Tolazoline Decreases Survival Time During Microwave-Induced Lethal Heat Stress in Anesthetized Rats (43966)

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Abstract. **Effects of α-adrenergic antagonists have been studied during environmental heating but not during microwave-induced heating. Tolazoline may exert some of its effects via α-adrenergic blockade. In the present study, ketamine-anesthetized Sprague-Dawley rats were exposed to 2450-MHz microwaves at an average power density of 60 mW/cm^2 (whole-body specific absorption rate of approximately 14 W/kg) until lethal temperatures were attained. The effects of tolazoline (10 mg/kg body weight) on physiological responses (including changes in body temperature, heart rate, blood pressure, and respiratory rate) were examined. Survival time was significantly shorter in the tolazoline group than in saline-treated animals. In general, heart rate and blood pressure responses were similar to those that occur during environmental heat stress. Heart rate, however, was significantly elevated in animals that received tolazoline, both before and during terminal microwave exposure. It is possible that changes associated with the elevated heart rate (e.g., less cardiac filling) in tolazoline-treated animals resulted in greater susceptibility to microwave-induced heating and the lower survival time.** [P.S.E.B.M. 1996, Vol 211]

A better understanding of the processes involved in lethality due to heating and of the detrimental or beneficial effects of drugs on heat tolerance continue to be high priorities for research. Damanhouri and Tayeb (1) noted that most reports of heatstroke describe events occurring in late stages of the disorder, and, therefore, do not address what happens during the development of the syndrome. These investigators have stressed the need for the continued use of new animal models. Since an increase in body temperature is a primary effect of exposure to high levels of microwave radiation (MW), it may be advantageously used as a tool to study biological responses (particularly of the cardiovascular system) to heating, as discussed previously (2, 3).

The value of the anesthetized rat as a model for studying heat stress responses has been addressed by Kregel *et al.* (4) and Jauchem and Frei (3). Kregel and Gisolfi (5) have presented a comprehensive description of cardiovascular and peripheral vascular responses to environmentally induced hyperthermia in the rat, and we have extensively studied the cardiovascular and respiratory changes associated with thermalizing MW exposure (e.g., the most recent study is Ref. 3). In general, cardiovascular and respiratory changes that occur during environmental heating and MW-induced heating seem to be similar. Differences in thermal gradients within the body resulting from the two types of heating, however, may lead to quantitative differences in the magnitude of changes (2).

Homeostatic changes that occur during acute heat exposure, particularly adjustments in blood pressure and vascular resistance, are associated with activity of the sympathetic nervous system (6). Objective data relating to the effect of adrenergic receptor blockers on thermoregulatory responses to environmental heat-

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ing (or to exercise resulting in excessive metabolic heat production) are incomplete and often conflicting. Some of our earlier studies revealed effects of adrenergic antagonists and other agents on responses to MW-induced heating (3, 7–10). This area of research has been reviewed previously (11). During terminal exposure of rats to 2450-MHz (3) or 2800-MHz MW (7) (60 mW/cm^2; whole-body average specific absorption rate, 14 W/kg), β-adrenergic antagonism with propranolol (5–10 mg/kg) resulted in significantly decreased survival times and lethal colonic temperatures, compared with saline-treated animals. Heart rate (HR) and mean arterial blood pressure (MAP) changes were similar to those that occur during environmental heat stress. In the 2450-MHz study (3), respiratory rate was significantly elevated during most of the exposure period in the propranolol-treated animals (10 mg/kg) compared with saline controls. In the 2800-MHz study (7), a decrease in MAP that occurred immediately prior to death was significantly greater in animals treated with propranolol (5 mg/kg) than in saline-treated animals.

Tolazoline is an imidazoline α-adrenergic antagonist, with several possible modes of action. Although the agent has sometimes been considered a selective (12, 13) or "semiselective" (14) α_2 antagonist, or a selective α_{2A} antagonist (15), other studies have shown that tolazoline has a similar affinity for α_1 and α_2 adrenergic receptors (16). Tolazoline stimulates histamine receptors, and may also produce vasodilation due to a direct action on vascular smooth muscle, independent of any α-adrenergic antagonism. Other actions of the agent on imidazoline receptors have been reported by Miralles *et al.* (17).

In different studies, administration of α-adrenergic agonists have been reported to produce either hyperthermia (18) or hypothermia (19) in rodents. α-Adrenergic antagonists, including tolazoline, attenuated or prevented these responses.

Tolazoline can also affect the cardiovascular and respiratory systems. For example, when administered to sheep, tolazoline (2 mg/kg) attenuated the bradycardia and tachypnea caused by xylazine (20). Tolazoline also caused tachycardia in a wide variety of species, at doses ranging from 1 to 6 mg/kg (21–26). On the basis of our previous studies, possible associations of cardiovascular and respiratory changes with body temperature changes during MW exposure are of interest.

Behavioral thermoregulation, which is effective in conscious animals, has been extensively investigated in the laboratory rat, including studies involving MW exposure. Autonomic thermoregulatory responses in anesthetized rats, however, have been investigated less thoroughly. The purpose of this study was to examine effects of tolazoline on HR, MAP, respiratory rate, localized body temperature changes, survival times, and lethal body temperatures that occur during exposure of anesthetized rats to 2450-MHz MW.

Materials and Methods

Animals. Twenty-three male Sprague-Dawley CD-VAF/Plus rats (Charles River Laboratories, Wilmington, MA), weighing between 325 and 370 g (mean ± SEM, 357 ± 3 g) were used in this study. 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. Formal approval was received from the Armstrong Laboratory Animal Use Committee to perform these studies. Prior to experimentation, animals were housed in polycarbonate cages with free access to food and water, and maintained on a 12:12-hr light:dark cycle (lights on at 0600) in a climatically controlled environment (ambient temperature 24° ± 1°C).

Animals were fasted for 18 hr (water ad libitum) prior to experimentation. Ketamine HCl (Vetalar, Parke-Davis and Company, Detroit, MI), 150 mg/kg im, was administered as a general anesthetic, with supplemental doses provided as necessary during experimentation. Administration of ketamine at approximately this dose provides adequate anesthesia in Sprague-Dawley rats, and results in a stable animal preparation compatible with physiological monitoring (27). Although ketamine can markedly attenuate contractile responses of vascular smooth muscle *in vitro* (28), the anesthetic has minimal effects on temperature regulation in rats (29), and is known for its absence of serious autonomic, respiratory, or cardiovascular effects *in vivo*. Other aspects of ketamine that are pertinent to the present experiments have been discussed previously (3).

The left carotid artery was catheterized for measurement of MAP and to provide an injection route for administration of drugs. The tip of the catheter was positioned at the junction of the aorta. Immediately after surgery, the animal was placed on a holder in the MW exposure chamber. The holder consisted of seven 0.5-cm (o.d.) Plexiglas rods mounted in a semicircular pattern on 4 × 6–cm Plexiglas plates (0.5-cm thick). The catheter was attached to a pre-calibrated blood pressure transducer (Century CP-01) that was interfaced with a pressure processor (Gould 13-4615-52) to give permanent records via a Gould 2600S recorder. To determine HR, a lead II ECG was obtained by use of nylon-covered fluorocarbon leads attached to shielded cables outside the MW field. Respiratory rate was monitored by a pneumatic transduction method employing a piezoelectric pressure transducer (Model 320-0102-B; Narco Biosystems, Houston, TX). A de-

tailed description of these techniques has been reported previously (30).

Temperature of each rat was monitored at four sites: (i) colonic (5–6 cm post-anus); (ii) left subcutaneous (lateral, midthoracic, side facing the antenna); (iii) right subcutaneous (lateral, midthoracic, side away from MW source); and (iv) tail. The tip of the tail probe was inserted under the skin approximately 2 cm from the base of the tail. The temperatures were monitored with BSD thermistor probes, which were attached to a BSD-200 Precision Thermometry System (BSD Medical Corporation, Salt Lake City, UT) to obtain continuous (12-sec sampling interval) temperature readings.

MW Equipment. The continuous-wave MW fields were produced by a model 1325 MW power source (Cober Electronics, Inc., Stamford, CT,) and transmitted by a Model 644 antenna (Narda Microwave Corporation, Hauppauge, NY). The exposures were performed under far-field conditions (animal positioned on boresight 115 cm from antenna); the incident power of the field was determined with an electromagnetic radiation monitor (Model 8616; Narda Microwave Corp.), employing a Model 8623 probe. During exposures, the generator power was monitored constantly with a model 432-B power meter (Hewlett-Packard, Palo Alto, CA). Irradiation was conducted in an Eccosorb MW-shielded anechoic chamber (Rantec; Emerson Electric Co., Calabasas, CA). The temperature and relative humidity in the chamber were held constant for all experiments (27° ± 0.5°C, 20% ± 5% RH).

Exposure Conditions. The animals were exposed individually, in H orientation (left lateral exposure, long axis of body parallel to magnetic field), to far-field 2450-MHz continuous-wave MW (average power density of 60 mW/cm^2). This exposure resulted in a whole-body average specific absorption rate of 14 W/kg, determined calorimetrically by methods reported previously (31). Because each animal would be expected to exhibit a different starting colonic temperature (T_c), an initial MW exposure was performed to increase T_c to a standard level—in this case, 39.5°C. This temperature was selected for several reasons. Our previous studies had shown that responses to MW exposure are more stable and reproducible at T_c of 38.5°C and above. When T_c reached 39.5°C, MW exposure was temporarily halted, allowing personnel access to the exposure chamber to administer the antagonist. Injecting the drug during the T_c drop from 39.5° to 38.5°C allowed for initiation of blockade before starting the final lethal exposure to MW at 38.5°C.

After T_c had reached 39.5°C, tolazoline hydrochloride (Priscoline, 10 mg/kg; Ciba, Summit, NJ), prepared in 0.9% saline, was administered intra-arterially at a volume of 2.0 ml/kg body wt (followed by enough saline to flush the total injection volume and refill the catheter space) (n = 9). This dose of tolazoline has been shown to affect body temperature in the rat (18, 32). Although tolazoline can antagonize xylazine-ketamine anesthesia, the antagonism is due to reducing the effects of xylazine rather than ketamine (33). One series of control animals received an identical volume of saline (n = 14). After T_c returned to 38.5°C, exposure to MW was performed until a lethal temperature was attained. (The lethal event in hyperthermia due to both MW [3] and environmental heating [34] is cessation of respiration). Survival times and temperatures at which death occurred were recorded. Since this study focused on thermoregulation, the physiological data (T_c, tympanic, and subcutaneous temperatures, HR, MAP, and respiratory rate) were plotted as a function of temperature change rather than duration of exposure.

Statistical Analysis. Data are presented as the group mean ± SEM. For comparisons of temperatures and survival times, Student's t test for unpaired data was applied to determine if there were significant differences between group means obtained in the tolazoline- and saline-treated groups. Since comparisons between groups were also of primary interest regarding HR, MAP, and respiratory rate, Student's t test for unpaired data was also applied for analyses of these data. For these tests, however, a Bonferroni correction factor for multiple comparisons was used. (Since there were several different periods of exposure or nonexposure [i.e., MW power on versus MW power off] rather than a continuous time course, repeated-measures analyses of variance were not considered appropriate.) A P value of less than 0.05 was considered to indicate significance in all cases.

Results

The times required for T_c to decrease from 39.5° to 38.5°C following drug administration in each group were (mean ± SEM): saline (n = 14), 24.7 ± 1.2 min; and tolazoline (n = 9), 19.1 ± 2.0 min. The T_c at which respiration ceased (lethal T_c), survival times (time from T_c of 38.5°C until death), and rates of increase in T_c are shown in Table I. Survival time in the tolazoline group was significantly less than that in the saline group. The rate of temperature rise in the tolazoline group was significantly greater than the rate in the saline group.

Initial (at the beginning of terminal exposure) and terminal (at time of death) values of tail and right and left subcutaneous temperatures are given in Table II. When comparing the different groups of animals, there were no significant differences in initial or terminal temperatures at any given site.

HR changes, recorded each 0.5° of T_c change, are illustrated in Figure 1. HR increased in each group

Table I. Lethal Colonic Temperatures, Survival Times, and Heating Rates of Rats Exposed to 2450-MHz Microwaves

	Lethal colonic temperature (°C)	Survival time (min)	Rate of colonic temperature increase (°C/min)
Saline (n = 14)	44.2 ± 0.1	33.9 ± 0.6 [a]	0.17 ± 0.005 [a]
Tolazoline (n = 9)	44.1 ± 0.2	29.3 ± 1.7	0.19 ± 0.004

Note. Values are expressed as mean ± SEM.
[a] Values between groups significantly different at $P < 0.05$.

Table II. Initial and Terminal Temperatures of Rats Exposed to 2450-MHz Microwaves

	Tail		Left subcutaneous		Right subcutaneous	
	Initial	Terminal	Initial	Terminal	Initial	Terminal
Saline	29.8 ± 0.7	35.4 ± 0.7	37.8 ± 0.2	44.1 ± 0.2	38.1 ± 0.2	42.8 ± 0.2
Tolazoline	32.1 ± 1.0	36.1 ± 1.3	38.0 ± 0.3	44.3 ± 0.3	38.3 ± 0.1	43.1 ± 0.1

Note. Values are expressed as mean ± SEM.

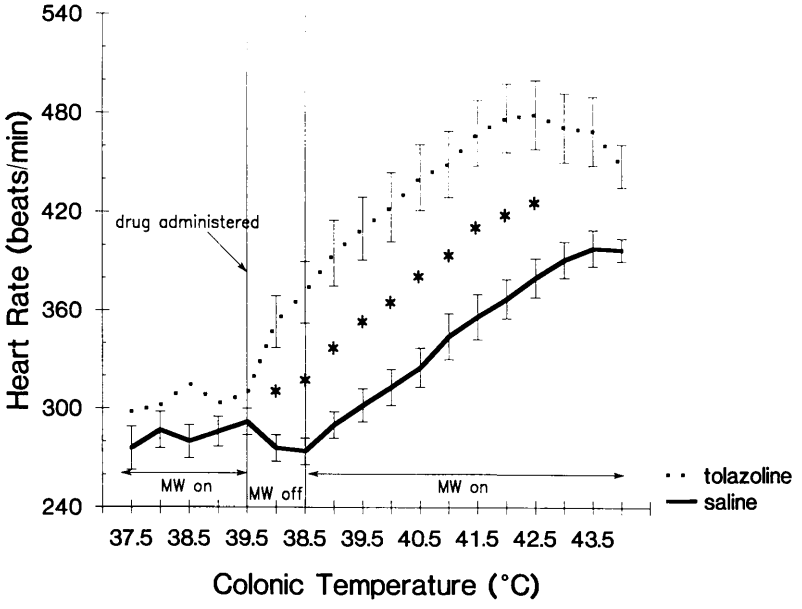

Figure 1. Heart rate in tolazoline- (n = 9) and saline-treated (n = 14) animals during exposure to microwaves. After an initial exposure period, in which each animal's colonic temperature was raised to 39.5°C, one of the agents was administered. After colonic temperature returned to 38.5°C, microwave exposure was then continued until death. Heart rate measurements were recorded at every half-degree temperature increment. Standard errors of the mean are shown for the saline group and, at selected points (where there is no overlapping between groups), for the tolazoline group. *Significant difference between saline- and tolazoline-treated groups.

during MW exposure. During the period immediately after drug administration (from 39.5° to 38.5°C, with MW off), HR decreased slightly in the saline groups, but increased substantially in the tolazoline group. At T_c of 39.0° and 38.5°C, the HR values were significantly greater in the tolazoline group than they were in the saline group. During terminal exposure, a continuous increase in HR occurred in each group throughout the irradiation period. The HR values in the tolazoline group were significantly greater than those in the saline group at T_c of 38.5° through 42.5°C.

Following drug administration (the period of T_c changing from 39.5° to 38.5°C), MAP decreased in each group (Fig. 2). During terminal exposure, in general, MAP increased until T_c reached 41.5° or 42.0°C, and then decreased until death. Respiratory rate change during irradiation is shown in Figure 3. At T_c above 41.5°C, respiratory rate gradually declined in each group. This decrease continued until death. There were no significant differences in values of MAP or respiratory rate between groups at any point.

Discussion

Due to the multiple mechanisms of action of tolazoline, interpretation of the mechanisms of changes due to the drug in the present study would be largely speculative. Effects on body temperature change, however, were consistent with earlier studies of α-adrenergic antagonism. Most previous thermoregulatory studies of tolazoline have involved attenuation or prevention of hypothermic or hyperthermic changes due to prior or concurrent administration of α-adrenergic agonists. These changes may be related to survival times during MW exposure, since these times are par-

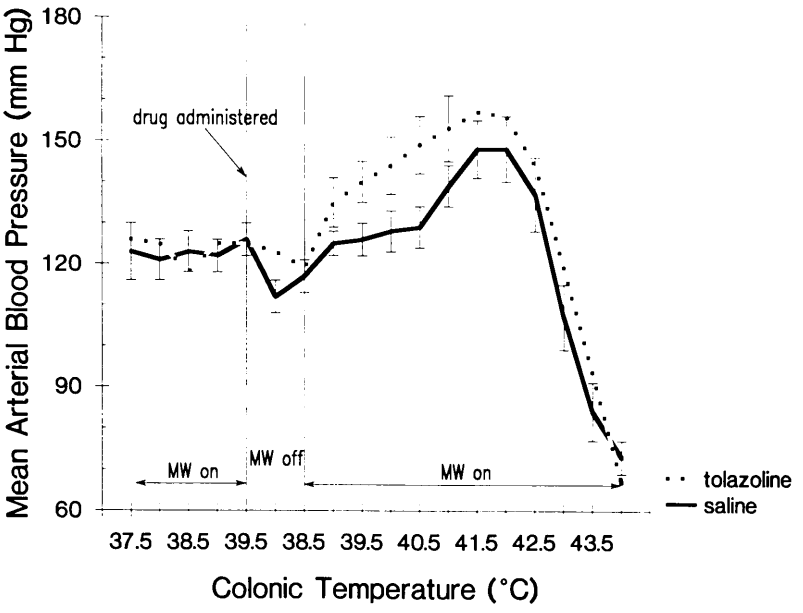

Figure 2. Mean arterial blood pressure in tolazoline- (n = 9) and saline-treated (n = 14) animals during exposure to microwaves. Experimental procedures are explained in Fig. 1 legend. Standard errors of the mean are shown for the saline group and, at selected points (where there is no overlapping between groups), for the tolazoline group.

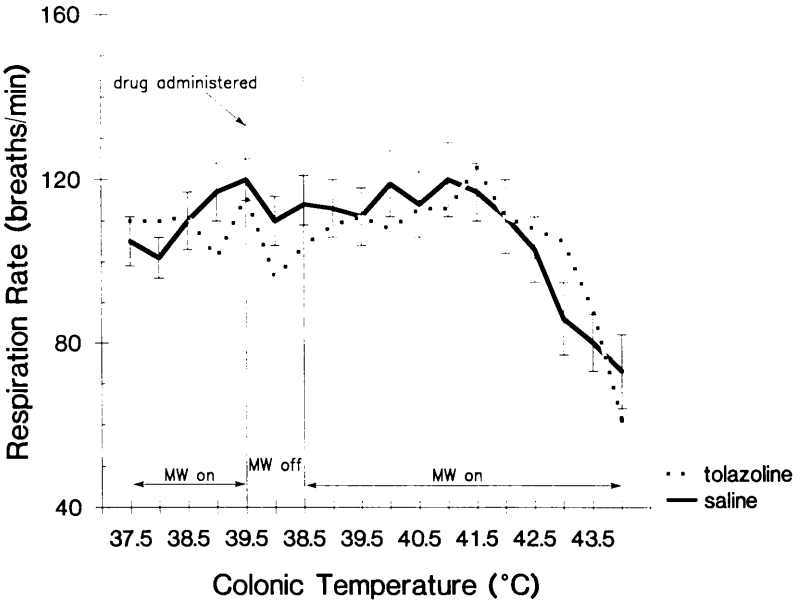

Figure 3. Respiratory rate in tolazoline- (n = 9) and saline-treated (n = 14) animals during exposure to microwaves. Experimental procedures are explained in Fig. 2 legend. Standard errors of the mean are shown for the saline group.

tially dependent on rate of temperature change. Thus, an agent that attenuates hypothermia in any given situation may be expected to cause greater heating during MW exposure. The shorter survival time (reflecting a faster rate of temperature rise) in the tolazoline-treated animals is consistent with the earlier study of Bill *et al.* (19), which revealed attenuation of hypothermia in rodents given an α-adrenergic antagonist. Similar results were found in other studies of goats (35).

We previously reported an increased HR in rats exposed to MW. During terminal exposures of anesthetized rats to 2450-MHz (3) and 2800-MHz MW (7), there was a gradual rise in HR throughout the entire exposure period, and an increase in MAP until T_c of 41.0° or 41.5°C; after this point a significant decrease in MAP occurred. These observations are similar to those by other investigators during experiments of lethal environmental heat stress in anesthetized rats. For example, Kregel *et al.* (36) reported an increase in HR in chloralose-anesthetized rats exposed to 40°C until MAP fell to 60 mm Hg. In their experiments, the core body heating rate was slightly less than half that in the present experiments. HR increased during the entire period of heating (at a core temperature of 37°C through 44°C). MAP increased at core temperatures of approximately 39°C and above, and then decreased at temperatures above 42°C. Takamata *et al.* (37) also noted that, in anesthetized rats exposed to thermal stress, HR continued to increase while MAP started to decrease at core temperatures above 43°C.

In the present experiments, the HR and MAP

changes were qualitatively comparable to those in the previous studies of anesthetized animals. There was a steady rise in HR throughout the exposure period, and an increase in MAP until T_c of 41.5°C; after this point, a large decrease in MAP occurred. Although absolute values of HR in our ketamine-anesthetized rats were substantially lower than values in chloralose-anesthetized rats in the experiments of Kregel *et al.* (36), maximal percentage increases in HR were similar (45% in our saline control experiments and 56% in the Kregel *et al.* experiments), despite differences in experimental protocols.

Although ketamine may cause an increased HR in some species, administration of ketamine to rats results in a decreased HR (see Ref. 3 for details). Thus, in the present experiments (and in our previous experiments [e.g., Ref. 3]), baseline levels of HR were relatively lower than they were in other studies. For comparative purposes, the work of Musch *et al.* (38) is one example of a study using conscious Sprague-Dawley rats of approximately the same body weight as in the present experiments. In their study, resting HR in sham rats was 399 bpm. Maximal HR, during a high level of exercise, was 529 bpm. Although this HR was slightly above the highest HR obtained in tolazoline-treated rats in our study (Fig. 1), on a percentage basis the increase in HR was much greater in our study.

The pattern of HR and MAP changes during hyperthermia could be the result of reduced cardiac output associated with decreased stroke volume. The decreased stroke volume could be caused by diminished venous return as a result of massive venodilation. Miki *et al.* (39) have observed a striking reduction in central venous pressure during severe hyperthermia. The mechanisms controlling this decrease in pressure during heat stress are unclear. This pressure decrement, along with an accompanying decrease in cardiac filling, may be the limiting factor in survival during heat stress. Kregel and Gisolfi (5) suggested that hyperthermia may prevent vasomotor stimuli from exerting an effect on the contractile apparatus of blood vessels. Takamata *et al.* (37) also suggested that the sudden drop in MAP during heating may be due to a dysfunction in the peripheral circulation and a reduction in venous return, but not cardiac failure. Previously, Morimoto and Nose (40) had shown that vascular compliance is lower during hyperthermia.

In two of our previous studies, chlorpromazine administration decreased survival time of rats during lethal MW exposure to 2800-MHz (7) and 5600-MHz MW (10). It has been postulated that chlorpromazine may exert some of its effects via α-adrenergic blockade (41). It is interesting to note that, in the 2800-MHz MW study (7), HR increased significantly greater in chlorpromazine-treated animals than in saline-treated animals during lethal MW exposure. In the present experiments, the tolazoline-treated animals also exhibited both a greater increase in HR and a decreased survival time.

In another previous study, rats treated with the β-adrenergic antagonist propranolol exhibited a significantly elevated respiratory rate during MW exposure period, along with a significantly lower survival time (3). Others have postulated that, during stressful conditions (such as hemorrhagic shock), hyperventilation could be detrimental due to the consumption of large amounts of energy, which would be in short supply (42). Hubbard *et al.* (43) have also theorized that energy depletion could be involved in the pathophysiology of heatstroke. An increase in HR, such as that which occurred in the tolazoline-treated animals in the present study, could likewise contribute to energy depletion.

On the basis of these findings, it appears that a significantly elevated HR, such as that which occurred in the tolazoline-treated rats, could influence susceptibility to MW-induced heating. An increased HR will generally result in an increase in cardiac output. During heating, however, a decrease in central venous pressure (mentioned above) could lead to a decrease in venous return and cardiac filling. (During autonomic blockade, even without concurrent heating, a decrease in central venous pressure has been reported along with an increase in HR in humans [44].) In this case, increasing HR would not necessarily result in increased cardiac output and could actually result in less blood being pumped from the heart. An increased HR results in a greater proportion of each cardiac cycle occupied by systole. During severe tachycardia, a concurrent decrease in the duration of diastole would interfere with ventricular filling. This hypothesized relationship between increased HR and decreased cardiac output, however, cannot be proven from the results of the present experiments of tolazoline-treated rats exposed to MW.

Venous return and ventricular filling can also be affected by respiration. Thus, in our previous study of propranolol-treated rats (3), the association of change in respiration with survival time could also have been due to changes in venous return.

In earlier studies of MW exposure (45, 46), we found that HR changes were related to the rate of change in body temperature, and not simply to the absolute change in temperature. In the present study, rats treated with tolazoline exhibited both a faster rise in temperature and increased HR. The greater HR, however, was established before the terminal period of MW exposure, and thus appeared to be due directly to the tolazoline administration. This increase in HR was consistent with results in other studies of tolazoline's effects (21–26).

The maximum HR obtained in the tolazoline group

was considerably higher than in any of our previous studies (3, 7, 10, 47) of lethal MW exposure. In contrast with saline-treated animals in the present study, HR in the tolazoline-treated animals decreased slightly at T_c above 42.5°C, immediately prior to death. A greater HR, as mentioned above, could have been associated with decreased cardiac filling. This could have contributed to the faster rise in body temperature and the lower survival time in these animals. With less blood being pumped from the heart, there could be less peripheral blood flow and less heat exchange at the surface of the body.

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