repeated exposure, since the air trials were always conducted last. Rectal temperatures did not approach hyperthermic limits in any of the subjects (average peak rectal temperature = 38.0 °C, average increase during the 7-hour exposure = 0.9 °C). Perceived thermal sensation was unaltered by pyridostigmine throughout the exposures. These results indicate that pyridostigmine does not alter thermal balance during warm water diving, and that light to moderate work would not impose thermal limitations on diver performance.

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1. INTRODUCTION

Pyridostigmine bromide may be issued to military personnel as a prophylactic measure against exposure to organophosphate nerve agents. The effects of pyridostigmine ingestion on tolerance to heat stress, cognitive function, and exercise performance have been studied under dry experimental conditions, but not during immersion. There are known side effects of this drug (cardiovascular, neuromuscular, thermoregulatory) which may limit a diver's performance. A description of the pharmacology of pyridostigmine can be found in a companion NMRI Technical Report.[1]

Monkeys exposed to 35 °C air demonstrated no effect of pyridostigmine on core temperature at rest when compared to controls.[2] In humans,[3] pyridostigmine pretreatment did not significantly alter the rectal temperature of men performing light exercise while wearing chemical protective clothing in 33 °C air. Higher workloads (58% of $\dot{V}_{O_{2max}}$) caused an average 0.1 °C increase in rectal temperature in subjects exposed to 36 °C air.[4] Skin blood flow was shown to decrease in humans when pretreated with pyridostigmine.[5] A reduced blood flow to the cutaneous vasculature would limit the dissipation of heat and might lead to decreased heat tolerance. Sweating rates have been shown to be higher with pyridostigmine;[2] which would promote heat loss in air, but not during immersion.

Since pyridostigmine antagonizes the breakdown of acetylcholine at nerve endings, it would be expected to increase vagal tone. Bradycardia during exercise in different environmental conditions has been shown by Kolka and Stephenson,[4] while Epstein et al.[3] measured no differences as a result of pyridostigmine treatment.

Warm water presents a thermal challenge which in itself may be a limiting factor. The study of diver performance in warm water is of interest to both military and commercial operations, since working dives are conducted at water temperatures >28 °C. The combination of pyridostigmine ingestion and warm water may produce greater limitations of diver performance than either the drug or water temperature alone.

Studies have attempted to determine thermoneutral water temperatures at given metabolic rates. Thermoneutral temperature is defined as that temperature at which the rate of heat loss is equal to the rate of heat production.[6] Craig and Dvorak[7] studied ten male volunteers during rest and at two different workloads ($\dot{V}_{O_2}$ ~ 0.70 and 0.92 L/min) during head out immersion in water temperatures ranging from 24 to 37 °C. At rest the thermoneutral water temperature was 35.5 °C, while at the respective exercise workloads it was 34 and 29 °C. Another study,[8] noted that individuals who were exercising in water warmer than 33 °C had increased rates of heat storage and symptoms of heat exhaustion, prompting a recommendation of 28-30 °C water as the ideal temperature for short duration maximal swimming efforts. Wells[9,10] found that water temperatures over 28 °C limited the intensity and duration of dives conducted in the coolant pools of nuclear reactors.

The primary purpose of this investigation was to determine whether pretreatment with pyridostigmine altered thermal balance during warm water diving. A secondary purpose was to examine the effect of oxygen breathing on thermal status. Breathing 100% oxygen at 1 ATA and shallow depths (< 3 ATA) increased oxygen consumption

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when compared to air breathing at equal work rates,[11,12] while heart rate[12] and cardiac output,[13,14] were reduced by oxygen breathing at depths up to 3 ATA. Regional vasoconstriction in the eye, kidney, brain, and heart has been shown with 100% oxygen breathing at the surface and at depths up to 4 ATA.[15-17] The precise effect of oxygen-induced peripheral vasoconstriction on heat production or loss is unknown at present.

The effects of pyridostigmine and 100% oxygen breathing on thermal status would be relevant to operational dives conducted under similar environmental conditions.

2. METHODS

Ten U.S. Navy divers volunteered to participate in the study after giving their informed consent. The study was approved by the NMRI Committee for Protection of Human Subjects. The physical characteristics of the divers are presented in Table 1. Prior to participation, subjects underwent a maximal aerobic exercise test on a cycle ergometer as part of pretest workups to assess fitness. None of the subjects had a known history of cardiovascular disease, neuromuscular injury, or intolerance to heat stress. Subjects ate standard military issue Meals-Ready-to-Eat (MRE) rations for two days prior to each test, and were instructed to refrain from consumption of alcohol, caffeine, and nicotine, as well as avoid strenuous exercise for 48 h prior to each test.

Subjects were acclimated to heat for 5 days prior to their first exposure and on alternate days between subsequent exposures. Acclimation consisted of exercise on a cycle ergometer in an environmental chamber with air temperature controlled at 100 ° F. Subjects exercised for three consecutive bouts of 25 min (5 min at 50 W and 20 min at

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1 W/kg), each followed by 5 min of rest. Subjects drank 2 L of fluid during each session.

All exposures were conducted in the Man-Rated Chamber Complex in the Diving Medicine Department. Divers wore camouflage utilities and protective footwear throughout each exposure. Each exposure was divided into two phases. A 4-hour "dry phase" preceded the dive phase where subjects sat in the dry in "A" chamber of the complex breathing air. The chamber remained at the surface (1 ATA), air temperature (T_a) was controlled to 37.8 ± 0.1 °C (100 °F), and relative humidity was 50%. The subjects ingested 1 liter of water per hour during the dry phase.

Subjects moved to "D" chamber of the complex and a 3-hour "wet phase" occurred after the 4-hour dry exposure. Once in "D" chamber the subjects donned a full face mask supplying breathing gas through a demand regulator and entered the wet pot. Subjects were fully submerged with water just covering their heads, and were seated in a semi-recumbent position on a cycle ergometer. Water temperature (T_w) was controlled to 34.4 ± 0.1 °C (94 °F). After subjects were comfortably seated and all systems determined to be operational, the chamber was compressed with air to a diver depth of 20 fsw and the 3-hour exposure was begun. The time between leaving "A" chamber and the beginning of the wet phase in "D" chamber (approximately 15-20 minutes) was not included in overall exposure time.

Subjects began leg exercise at a light workload (25 Watts) resulting in an oxygen consumption of approximately 1.0 L/min. During the first 2 h of immersion, the subjects followed a pattern of 30 min of exercise at 25 W and 10 min of rest (repeated 3 times).

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The last hour of immersion consisted of 3 repeated bouts of 5 min at 25 W, 10 min at 1 W/kg ($\dot{V}_{O_2} \sim 2.0$ L/min), followed by 5 min of rest.

Each subject was scheduled to perform 3 test exposures. The dry and wet phase profiles were identical for all 3 exposures. Differences consisted of one exposure being conducted after ingestion of pyridostigmine (PYR) for 2 days prior to testing (30 mg tablet once every 8 h; last tablet ingested 2 h prior to the start of the exposure), and another after ingestion of a placebo (saccharin) for 2 days as a control (CON). These first two exposures were conducted with the subjects breathing 100% oxygen during the immersion phase of the trial. The third exposure was conducted without any drug treatment and with the subjects breathing air (AIR) during the wet phase in order to assess any differences between air and 100% oxygen. An additional 2 subjects were recruited for the AIR vs CON exposures, and were not part of the drug trials. Subjects acted as their own controls when comparing PYR vs CON and AIR vs CON.

Prior to each exposure on a test day, the subjects consumed their MRE rations for that morning, were given a brief physical by a Diving Medical Officer and had their body weight measured. Subjects drank a volume of water equivalent to 5 ml/kg of body weight in order to ensure an adequate hydration status.

Instrumentation on each diver consisted of EKG electrodes, heat flux/skin temperature sensors, and a rectal temperature sensor. Heat flux and skin temperatures were measured at eight sites using combination sensors (Concept Engineering, Old Saybrook, CT). The sites were located on the forearm, chest, abdomen, upper back, tricep, anterior thigh, posterior thigh, and calf. Rectal temperature was obtained using

YSI 400-Series presterilized sensors inserted 15 cm beyond the anal sphincter. An EKG was obtained and heart rate monitored using a 3-lead waterproofed placement on the sternum. This placement was used in order to minimize EKG signal disturbance caused by a diver safety harness worn during the immersion. All EKG and heat flux/temperature sensor leads were attached to a molded waterproof block which the divers wore on a waist belt under their utility jacket. This block was connected by cable to a data acquisition system. Data collection was begun after the subjects had entered "A" chamber and all instrumentation was determined to be functioning properly. This point was then designated as Time 0 for the dry phase. Time 0 for the wet phase denoting the start of data collection began after reaching 20 fsw (approximately 15-20 min after the end of the dry phase).

The eight regional heat fluxes and skin temperatures, along with rectal temperature, were visually displayed and recorded every minute by computer. Heart rate was continuously monitored and recorded every 5 min. "A" chamber ambient air and "D" chamber wet pot temperatures were monitored continuously and adjusted by chamber operators to maintain them at the previously specified temperatures. Mean heat flux and skin temperatures were calculated by using body surface area weighting.[18]

Experimental abort criteria consisted of a rectal temperature $\geq 39.5\,^\circ$ C for 1 min, or heart rate reaching 90% of the subject's previously determined maximum exercise heart rate for 30 sec. The heart rate abort criteria was used as an indicator of excessive cardiovascular strain.

Oxygen consumption, CO_2 production, and minute ventilation were measured every 30 min during the dry phase using open circuit spirometry. The same variables were measured every 8-10 min during the wet phase using a pneumotachometer to measure expired gas flow and by sampling the expired gas for O_2 (Sybron Analyzer, Servomex Ltd., Crowborough, England) and CO_2 (Anarad Infrared Analyzer, Santa Barbara, CA) concentrations. Details of the respiratory measurements during the wet phase are reported elsewhere.[19]

Perceived thermal sensation (PTS) was subjectively evaluated in each subject using the 0-8 scoring method of Gagge,[20] where 0 is described as "unbearably cold" and 8 is "unbearably hot". A PTS score was obtained every 30 minutes during the dry phase, and immediately after each work period during the wet phase.

Thermal balance was determined from the calculation of heat storage for both the dry (ΔS_D) and wet (ΔS_W) exposures and was defined as:

$$\Delta S_D = 0.83 \ m_b[0.8(\Delta T_{re(0-240)}) + 0.2 \ (\Delta T_{sk(0-240)})] \qquad (1)$$

$$\Delta S_W = 0.83 \ m_b[0.8(\Delta T_{re(0-180)}) + 0.2 \ (\Delta T_{sk(0-180)})] \qquad (2)$$

where 0.83 = specific heat of body tissue ($kcal \cdot kg^{-1} \cdot °C^{-1}$), m_b = body mass (kg), 0.8 = fractional distribution of stored heat residing in the core, 0.2 = fractional distribution of stored heat residing in the body shell, $\Delta T_{re(0-240)}$ and $\Delta T_{sk(0-240)}$ = change in rectal and skin temperatures (°C) during the dry exposure, $\Delta T_{re(0-180)}$ and $\Delta T_{sk(0-180)}$ = change in rectal and skin temperatures (°C) during the wet exposure.

Statistical analyses of heat flux, skin temperature, rectal temperature, oxygen consumption, and heart rate data were conducted using one-way Analysis of Variance (ANOVA) for repeated measures when comparing drug vs placebo and oxygen vs air, as well as the effect of repeated exposures (irrespective of drug condition). Heat storage data was analyzed using a paired t-test. Scores for PTS were evaluated by two-way ANOVA for repeated measures when comparing drug vs placebo, oxygen vs air, and on repeated exposures for each subject to determine if multiple exposures to the warm environment influenced PTS scores. The dry and wet phases were treated separately during all analyses when comparing drug vs placebo and oxygen vs air breathing. Statistical significance was accepted at the $p < 0.05$ level. Data are presented as mean $\pm$ SEM.

Additional details on the overall experimental protocol can be found in a companion NMRI Technical Report.[1]

3. RESULTS

All subjects completed the dry phase of each exposure. One trial during the wet phase of both the CON and AIR exposures was terminated early because of regulator malfunction. The aborted trials involved different subjects, and each subject was his own control for the PYR vs CON comparison (n = 9) and for the CON vs AIR comparison (n = 8). No immersions were aborted because of high rectal temperature or heart rate.

Total Body Heat Flux

Figure 1 illustrates total body heat flux during the 4-hour dry phase when comparing PYR to the CON condition. During the first 30 min of the exposure, heat flux decreased to approximately 5 W/m^2 with PYR and 7-8 W/m^2 in the CON trials. Heat flux slowly increased in both conditions to 15-20 W/m^2. Since Time 0 measurements were taken after the subjects had been exposed to T_a of 100 ° F for several minutes (considerably warmer than ambient air temperature outside the chamber) heat flux would be expected to be reduced when compared to room temperature. Differences between the drug and placebo during the dry exposure were not statistically significant.

Figure 2 presents total body heat flux for PYR and CON during the immersion phase. Cyclic changes in heat flux followed the pattern of the work-rest periods, with peak heat fluxes of approximately 100 W/m^2 during the first two 25 W workloads, and 90 W/m^2 during the third 25 W workload. During the rest periods between the 25 W work cycles heat flux decreased approximately 25 W/m^2. During the last hour of immersion (when workload was increased) heat flux peaked at approximately 110-115 W/m^2 during exercise and again declined approximately 2^5 W/m^2 during the rest periods. The differences between PYR and CON during immersion were not statistically significant.

A comparison of total body heat flux between CON and AIR conditions yielded results similar to the PYR vs CON trials during both the dry exposure (Fig. 3) and during immersion (Fig. 4). Relative changes and average peak values followed the same

pattern noted with PYR vs CON. Again, there were no significant differences between the conditions.

While there were some small differences in heat flux at various times during the dry and immersed phases, there was no consistent pattern of increased or decreased heat flux among the subjects as a result of drug or breathing gas conditions.

Rectal Temperature

Rectal temperature (T_{re}) in the PYR condition was 0.1 °C lower (Fig. 5) than CON (37.1 vs 37.2 °C) at the start of the dry phase, and except for short periods, this difference was maintained throughout the 4-hour exposure. At the end of the dry phase the average increase for PYR was 0.2 °C and 0.1 °C for CON.

Rectal temperature increased initially upon immersion by 0.2 (PYR) and 0.3 °C (CON). During light exercise (Fig. 6) T_{re} remained at 37.7 °C for both trials and increased slowly during the heavier workload to peak at 38.0 °C by the end of immersion. No significant differences occurred between PYR and CON conditions.

A similar pattern was repeated in the dry (Fig. 7) for CON vs AIR, with T_{re} during the AIR trial being 0.1 °C lower than CON throughout most of the exposure. Again, the absence of a consistent pattern among the subjects resulted in no significant effect of either drug or breathing gas during the dry phase. Rectal temperature for the AIR trials during immersion (Fig. 8) was initially 0.3 °C lower than CON, and remained 0.1-0.3 °C lower throughout most of the immersed phase, while exhibiting a temporal pattern similar to the PYR and CON immersions. The differences between CON and AIR

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during the 25 W workloads were significant ($p < 0.05$), with no significant variances observed at the higher (1 W/kg) workload.

Since Trial 1 and Trial 2 were conducted breathing 100% oxygen in a balanced order (drug vs placebo), while Trial 3 was always air (with no drug), an effort was made to determine if repeated exposure (irrespective of drug condition) had any effect on T_{re} (Fig. 9). In fact, T_{re} during Trial 3 is significantly different when compared to Trial 1 ($p < 0.05$) during the lighter exercise periods. This difference did not occur at the heavier (1 W/kg) exercise periods. T_{re} measurements in Trial 2 were intermediate between Trials 1 and 3 at the lighter workloads, but not significantly different from either Trial 1 or 3.

Mean Skin Temperature

Mean skin temperatures (T_{sk}) for PYR trials during the dry phase (Fig. 10) were 0.1-0.2 °C lower than CON, however, this difference was not statistically significant. During the dry exposure T_{sk} increased to approximately 35.5 °C (3-4 °C higher than Tsk recorded prior to entering "A" chamber) and remained relatively constant during the last 3 h among all trials. The immersed phase (Fig. 11) also exhibited no differences due to the drug. During immersion, skin temperatures fluctuated slightly around 35.0 °C, depending on the work/rest cycles. T_{sk} of ~ 35.0 °C is 0.6 higher than T_w with part of this increase most likely due to the insulating effect of the camouflage utilities. The average increase in T_{sk} by the end of the immersed phase was 0.5 °C. When comparing CON vs AIR (Figs. 12 and 13) there were also no differences between the conditions. In

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fact, the air trials for both dry and immersed phases were remarkably similar to the PYR vs CON trials.

Perceived Thermal Sensation

Figure 14 presents PTS scores during the dry phase, comparing PYR vs CON trials (n = 10). No significant drug effect occurred. For both trials the PTS score gradually increased from 4.0 to 4.5 by the midpoint of the exposures, and remained constant thereafter.

Figure 15 illustrates PTS during the immersed phases. After the first work cycle (min 30) the PTS values were higher than at the start of immersion, and did not change subsequently during the 25 W work periods. Significant increases, although small, were detected between the last 25 W workload and the end of the first workload at 1 W/kg (min 110 to 135). No meaningful differences were noted between pyridostigmine vs placebo, nor between breathing oxygen (CON) and air (AIR). Not shown in the figure is the fact that there were no significant differences between repeated exposures (regardless of drug or breathing gas treatment).

Heart Rate

During the dry phase heart rate (HR) was significantly reduced (Table 2) in the PYR trials when compared to the CON trials (69 ± 4 vs 76 ± 3, respectively). Table 2 also illustrates that, in the immersion phase, there were no differences noted between PYR and CON during exercise. No significant differences occurred between CON and AIR during the dry phase nor at the 25 W workload during immersion. At 1 W/kg

breathing oxygen (CON) significantly (p<0.05) reduced mean HR when compared to AIR (136 ± 4 vs 145 ± 4 beats/min respectively).

Oxygen Uptake

Table 2 indicates that oxygen consumption during the 4-hour dry phase was not significantly different between PYR and CON. There were also no significant differences in oxygen consumption among the three conditions for either workload during the immersion phase.

Thermal Balance

Changes in heat storage [calculated from Eqns. (1) and (2)] are presented in Table 2. Heat storage, and therefore thermal balance, was not appreciably affected by either drug (PYR vs CON) or breathing gas (CON vs AIR) during either the dry or the wet phase.

4.   DISCUSSION

The results of this study indicated that pretreatment with pyridostigmine did not significantly alter the thermal status (heat production and heat loss) of divers performing light to moderate work in warm (34.4 °C) water. In addition, there was also no difference in thermal balance between breathing 100% oxygen or air at 20 fsw. Therefore, it may be concluded that low dose pyridostigmine pretreatment would not affect the thermal status of divers working in warm water, regardless of whether breathing 100% oxygen or air. If the drug had increased heat storage, either by increasing heat production or decreasing heat loss, then rectal temperature would have

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increased proportionately. The fact that T_{re} was not significantly different between drug and placebo advances the argument for the absence of a drug effect on net heat storage.

During immersion, T_{re} was initially lower with the air trials and converged with T_{re} of the oxygen trials. Predive thermal data were not different between the trials. The time between the end of the dry phase and the start of the wet phase, environmental temperatures, and workloads were the same between trials. The only readily apparent explanation of why rectal temperature was significantly lower during the lighter workloads of the air trials when compared to Trial 1 (breathing 100% oxygen) is the effect of repeated exposures. The drug vs placebo trials were conducted in a balanced fashion, and the air trials were always the third exposure. Because of time constraints prior to the study, subjects may not have been fully acclimated prior to Trial 1. Subsequent exposures could have resulted in enhancement of the state of acclimation of the subjects. The higher workloads (1 W/kg) may have been sufficient to overcome the slight improvement in acclimation, resulting in significantly different rectal temperatures at only the lighter workloads. The lower T_{re} during the air trials is putative evidence that the subjects began the immersions and continued for the first 2 h with lower net body heat stores.

Pyridostigmine has been shown to reduce skin blood flow in humans in the dry.[5] While T_{sk} was 0.1 °C lower in the dry with PYR, heat loss was not different. During immersion, T_{sk} was not different and heat loss was unchanged overall with the drug. The absence of significant differences suggest no appreciable effect of pyridostigmine on skin

blood flow. There was also no effect on heat loss or oxygen consumption when breathing 100% oxygen vs air during exercise in this study.

Peripheral blood flow increases in order to dissipate heat through the skin. Heart rate will increase to meet this added circulatory demand. The lower resting heart rate noted with PYR in the dry phase (Table 2) was more likely due to a drug effect than to thermal stress. Other studies have shown reductions in resting heart rates,[2,4] no change in exercise heart rates,[3] or reductions at both rest and during exercise[5] after pyridostigmine administration. Breathing 100% oxygen during the immersed phase also resulted in lower heart rates at the higher workload when compared to air breathing. The well known bradycardic effect of high oxygen partial pressures, and not thermal stress or changes in hydration status, may account for this reduction. In any case, the magnitude of the change in heart rate with either drug administration or oxygen breathing was insufficient to have an adverse effect on tolerance to heat.

Perceived thermal sensation did not vary as a function of drug or breathing gas. This is not surprising since PTS is, in large measure, determined by mean skin temperature; and this variable was not influenced by experimental treatments. Furthermore, the PTS scores did not change within subject as a function of repeated exposure to the warm environment. All PTS values ranged between 4 and 5; which are subjectively described as feeling "comfortable" and "warm", respectively.

Since metabolic heat production and heat loss were not significantly different across experimental conditions, thermal balance based on heat storage calculations would not be expected to change. The similarity in heat storage between the dry and the wet

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phases can be explained by the much greater changes in skin temperature in the dry and the relative contribution of those changes to the heat storage calculations. Heat storage calculated in this manner agreed closely with a model developed by Goldman.[27] The model attempts to predict the incidence of heat stress casualties as a function of rectal temperature, or calculated heat storage. According to Goldman,[27] in order to maintain an individual in a subjectively tolerable condition in a hot air environment with less than a 5% chance of heat stress injury, heat storage should be less than 1.1 kcal/kg of body weight. The average amount of heat stored by the subjects in the present study was calculated to be approximately 0.8-0.9 kcal/kg [heat storage from Table 2 divided by average subject weight (79.3 kg)], indicating that the subjects were not thermally stressed to the point where heat injuries would occur. At the light-to-moderate workloads used in this study, Goldman's prediction[27] of the chance of heat stress injury in air would seem to be in reasonable agreement with our data during immersion.

Of particular interest is the lack of expected thermal stress as a result of exercising in warm water. Based on information in the current literature,[7-10] as well as pre-experiment predictions using a thermal model by Wissler,[28] the thermal stress induced by the protocol was expected to be a limiting factor. However, expected increases in T_{re} during the 25 W workloads did not materialize, only becoming evident at the higher (1 W/kg) workloads, and did not approach thermal abort criteria. Initial pre-experiment predictions of thermal stress utilized estimated $\dot{V}_{O_2}$ measurements in Wissler's model that were higher than measured experimentally. In addition, there are two other points which must be considered relative to the observed thermal stress in this study.

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First, subjects in the present study were heat acclimated. In other warm water studies, heat acclimation was questionable or non-existent. Second, subjects in the present study were also well-hydrated during the dry phase prior to immersion. Other studies rarely controlled hydration state.

One possible conclusion with respect to these two points is that proper acclimation and adequate hydration prior to operational dives in warm water may be extremely important in avoiding heat stress injury. Further studies would seem warranted to address how much acclimation or hydration is sufficient to minimize heat stress casualties in warm water diving.

The purpose of this study was to examine whether pyridostigmine pretreatment altered thermal balance. The recommended dosing pattern of 30 mg every 8 h was followed with the last dose taken 2 h before the start of the 7-hour exposure. Blood concentrations of the drug should peak at about 2.5 h after ingestion of the last tablet, and may account for the small, but nonsignificant effects on skin and rectal temperature noted after the first hour of dry exposure. These small effects were not observed during the immersed phase. Given that excretion by the kidneys is an avenue of pyridostigmine elimination, elevated urine flow rates during the dry coupled with immersion diuresis may increase the rate of elimination. This may account for the absence of even a small drug effect during the dive phase. More importantly, a more rapid clearance of the drug may reduce the efficacy of pyridostigmine pretreatment against chemical warfare agents. Additional studies would seem warranted to determine the extent to which immersion alters effective blood concentrations of pyridostigmine.

5. SUMMARY

In this study, pretreatment with pyridostigmine during warm water diving had no effect on thermal balance. Neither metabolic heat production nor heat loss was significantly different from the placebo condition. When breathing 100% oxygen was compared to air, there was also no difference in thermal balance between the conditions. As measures of thermal stress; rectal temperature was not different as a result of drug or oxygen, and reductions in heart rate were not sufficient to affect thermal balance. Heat storage was also not significantly different among experimental conditions. The results indicate that neither drug nor breathing gas will adversely affect the thermal status of a diver performing light-to-moderate work in warm water. Furthermore, while unexpected. the exercise paradigm used in this study should not result in thermal casualties in heat-acclimated and well-hydrated divers. Further inquiry may be necessary to quantify the pharmokinetics of pyridostigmine during immersion and to clarify the factors associated with thermal stress in warm water diving.

6. LAY LANGUAGE SUMMARY

Pyridostigmine bromide has been advocated as a useful method of pretreatment against potential exposure to organophosphate nerve toxins. The effects of pyridostigmine ingestion on tolerance to heat stress have been studied under dry experimental conditions, but not during warm water diving.

The purpose of this study was to investigate whether pretreatment with pyridostigmine altered the thermal status of a diver working in warm water. A secondary purpose was to examine the effect of oxygen breathing on thermal status.

Ten U.S. Navy divers took part in three exposures. Each exposure consisted of a 4-hour predive exposure at the surface with air temperature at 37.8 °C (100 °F), followed by a 3-hour dive in 34.4 °C (94 °F) water at 20 fsw. The subjects performed light-to-moderate exercise (equal to swimming with fins at 0.6-1.1 knots). One exposure was conducted after ingesting pyridostigmine (PYR) for 2 days (30 mg tablet once every 8 h), once after ingestion of a placebo (saccharin) for 2 days as a control, and once without any drug treatment and with the subjects breathing air (AIR) during the wet phase.

In the dry phase, rectal temperature and skin temperature were slightly lower with the drug, while heat loss and production were unchanged. There were no significant changes in heat storage. Heart rate was also slightly lower (7 beats per min) with the drug.

During the dive there were no significant effects of pyridostigmine on heat production, heat loss, or heat storage. There were also no differences in thermal balance when comparing air vs 100% oxygen breathing. Rectal temperature was lower (0.1-0.3 °C) when breathing AIR and heart rate was slightly lower (9 beats per minute) when breathing oxygen. The diver's perception of the thermal stress during the exposure was also unchanged as a result of the drug or oxygen.

The heat stress imposed in this study resulted in an average peak rectal temperature of 38.0 °C (normal = 37.0 °C), well below the limit considered to represent hyperthermia (39.0 °C).

The results of this study indicate that pretreatment with pyridostigmine had no effect on thermal balance, and should not limit a diver's ability to work in warm water at light to moderate workloads as long as the diver is acclimated and adequately hydrated. Breathing oxygen instead of air at 20 fsw also does not significantly affect thermal balance or overall diver performance.

The drug regimen used in this study followed the recommended pretreatment schedule developed for land-based personnel. Diving results in an increased rate of urine production, which is a pathway for elimination of the drug from the body. It is uncertain to what extent this higher urine flow rate influenced the present results, but any such effect would unlikely alter the present conclusions. An important caveat, however, is that immersion effects might reduce the efficacy of pyridostigmine pretreatment on subsequent exposure to nerve agents.

Additional work may be indicated to quantify the effectiveness of the drug regimen used in this study and to further evaluate heat stress while exercising in warm water.

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TABLE 1

SUBJECT CHARACTERISTICS
(N = 10; MEAN ± SEM)

AGE (yrs)	30.0 ± 1.3
HEIGHT (cm)	179.0 ± 1.6
WEIGHT (kg)	79.3 ± 3.0
BSA (m^2)	1.98 ± .04
MEAN SKIN FOLD (mm)	7.1 ± 0.3
BODY FAT (%)	15.0 ± 0.9
MAX $\dot{V}_{O_2}$ (ml/min/kg)	44.0 ± 1.6
MAX HR (bpm)	190.0 ± 2.8

TABLE 2

COMPARISONS: PYR vs CON; CON vs AIR
(MEAN ± SEM)

		PYR	CON	AIR
Heart Rate (beats/min)	DRY REST	69 ± 4*	76 ± 3	76 ± 3
	25 W	115 ± 3	112 ± 3	115 ± 4
	1 W/kg	133 ± 4	136 ± 4#	145 ± 4
Oxygen Consumption (ℓ/min)	DRY REST	.38 ± .02	.37 ± .01	.35 ± .01
	25 W	1.16 ± .06	1.13 ± .08	1.08 ± .05
	1 W/kg	1.83 ± .13	2.05 ± .19	1.93 ± .12
Heat Storage (kcal)	DRY	35 ± 5	30 ± 6	33 ± 6
	IMMERSION	28 ± 6	32 ± 8	37 ± 6

* = PYR vs CON significant at p<0.05 level
\# = CON vs AIR significant at p<0.05 level

FIGURE LEGENDS

Figure 1:   Total body heat flux (mean ± SEM) measured during the 4-hour dry exposure. Comparison of drug (PYR) vs placebo (CON) for 10 subjects.

Figure 2:   Total body heat flux (mean ± SEM) measured during the 3-hour wet exposure. Comparison of drug (PYR) vs placebo (CON) for 9 subjects.

Figure 3:   Total body heat flux (mean ± SEM) measured during the 4-hour dry exposure. Comparison of CON vs AIR trials for 10 subjects.

Figure 4:   Total body heat flux (mean ± SEM) measured during the 3-hour wet exposure. Comparison of oxygen (CON) vs air (AIR) breathing for 8 subjects.

Figure 5:   Rectal temperature (mean ± SEM) measurements during the 4-hour dry exposure. Comparison of drug (PYR) vs placebo (CON) for 10 subjects.

Figure 6:   Rectal temperature (mean ± SEM) measurements during the 3-hour wet exposure. Comparison of drug (PYR) vs placebo (CON) for 9 subjects.

Figure 7:   Rectal temperature (mean ± SEM) measurements during the 4-hour dry exposure. Comparison of CON vs AIR trials for 10 subjects. All subjects breathing air during the predive exposure.

Figure 8:   Rectal temperature (mean ± SEM) measurements during the 3-hour wet exposure. Comparison of oxygen (CON) vs air (AIR) breathing for 8 subjects.

Figure 9:   Rectal temperature (mean ± SEM) measurements during the 3-hour wet exposure. Comparison of first, second, and third exposures for 7 subjects (irrespective of drug treatment).

Figure 10:   Mean skin temperature (mean ± SEM) measurements during the 4-hour dry exposure. Comparison of drug (PYR) vs placebo (CON) for 10 subjects.

Figure 11:   Mean skin temperature (mean ± SEM) measurements during the 3-hour wet exposure. Comparison of drug (PYR) vs placebo (CON) for 9 subjects.

Figure 12:   Mean skin temperature (mean ± SEM) measurements during the 4-hour dry exposure. Comparison of CON vs AIR trials for 10 subjects.

Figure 13:   Mean skin temperature (mean ± SEM) measurements during the 3-hour wet exposure. Comparison of oxygen (CON) vs air (AIR) breathing for 8 subjects.

Figure 14:   Perceived thermal sensation scores (mean ± SEM) during the 4-hour dry exposure. Comparison of drug (PYR) vs placebo (CON) for 10 subjects.

Figure 15: Perceived thermal sensation scores (mean ± SEM) during the 3-hour wet exposure. Comparison of drug (PYR) vs placebo (CON) for 9 subjects and oxygen (CON) vs air (AIR) breathing for 8 subjects.
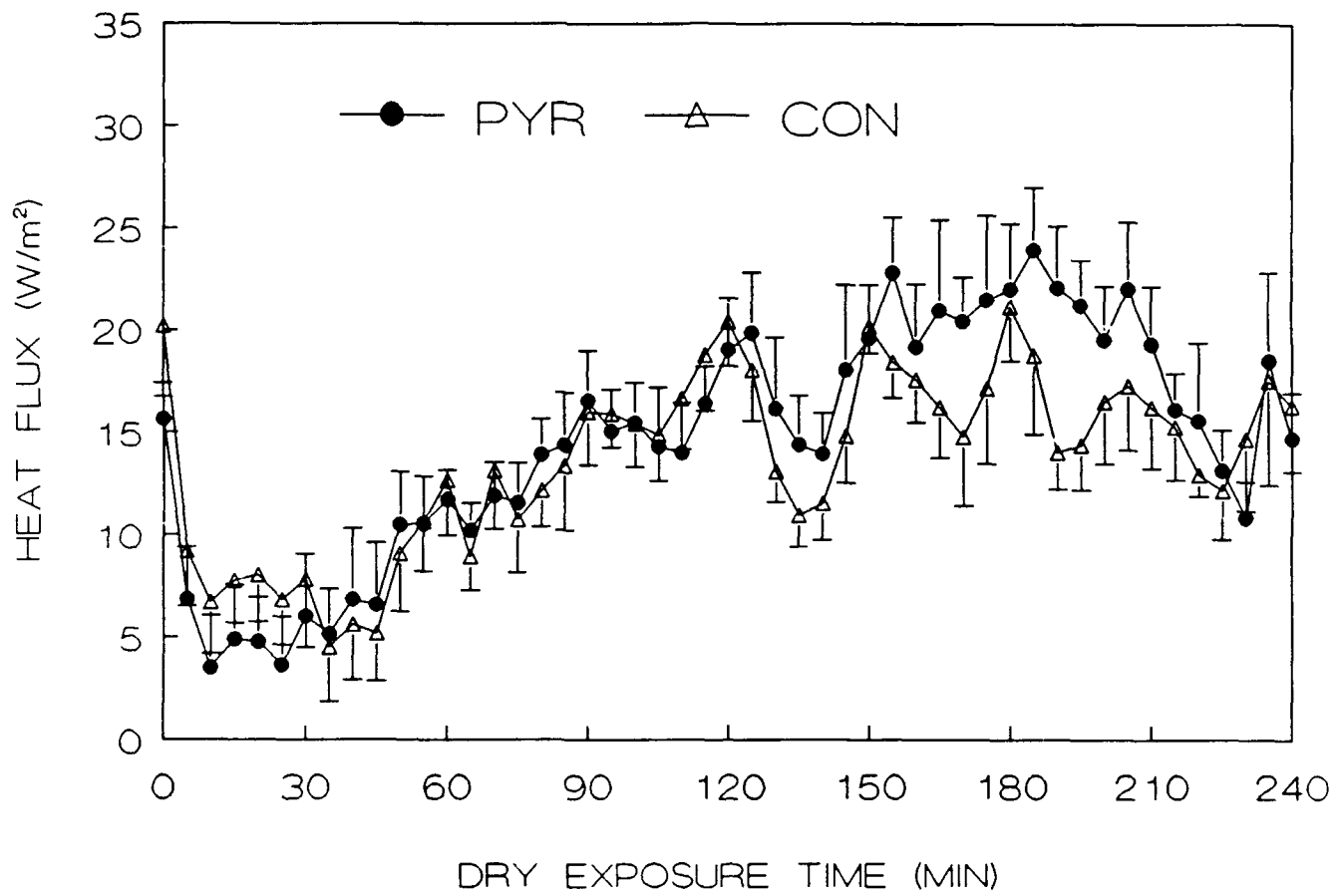
FIGURE 1

FIGURE 2

FIGURE 3

FIGURE 4

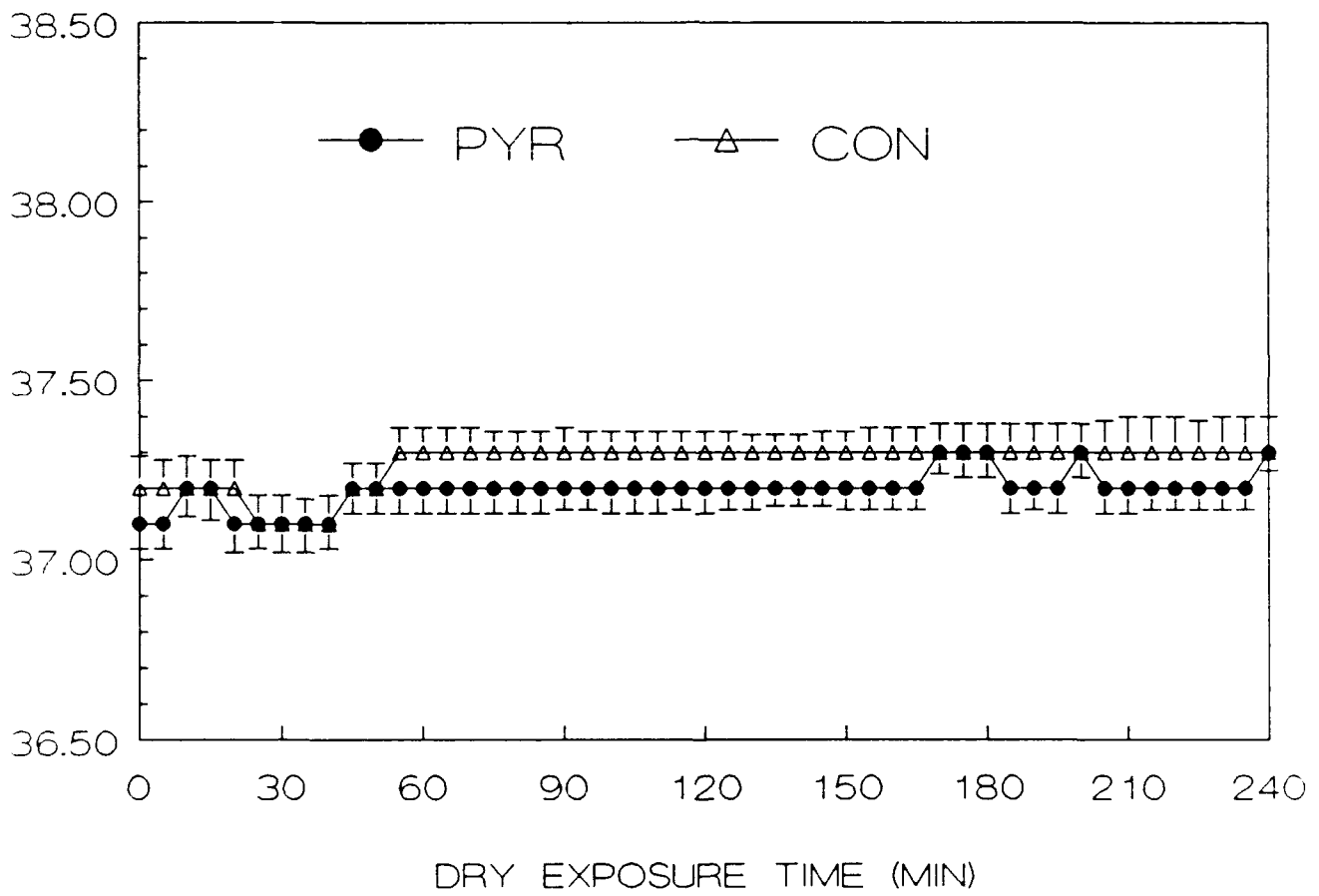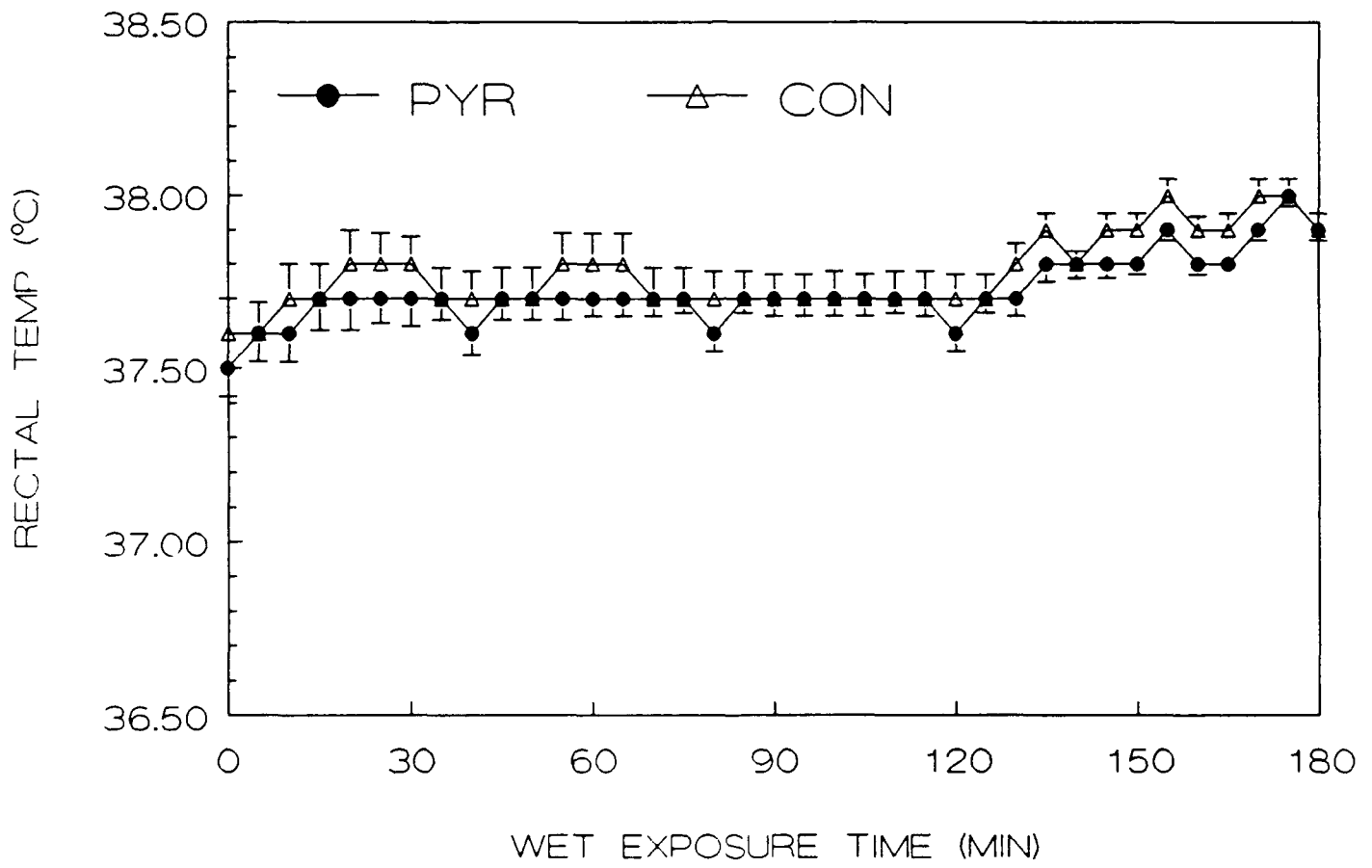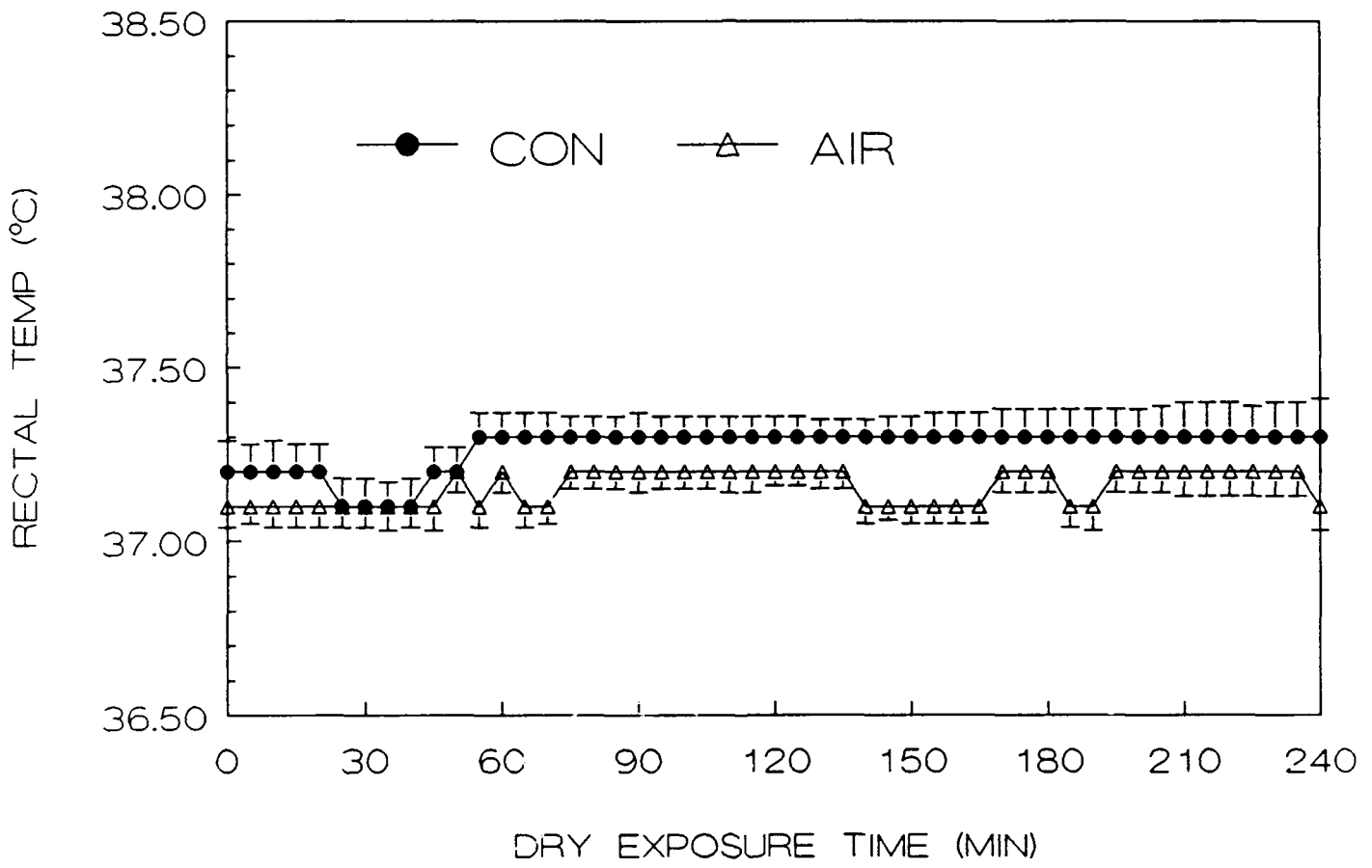Figure showing HEAT FLUX (W/m²) versus WET EXPOSURE TIME (MIN) with two series: CON (●) and AIR (△).
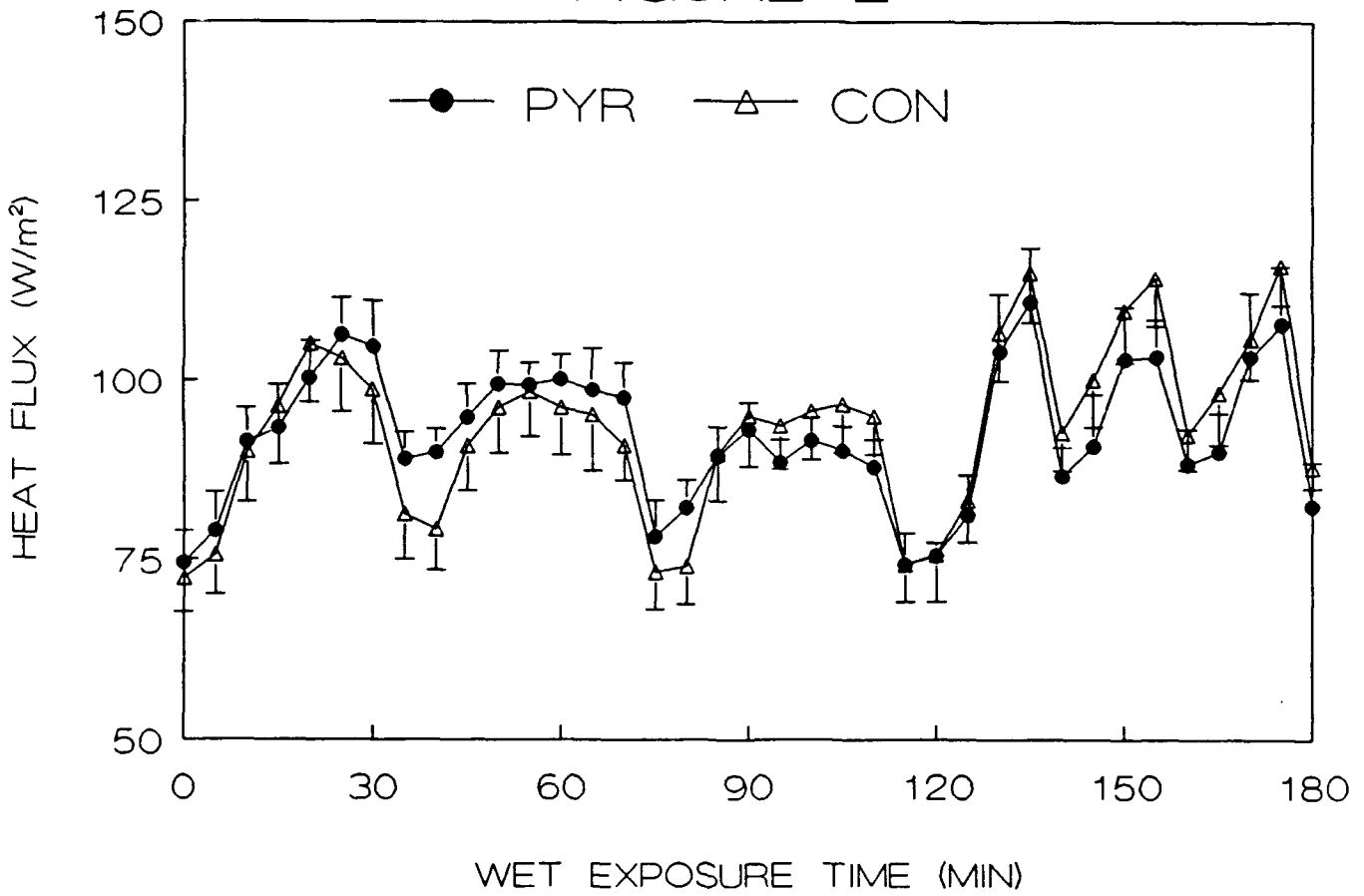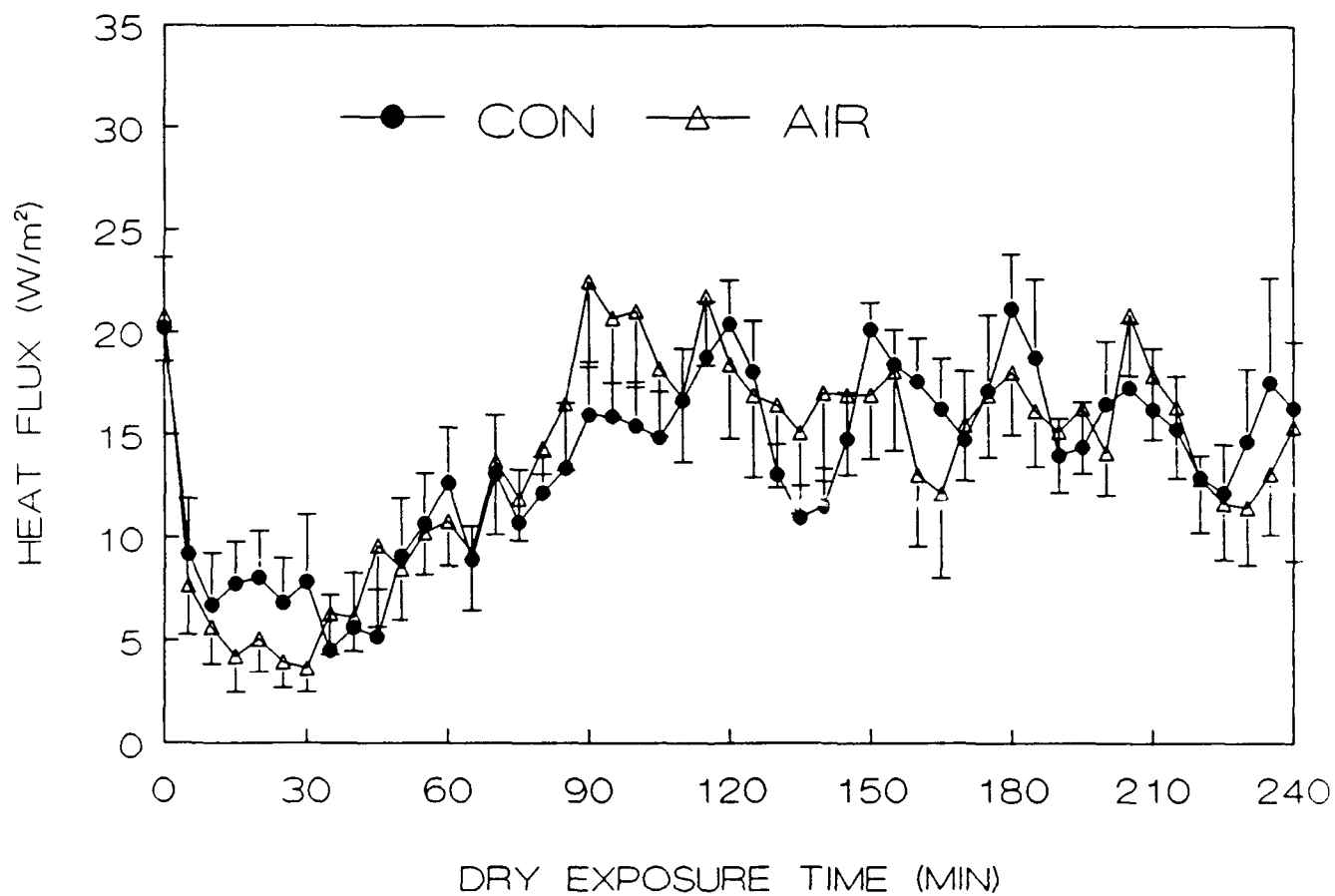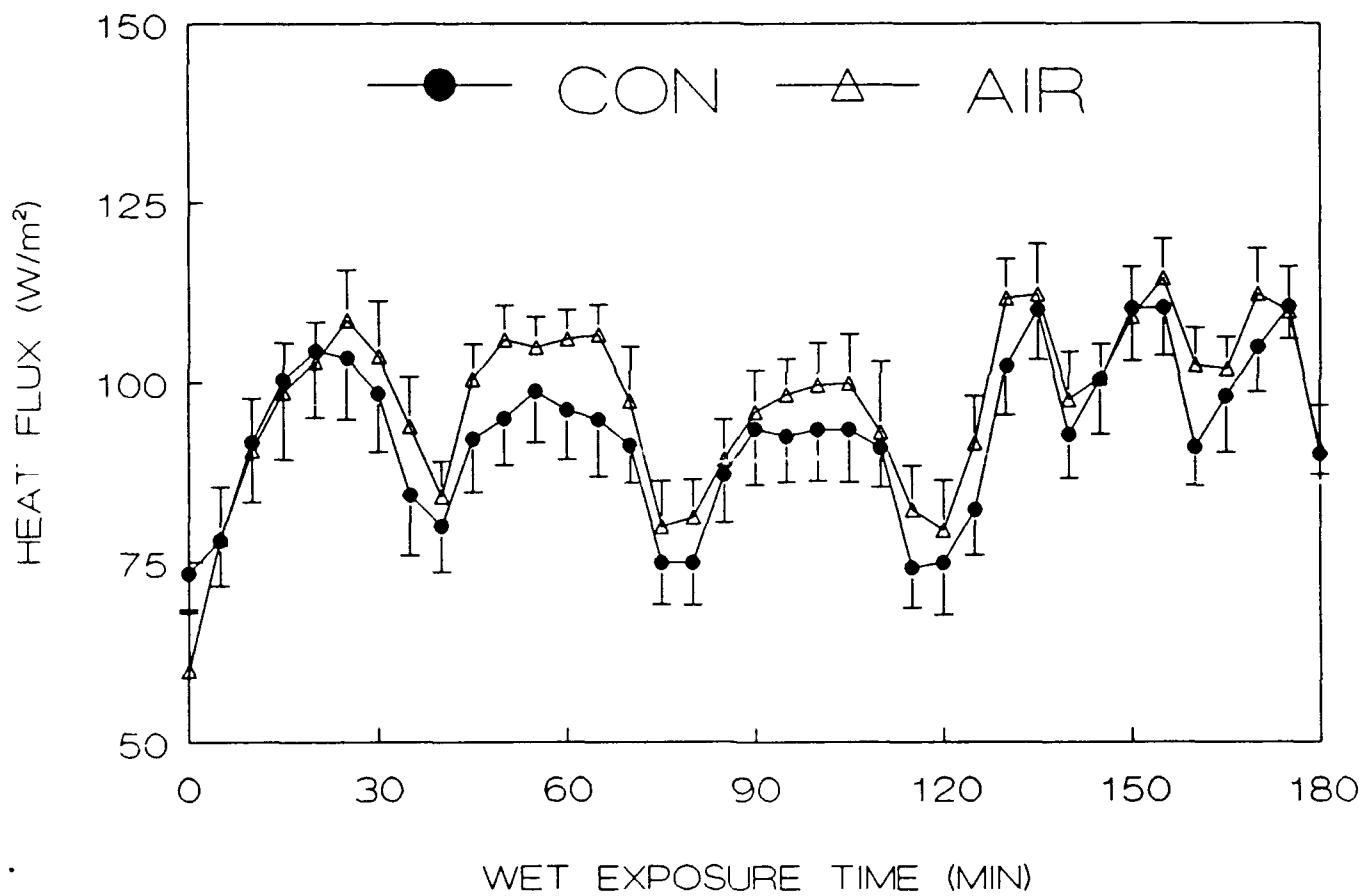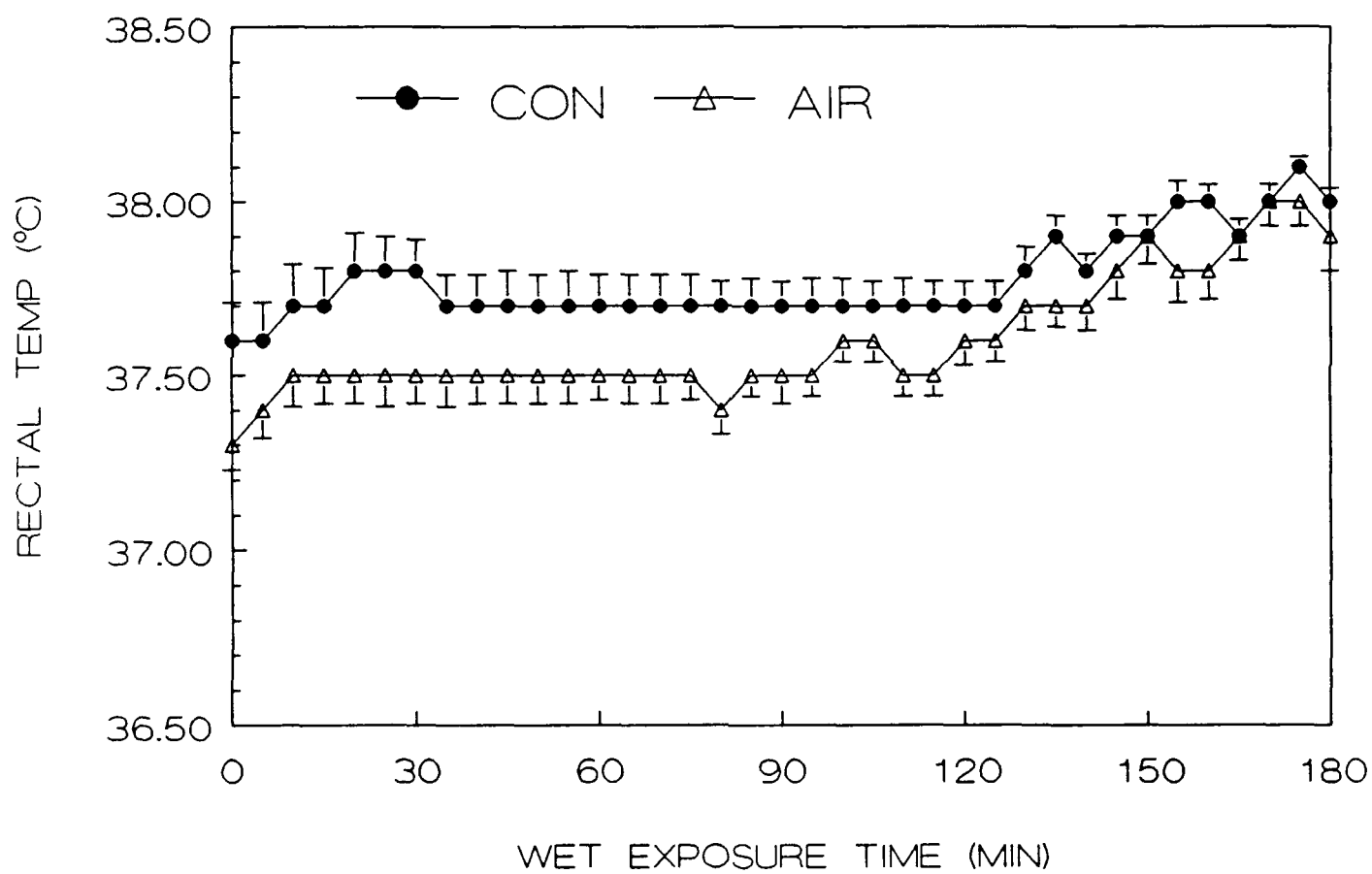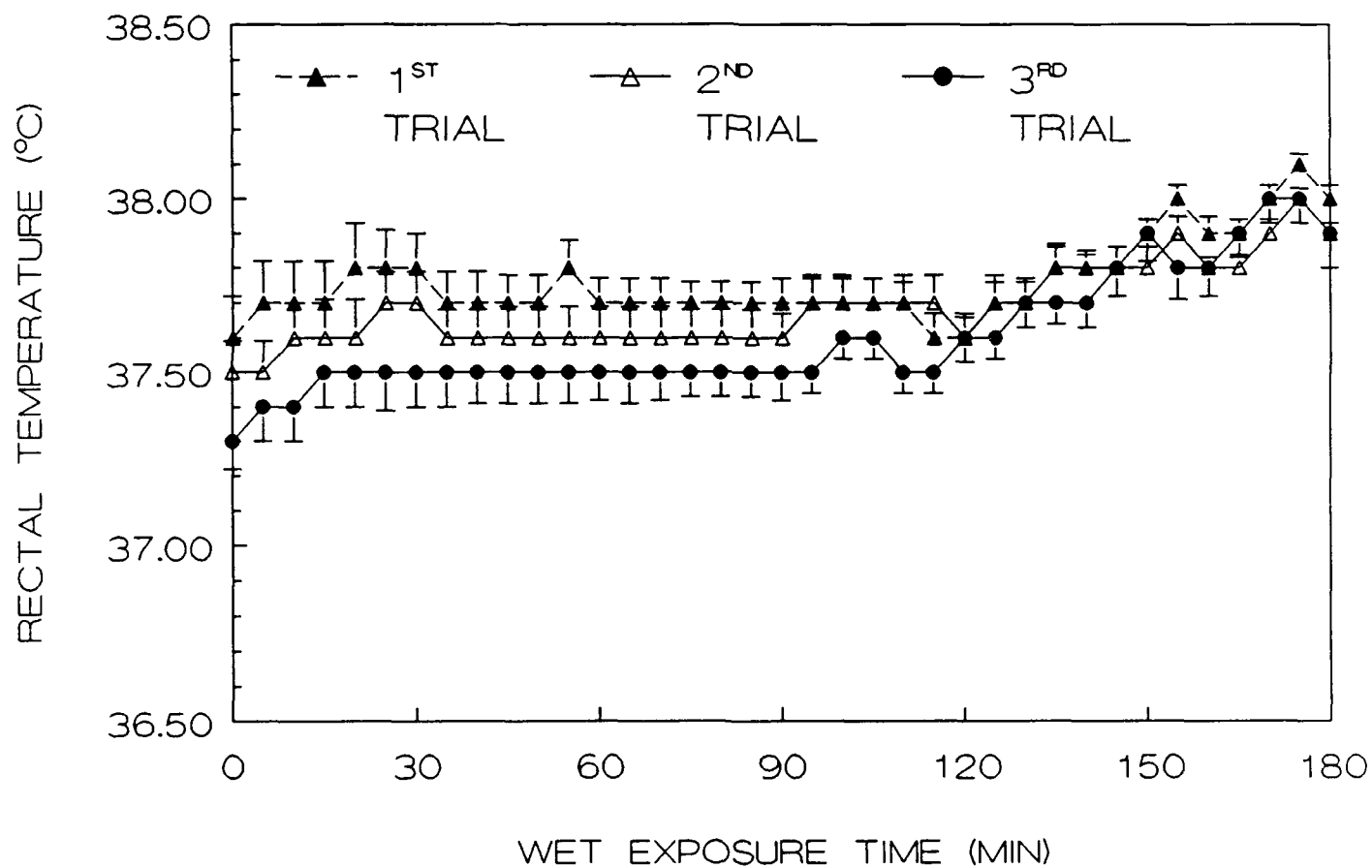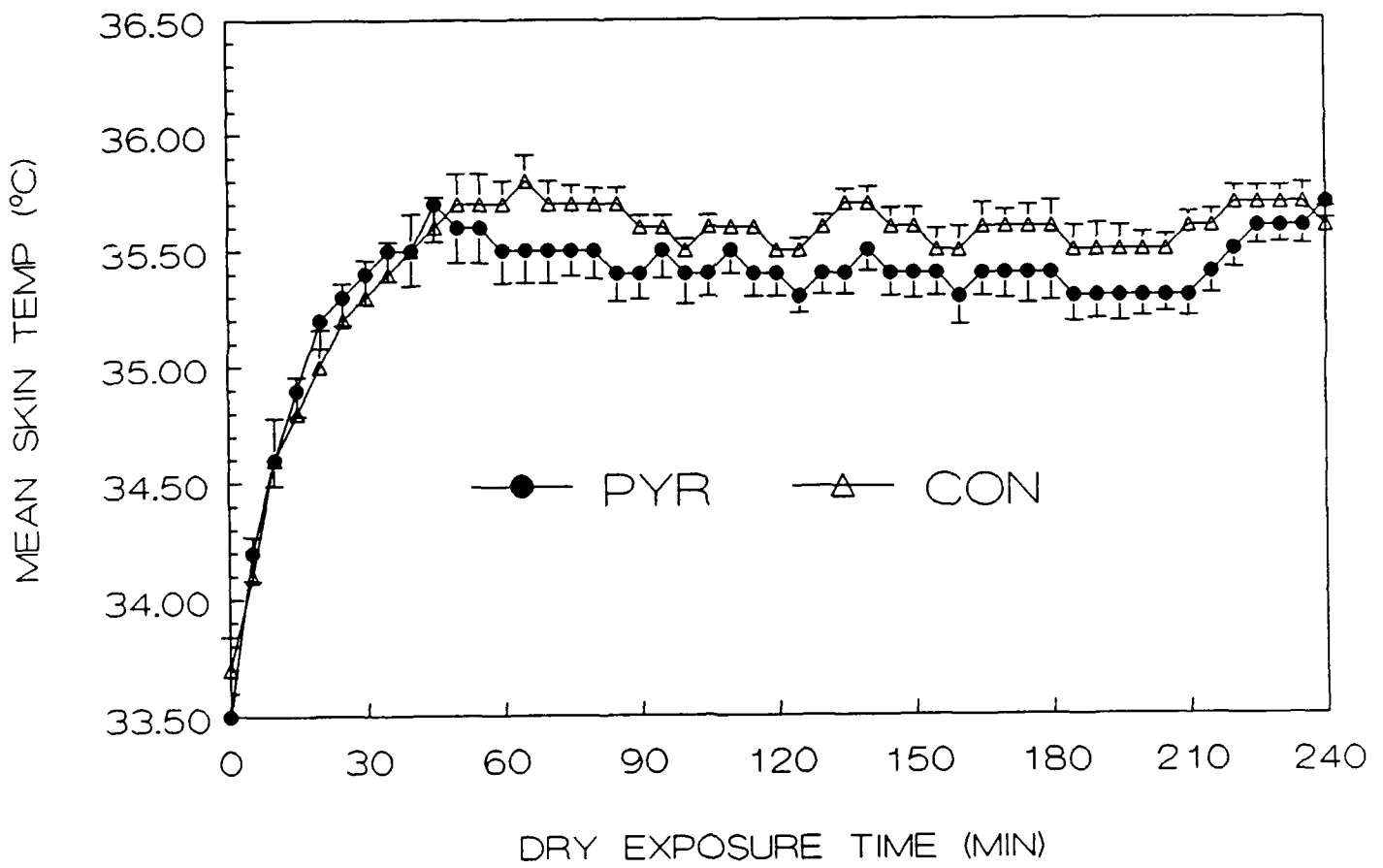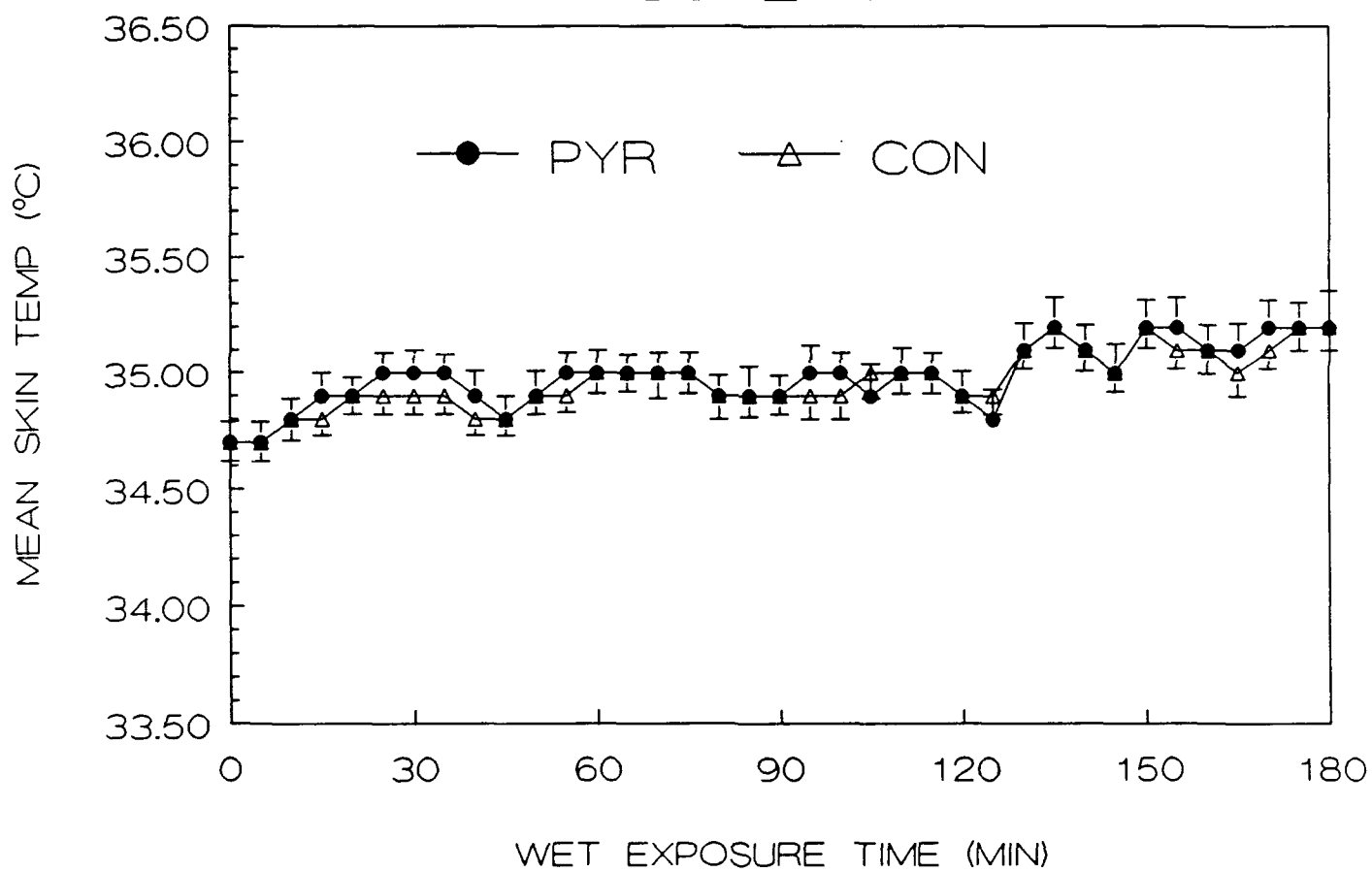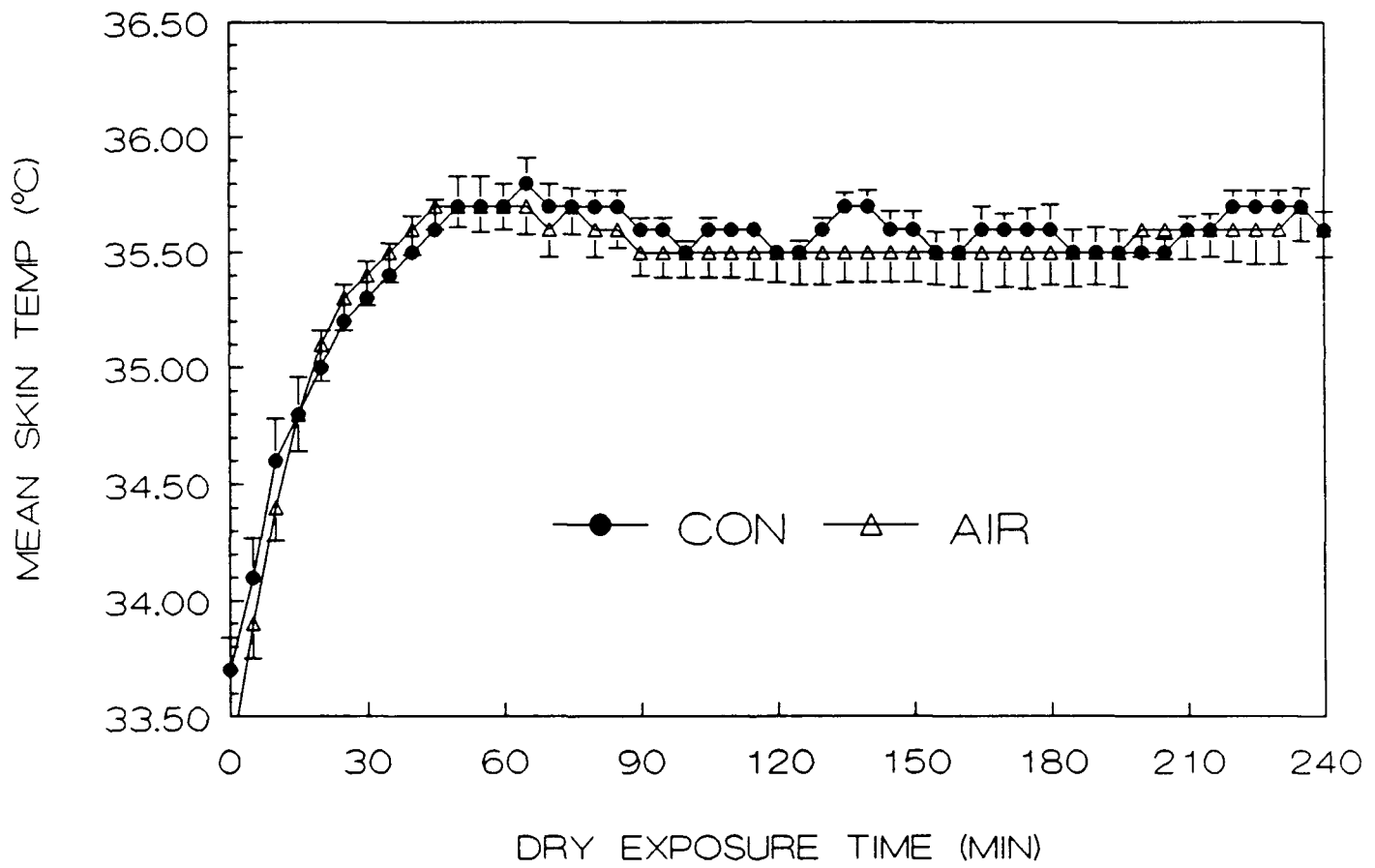
FIGURE 5

FIGURE 6

FIGURE 7

FIGURE 8

FIGURE 9

FIGURE 10

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FIGURE 11

FIGURE 12

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FIGURE 13

Y-axis: MEAN SKIN TEMP (°C), ranging from 33.50 to 36.50

X-axis: WET EXPOSURE TIME (MIN), ranging from 0 to 180

Legend: CON ● AIR △

FIGURE 14

FIGURE 15