An Applied Model for the Evaluation of Multiple Physiological Stressors

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Exercise Primates

Physiological Stress Thermoregulation

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An Applied Model for the Evaluation of Multiple Physiological Stressors

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CONSTABLE, S. H., C. J. SHERRY AND T. J. WALTERS. *An applied model for the evaluation of multiple physiological stressors.* NEUROSCI BIOBEHAV REV **15**(1) 115–121, 1991.—In everyday life, a human is likely to be exposed to the combined effects of a number of different stressors simultaneously. Consequently, if an applied model is to ultimately provide the best 'fit' between the modeling and modeled phenomena, it must be able to accommodate the evaluation of multiple stressors. Therefore, a multidimensional, primate model is described that can fully accommodate a large number of conceivably stressful, real life scenarios that may be encountered by civilian or military workers. A number of physiological measurements were made in female rhesus monkeys in order to validate the model against previous reports. These evaluations were further expanded to include the experimental perturbation of physical work (exercise). Physiological profiles during activity were extended with the incorporation of radio telemetry. In conclusion, this model allows maximal extrapolation of the potential deleterious or ergogenic effects on systemic physiological function under conditions of realistic operational demands and environments.

Animal model | Core temperature | Exercise | Extrapolation | Heart Rate | Oxygen consumption | Patas monkey | Physiological stressor | Primate exercise wheel | Rhesus monkey | Thermal balance

ANY number of biological/environmental stressors may be present during industrial or military operations. In certain real life scenarios, the wearing of individual protective equipment may be required. This may expose the individual to microclimate extremes that, when combined with the possibility of self directed or prescribed prophylactic/ergogenic pharmaceuticals, may further complicate the normal physiological response. Daily job performance and mission accomplishment are important measures of productivity, however personal health and safety are always of utmost concern. Therefore, the possible combined effects of these stressors on the individual(s) must ultimately be evaluated and quantified so that medical or environmental health advisors can, if necessary, either take optimum countermeasures or otherwise avoid the apparent risks. Because of uncertainty of the outcomes of some combined exposures, laboratory studies in humans may not always be practical, safe, or ethical. Therefore, human experimental subjects often cannot be used to obtain such information, so alternative approaches have been proposed. These include: a) analysis of clinical reports of accidental or unexpected exposures; b) use of mathematical or computer models; and c) the use of in vitro and in vivo animal models.

One of the ultimate goals of most animal models, whether in vitro or in vivo, is to extrapolate from animal findings to the human conditions that they are used to model. Many factors make extrapolation from these animal models to human conditions difficult, even when in vivo models are used. For example, scaling focuses on differences in size: a mouse is $\frac{1}{1000}$ the size of a man and takes 14 breaths for every single breath a man takes. Body heat flow and metabolism are likewise affected by differences in relative body surface areas, i.e., size. Scaling factors become especially important when one attempts to determine a 'safe' dose of a xenobiotic or a 'therapeutic' dose of a drug in an animal model and then extrapolate from the animal model to determine the appropriate dose in humans. Pharmacokinetic factors such as species specific differences in route/rate of absorption, tissue distribution (binding to plasma proteins, tissue compartments, etc.), metabolism, and route/rate of excretion also become important when evaluating drug effects in a model (6, 10, 17). These considerations make nonhuman primates an attractive selection to many investigators.

Rhesus and patas monkeys are qualitatively similar and both species possess arteriovenous anastomoses and sweat over the entire body (9,12). However, there are some quantitative differences between these two species of monkeys. The sweat glands of the patas monkeys are larger and the maximum amount of evaporative heat loss due to sweating is approximately 40% higher, which is closer to the sweat capacity observed in humans (9). Because of the higher sweat capacity and other similarities to humans, patas monkeys may be a more appropriate animal model of the human thermoregulatory system, particularly at ambient conditions at or above the upper limits of the thermal neutral zone of the animal. On the other hand, under the conditions of lower environmental stress, the rhesus monkey may be a more useful model because of the large behavioral, physiological, and pharmacolog-

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ical data base that is available for it (4).

Most modeling efforts, by their very nature, tend to focus on the effect of one independent variable on one or two dependent variables. But, in the everyday world, a human is likely to be exposed to the combined effects of a number of different stressors simultaneously. For example, if troops are under the threat of a nerve agent attack, they are usually forced to wear the chemical defense ensemble which includes a mask, overgarments and boots. When the environmental temperature exceeds 24°C, the effective temperature inside a chemical defense ensemble can reach 35°C or greater and the normal dissipation of body heat is greatly impaired. In addition to the effects of heat stress and the possibility of some contamination by very low doses of nerve agent, these individuals may also be exposed to a wide variety of pharmacological agents which have been either 'self directed' (caffeine, nicotine, over-the-counter drugs, alcohol, etc.) or prescribed (anticholinergics, antihistamines, tranquilizers, etc.). If an applied model is to provide the best 'fit' and allow robust and meaningful extrapolations, it must be able to support the evaluation of multiple stressors.

A Primate Exercise Wheel (PEW) system (7) is particularly well suited for these studies because it allows independent manipulation of physiological (e.g., exercise, drugs, training) and environmental (e.g., heat, cold) stressors, and can be adapted to evaluate physiological (heart rate, body temperature, etc.), as well as metabolic (oxygen consumption, carbon dioxide production, etc.) parameters. The basic task, walking or running above a threshold speed, is relatively easy to bring under stimulus control. It has been successfully used to evaluate the effects of exercise and chemical defense antidotes and prophylactics on the thermal balance of patas monkeys (2). Moreover, this approach can also be used to evaluate the effects of acclimation, hypobaria and physical fatigue on these variables and to determine what measures can be used to ameliorate the decrements in performance associated with exposure to physiological, environmental, or pharmacological stressors.

Therefore, a nonhuman primate model has been established that can fully accommodate a large number of stressful, real life scenarios that might be encountered by military or civilian workers. Relatively innocuous compounds (caffeine, antihistamines, alcohol, etc.) may even be of interest to study. Although it might be known, or highly expected, that the physiological effects of an individual stressor may be negligible at moderate exposure levels, there could be an additive or synergistic effect when combined with other potential stressors. Physiological monitoring, along with the measurement of work rate and capacity under adverse conditions, can be used to estimate the level of health risk or performance degradation that humans may encounter in similar scenarios. The most important aspect of this approach is that it should allow the best estimate of the potential deleterious effects on systemic physiological function under conditions of realistic operational demands and environments. Short of performing human experiments, there appears to be no better methodology available to make these important predictions of health and performance. This model is comprehensive, highly flexible, and an applied research resource that can make a unique contribution to the prediction of human physiological responses to multiple stressors.

METHOD

Animal Care

Six female rhesus monkeys (*Macaca mulatta*) weighing 3.98 ± 0.55 kg were housed individually in standard stainless steel monkey cages. The room temperature was maintained at 24 ± 2°C with a 12:12 hour light:dark cycle. The diet consisted of monkey chow supplemented with fresh fruit, with water available ad lib. The monkeys were fasted overnight prior to each experiment.

Surgical Procedures

In some experiments core temperature and heart rate were monitored with a telemeter (Mini-Mitter Physiotel amplifier-transmitter Model 270-0011) implanted intraperitoneally. After a surgical level of anesthesia was achieved (induction ketamine 10 mg/kg, IM; maintenance isoflurane) a small incision was made under sterile conditions near the ventral midline, over the abdominal cavity. An incision of ≈10 cm was then made through the abdominal muscles, along the linea alba, to accommodate the amplifier-transmitter package (≈5 cm in diameter, 0.5 cm thick). The two EKG leads were tunneled under the skin from the implantation site to a site above and lateral to the right nipple, and a second site slightly above the left iliac crest. The temperature probe was attached to the capsule of the left kidney. All incisions were closed with interrupted intradermal sutures and the monkey was provided with postoperative analgesia (butorphenol tartrate, 0.25 mg IM).

Resting Procedures

Each monkey was trained to sit quietly in a Plexiglas primate restraining chair by placing it in the chair for at least 2–4 hours per day for 10 days. Initially, the monkey was reinforced with small pieces of apple or other preferred food. By the end of the training period, the monkey normally stopped struggling and sat quietly.

Core temperature was measured by the telemeter temperature probe, as described above, as well as a probe inserted into the rectum approximately 10 cm from the anal sphincter and/or a probe inserted via a nostril into the esophagus to one of four different depths: 15, 17.5, 20, or 22.5 cm, as measured from the nasal flare. When esophageal temperatures were measured, the monkey was lightly anesthetized with ketamine (80–100 mg) to prevent the monkey from pulling the thermistor out. The relative placement of the esophageal and intra-abdominal thermistors, as well as the implanted telemeter and EKG sensors are shown on the radiograph in Fig. 1. Skin temperature was measured by thermistors attached to the inner thigh, chest, back, calf and tail.

Metabolic energy cost was determined by first drawing room air at a constant rate (4–5 l/min) through a Plexiglas hood enclosing the animal's head. The flow was adequate to ensure that no expired air can be blown out around the neck seal. FEO_2 and $FECO_2$ were measured downstream by a Perkin-Elmer 1100 Medical Gas Analyzer. The total airflow was measured using a Kurz 565-7A Mass Flowmeter. The metabolic parameters were calculated from VO_2, VCO_2, and respiratory quotient values, using the algorithm of Brown, Cole, Dauncey, Marrs and Murgatroyd (5), with all volumes and flows corrected to STPD.

Total evaporative heat loss was determined by weighing the animal before and after the experiment (including any urine and feces produced during the experiment). Respiratory water loss was determined by calculating the difference between the absolute humidities of the air entering and leaving the hood multiplied by the total airflow. Estimation of the humidity was done by employing two pairs of wet and dry bulb thermistors (11). The first pair monitored the absolute humidity of the ambient air flowing into the hood and the second pair, located downstream from the hood, monitored the absolute humidity of the air flowing out of the hood. Eccrine sweat rate was calculated as the difference between total evaporative heat loss and respiratory water loss.

Heart rate was obtained from two EKG leads implanted sub-

FIG. 1. A radiograph showing the placement of the telemeter unit, the EKG leads (the fine wires running along the chest), and the esophageal and intra-abdominal thermistors.

cutaneously, as described above, or alternatively from three standard disposable EKG electrodes, one attached to the chest at the level of the nipple and to both ankles. The EKG was recorded via a Hewlett-Packard Defibrillator (Model 43100A) and the heart rate was obtained from a locally built cardiotachometer.

The outputs of temperature probes, oxygen and carbon dioxide analyzers, and EKG cardiotachometer were connected via appropriate interfaces to National Instruments Multiple I/G Boards (NI-MIO-16L and NI-MIO-16H) in an Apple Macintosh II computer. These boards handled the analog to digital conversion of the signals. The data were conditioned, smoothed, and displayed on the computer screen (see Fig. 2) and stored into a computer file. Selected variables were printed on paper to provide a hard copy for analysis during the experiment. All data were collected, conditioned, and displayed under the control of a program written in LabVIEW graphical programming language, Version 2.0. Data reduction and statistical analysis were done off-line.

Exercise Procedures

Several investigators have attempted to use positive reinforcements (pellets and preferred fluids, respectively) to motivate exercise behavior (8,16). Using positive reinforcers causes two potential problems: 1) eating or drinking and swallowing may interfere with breathing and may limit the duration of exercise because of satiation; and 2) it may not be possible to obtain or maintain the desired level of physical exertion in food- or water-deprived animals.

Curren, Wiegel and Stevens (7) designed the Primate Exercise Wheel (PEW), which utilizes aversive stimuli (mild electric shock), which generally overcomes these problems. The wheel described here is a modification of Curren's wheel and was constructed of 3/4" Lucite plastic (Plexiglas) and 148 round aluminum bars which formed a circular cage, 48" in diameter and 17" wide, as shown in Fig. 3. The aluminum bars acted as a circular treadmill and provide the surface on which the monkey ran. They also functioned as a shocking grid to provide a negative reinforcement during the initial shaping and subsequent maintenance of the behavior (walking or running), using a free-operant (Sidman) avoidance paradigm with exteroceptive cues. These cues were provided by a pair of light bars mounted at each end of the wheel, a tone generator, and an overhead 'house' light. Each light bar was divided into three light panels (each 4" square), from left to right, colored red, green, and yellow (for the meaning of the lights, see below), respectively. The wheel was supplied with a mechanical friction brake, which prevents the monkey from operating the wheel faster than an upper, preset speed and stabilizes the wheel during rest periods.

Additional modifications in the PEW as described by Curren and his colleagues (7) were: 1) enlarging the light bar; 2) changing the 'meaning' of the light signals: (a) a green light indicated a work period (no tone); (b) a yellow light plus tone indicated an underspeed condition, where the animal must increase speed to avoid a mild shock; (c) light bar, lights off, house lights on indicated a rest period; and 3) monitoring the total distance traveled by the monkey, the number of grace periods (yellow light on) initiated, the cumulative grace period durations, and the number of shocks received in each work period and for the total session. Utilizing these changes in the present PEW along with appropriate behavioral shaping techniques, we were able to bring the monkey's behavior under stimulus control (that is, the monkey recognizes that a yellow light 'means' speed up and thus receives a minimum number of shocks) and train our monkeys to run at a minimum of 3.0 m.p.h. for six 10-min work periods interspersed with 1-min rest periods, within approximately 4 weeks.

A program written in LabVIEW graphical programming language, Version 2.0 and run on an Apple Macintosh IIX computer, allowed control of the exercise wheel by altering settings on the computer screen control panel (Fig. 4) for the minimum and maximum acceptable speeds, the number and duration of work and rest periods, the duration of grace period [e.g., the time between the onset of the underspeed signal (yellow light + tone)

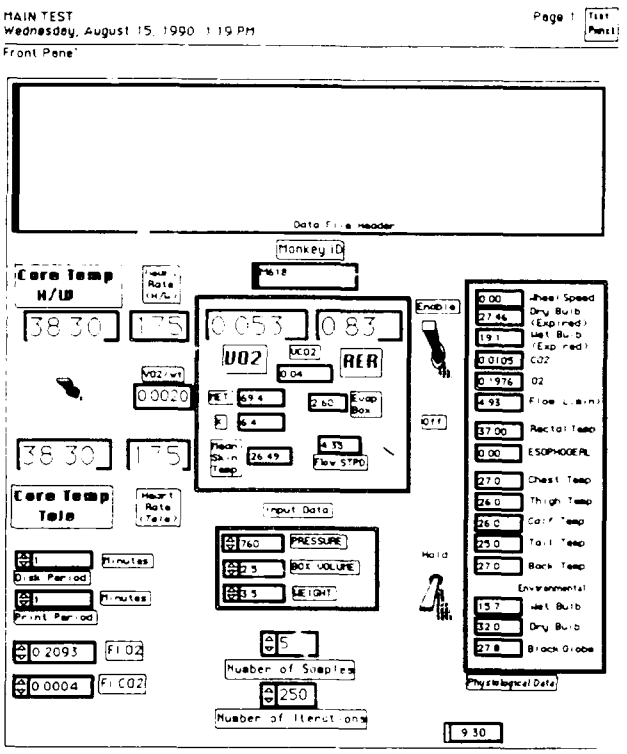

FIG. 2. The computer screen generated by a program written in LabVIEW graphical programming language showing the controls (toggle switches) that allow the experimenter to start data collection (Enable), choose between 'hard-wired' (H/W) or telemetered (Tele) heart rate and core temperature, and to stop data acquisition to replace leads, etc. (Halt). The lower left half of the screen contains experimenter entered variables, such as atmospheric pressure. The outputs of temperature probes, oxygen and carbon dioxide analyzers, and EKG cardiotachometer, after appropriate conditioning and smoothing, are shown in the box at the right side of the screen. Calculated variables based on this data are contained in the box in the middle of the screen. The data and results of the calculations are updated at intervals determined by the investigator.

and a mild shock], the duration of the shock, the frequency of the shocks, and the total number of sequential shocks. The monkeys rarely receive more than one or two sequential shocks (often a trained monkey did not receive any shocks or a maximum of 1 to 2 individual shocks during a one-hour training session). In the unlikely event that the monkey received the number of sequential shocks set on the controller, the computer automatically turned the program (and shocking capacity) off and turned the lights (and tones) on the light bar off and the house light on (thus indicating a rest period to the monkey). The computer beeped to signal the operator to manually turn the program back on. The monkey could not receive any shocks when the program was off. The intensity of the shocks was set on a separate controller.

The same program collected and displayed the speed of the wheel in m.p.h., the direction the wheel was turning, the distance covered, the number of grace period initiations, cumulative grace period duration, and the number of shocks in each work period and in the total session. The computer also collected the telemetered measurements, i.e., heart rate and core temperature, as described above. Metabolic energy cost was determined by drawing room air at a constant rate (30–40 l/min) through a large Plexiglas hood that enclosed the wheel and oxygen consumption and

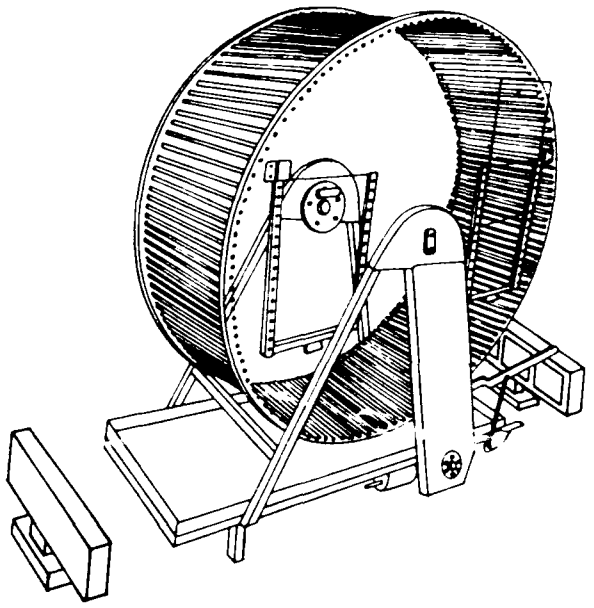

FIG. 3. The Primate Exercise Wheel (PEW). The light bars that provide exteroceptive cues are shown at either end of the wheel. The house light and sound generator that provide additional exteroceptive cues are not shown.

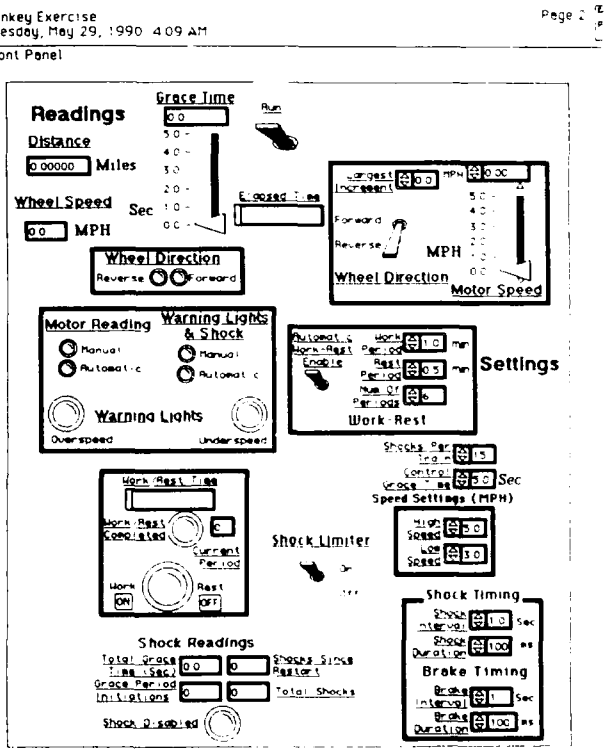

FIG. 4. The computer screen generated by a another LabVIEW program showing the controls that set the wheel parameters, such as minimum acceptable speed, are on the right half of the screen. Wheel variables, such as wheel speed, are on the left half of the screen.

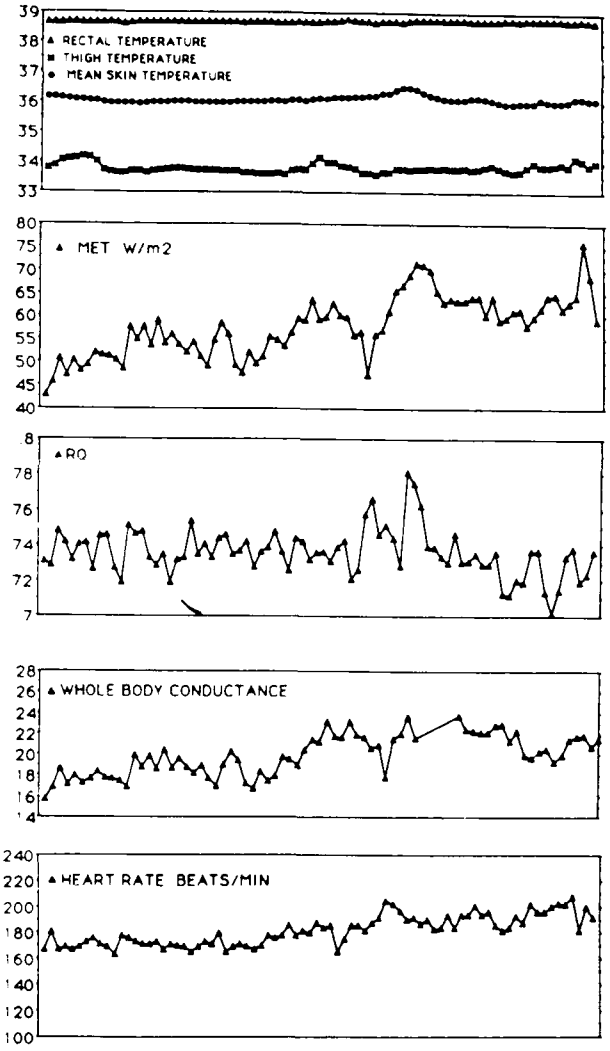

FIG. 5. Representative thermal, metabolic, and physiological responses of a young unacclimated female rhesus monkey at rest and equilibrated to 30°C across a 45-minute period.

carbon dioxide production, as well as flow rate were determined as described above. The wheel parameters (wheel speed, etc.), physiological, and metabolic variables were printed out both on paper to provide a hard copy for analysis during the course of the experiment and saved in a computer file for off-line analysis. Statistical comparisons among days of testing were examined using a repeated measures ANOVA.

Environmental Stressors

One other set of factors that can greatly affect physiological responses are the meteorological conditions that were present during operational exposure. Therefore a very important component of this model was the precise and consistent simulation of environmental conditions at the time of the experimental observations. This was accomplished by the use of well-insulated environmental chambers that had the capacity to both preheat and precool the ambient air which was then passed through the chamber interior. In this fashion both the ambient dry bulb temperature and absolute vapor pressure were controlled, that latter between 4 and 40 Torr. Under some conditions, heat lamps can be added as a source of radiant heat. The effective wind speed was normally kept low. In addition, the atmospheric pressure may be controlled over a broad range of selected experiments.

TABLE 1

	Females (n = 6)	Males* (n = 4)
Weight kg	3.98 ± 0.55	3.15–5.5
Core Temperature °C	38.6 ± 0.2	38.5 ± 0.2
Mean Skin Temp. °C	36.0 ± 0.9	35.5 ± 0.03
Metabolic Rate w/m²	54.3 ± 9.4	48.2 ± 2.4
VO^2 ml/min	45 ± 5	NR
Conductance w/m² °C	16.6 ± 3.1	15.3 ± 2.0
Heart Rate beats/min	171 ± 25	NR

*Based on adult male rhesus monkeys [Johnson and Elizondo (11)].

RESULTS

The typical thermal, metabolic, and physiological responses of a young unacclimated female rhesus monkey at rest and equilibrated to 30°C are shown in Fig. 5. In an attempt to partially validate our basic system, we compared our results with those obtained by Johnson and Elizondo (11) in adult, male rhesus monkeys under similar conditions. These comparisons are summarized in Table 1. No significant differences were observed between our responses and those reported by Johnson and Elizondo (11).

We also attempted to demonstrate the reliability of our system by making repeated observations from the same monkey under similar environmental conditions. The results of three separate experiments conducted over an 11-day time period (separated by 4 and 7 days, respectively) are shown in Table 2. A review of this table indicates that the monkey's metabolic and physiological responses were stable over time, as there were no statistically significant differences among the variables.

TABLE 2

	Day 1	Day 2	Day 3
Core Temperature °C	38.3 ± 0.03	38.9 ± 0.05	38.8 ± 0.05
Mean Skin Temperature °C	35.2 ± 0.12	36.1 ± 0.29	36.1 ± 0.15
Metabolic Rate w/m²	51.8 ± 3.5	59.9 ± 6.7	60.5 ± 5.7
VO^2 ml/min	45 ± 3	51 ± 6	52 ± 5
Conductance w/m² °C	21.9 ± 0.6	19.6 ± 2.7	21.2 ± 2.6
Heart Rate beats/min	188 ± 9	197 ± 8	195 ± 6

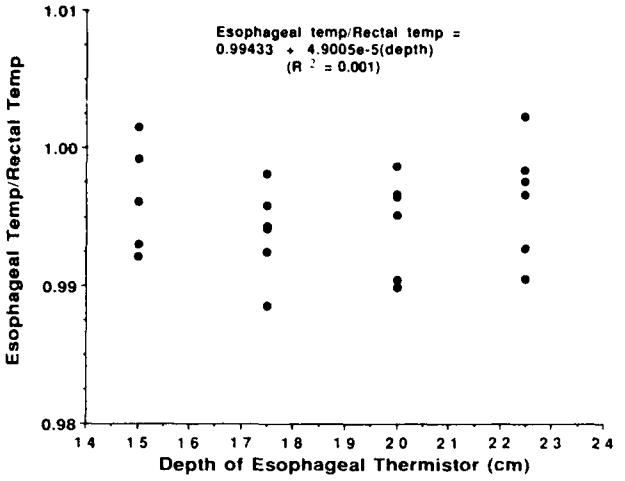

FIG. 6. The relationship between esophageal temperature and depth of thermistor placement. During these experiments it was necessary to lightly anesthetize the monkeys, as a result core temperature slowly declined during the testing period. In order to reduce this confounding influence on the comparison of esophageal temperature measurements at various depths with the rectal temperature, esophageal temperature was expressed relative to rectal temperature. Therefore a significant shift in this ratio from one depth to another would represent an influence of depth on esophageal temperature.

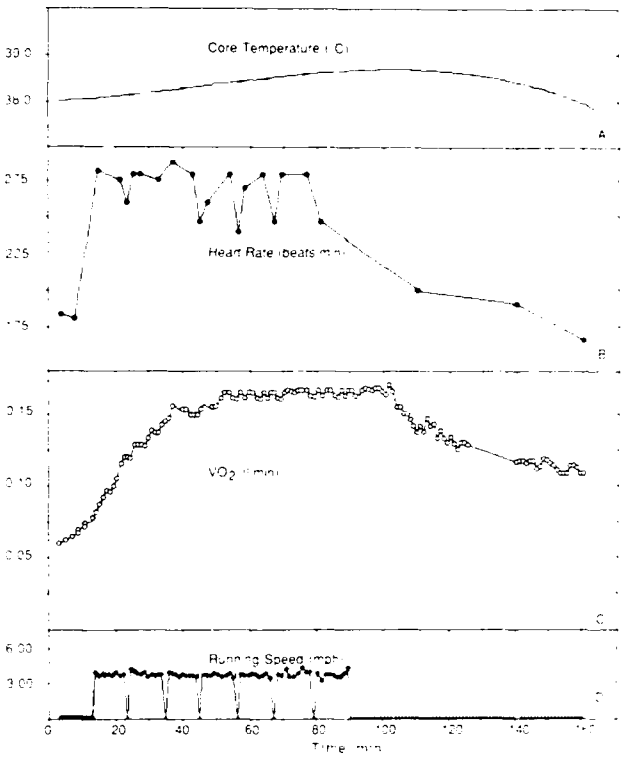

FIG. 8. (A–D) The effect of exercise on core temperature (A), heart rate (collected via telemeter) (B), and oxygen consumption (C). The speed of the PEW during the test is shown in 8D. Note that this exercise protocol involved a intermittent work/rest cycle of 10-min word/1-min rest. The average speed (during work) for this trial was 3.5 m.p.h.

Esophageal and rectal temperatures are often considered good estimates of body core temperature (15). Figure 6 shows that no physiologically significant differences were found between the various thermistor depths. Therefore all esophageal temperature measurements were included for the comparison with their respective rectal and intraabdominal temperatures. As shown in Fig. 7, there are strong positive correlations between core temperatures as measured by the esophageal probe and the rectal probe or the telemeter probe with the rectal probe. Moreover, absolute differences between any of these three indices of body core temperature are quite small.

Physical work significantly increases the basal metabolic rate of the organism. The effect of exercise (10-min work ≈3.5 m.p.h., with 1-min rest periods) on core temperature, oxygen consumption, and heart rate is shown in Fig. 8A–C, while

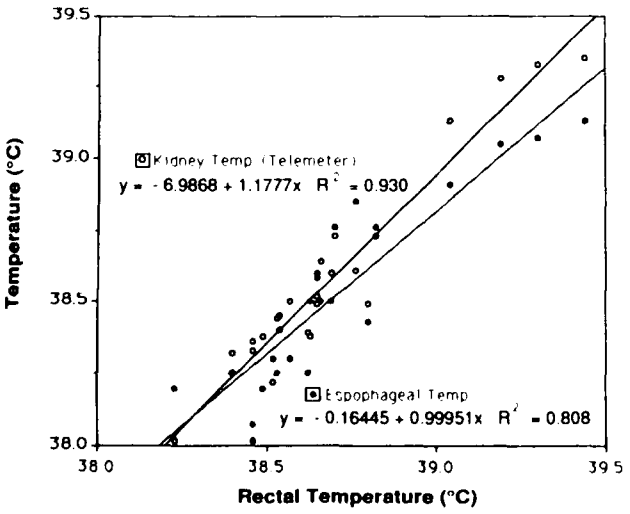

FIG. 7. The relationship between core temperature as measured by the esophageal probe, and the telemeter intraabdominal probe (located on the kidney capsule), versus rectal temperature.

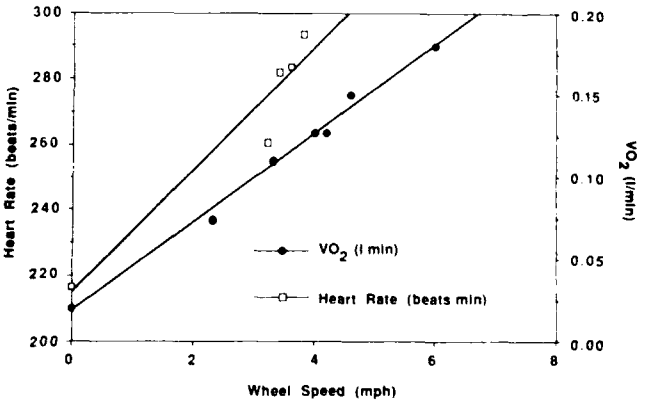

FIG. 9. The relationship between heart rate and oxygen consumption versus wheel speed. These relationships are qualitatively similar to those that would be obtained from human subjects under similar conditions. The slow response time until the achievement of steady state oxygen consumption is primarily a result of the large wheel canopy dead space volume.

TABLE 3

TYPICAL PHYSIOLOGICAL MEASUREMENTS MADE DURING ONE HOUR OF STEADY-STATE RUNNING IN THE PEW

Wheel Speed (m.p.h.)	Core Temp. (°C)	VO^2 (ml/min)	Heart Rate beats/min
3.44	39.93	161	268
(0.23)	(0.28)	(18)	(10)

The data represents the combined mean values (± SD) from eight trials.

Fig. 8D shows the relative consistency of wheel speed. The expected relationship between wheel speed (8D), core temperature (8A), and heart rate (8B) is demonstrated. For example, the transition from rest to running resulted in an increase in heart rate of ≈100 beats/minute (Fig. 8B). Moreover, with successive increases in submaximal steady-state workload, there is a linear increase in the metabolic responses. The relationship between wheel speed with oxygen consumption and heart rate are shown in Fig. 9. Finally, Table 3 summarizes the mean physiological responses to moderate exercise in juvenile, female monkeys.

DISCUSSION

The first step in developing a nonhuman primate model whose responses can be extrapolated to humans is to demonstrate that the model is valid (it measures what it purports to measure) and reliable (that the responses of the model, in the absence of perturbations, are consistent over time). We have demonstrated that the results obtained with our model are similar to both those obtained by Johnson and Elizondo (11) under resting conditions (see Table 1) and within the physiological ranges reported elsewhere in the literature (4). A strong positive relationship between our three measures of core temperature (Fig. 7) is also demonstrated. Along with the findings noted in Fig. 6, this provides evidence supporting the validity of using telemetered core temperature measurements. Further, we have demonstrated that the responses obtained during work are consistent with basic principles of exercise physiology, i.e., where changes in heart rate and oxygen consumption show a strong positive relationship with wheel speed (see Fig. 9). In fact, the heart rate responses observed in the present study during exercise are of similar magnitudes to those obtained by investigators using either, a treadmill (13), a primate rowing machine (8), or a bicycle ergometer (16) and our temperature changes were also similar to those obtained by others (2,8). These relationships are qualitatively similar to the relationship between running speed with heart rate and oxygen consumption as observed in humans (1).

It should be noted in Fig. 8C that there is a significant washout period required prior to reaching steady-state oxygen consumption. This is because of the inherently large dead space volume of the wheel canopy (1652 l) and the relatively small tidal volume of the monkeys. However, better than 90% of the steady-state response can be observed within 30 min of the initiation of exercise. Reports of metabolic rates in exercising primates are scarce. Mahoney (14) reported similar metabolic rates in a young patas monkey running on a conventional treadmill at a speed similar to those reported here. Avlonitou and Elizondo observed a doubling of the metabolic rate in patas monkeys while performing in a similar PEW at ≈2 m.p.h. (personal communication).

Curran et al. (7) found that a speed of approximately 3.2 m.p.h. could be maintained over six consecutive 10-minute exercise bouts, provided they were followed by five-min rest periods. We have shown that the rest periods can be easily reduced to one minute with no reduction in work rate (speed).

Based on the data gathered at this time, this approach appears to be valid and reliable. It should afford opportunities to obtain insights into the physiological effects of a host of environmental, toxicological and pharmacological stressors. Given the nature of the physical and environmental stressors that can be imposed, it should also prove to be a valuable model for the performance of studies that can provide data which can be used to predict responses in humans.

NOTE ADDED IN PROOF

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 Animal Resources* – National Research Council.

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