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Effects of esmolol on 35 GHz microwave-induced lethal heat stress

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1 The purpose of this study was to examine effects of the β_1-adrenoreceptor antagonist esmolol (infused at 2 or 4 mg kg^{-1} body wt min^{-1}) on heart rate, blood pressure, respiratory rate, localized body temperature changes, survival times, and lethal body temperatures that occur during the exposure of anesthaetized rats to 35 GHz microwaves.

2 Forty Sprague–Dawley rats, anaesthetized with ketamine, were exposed to 35 GHz microwaves at a level that resulted in heating and death. During irradiation, a continuous increase in heart rate and a biphasic response in blood pressure (initial increase followed by a decrease) were observed in all groups of animals.

3 Esmolol caused a significant dose-dependent decrease in blood pressure, relative to saline-treated animals, but only a small attenuation of the heat-induced rise in heart rate. In experiments in which esmolol was infused and microwave exposure was continued until death, drug-treated animals survived for significantly shorter periods and died at significantly lower body temperatures. The change in survival may have been related to the lower blood pressure due to esmolol treatment.

Introduction

The increased use of microwave (MW) exposure sources capable of generating millimetre wavelengths for military and civilian purposes (e.g. radar imaging/mapping, radiometry, communications, space power beaming) will continue to generate interest in possible biological effects of exposure to these sources. The use of MWs to study physiological changes during heat stress has been discussed previously (e.g. Jauchem & Frei, 1994). Using the ketamine-anaesthetized rat as a model, cardiovascular responses caused by MW-induced heating are, in general, similar to responses to environmental heating as described by Kregel & Gisolfi (1990). Differences in thermal gradients within the body resulting from the two types of heating, however, may lead to quantitative differences in the magnitude of cardiovascular changes (Jauchem & Frei, 1992).

Exposure to short-wavelength MWs would be expected to result in energy deposition at the body surface without deposition at deeper sites. Most studies of biological effects of exposure to these sources have involved *in vitro* cell preparations (see Rotkovská *et al*., 1993 for review). We recently reported the first studies of effects on physiological responses of anaesthetized rats to MWs at a frequency of 35 GHz (in the millimetre wavelength range) (Frei, Ryan, Berger & Jauchem, 1995). In these studies, circulatory collapse occurred when skin temperature was rapidly elevated to levels much greater than those measured at deeper sites within the body. Heart rate (HR) and mean arterial blood pressure (MAP) changes were similar to those that occur during environmental heat stress.

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 (Gisolfi, Matthes, Kregel & Oppliger, 1991). Some of our earlier studies revealed effects of adrenergic antagonists and other pharmacological agents on responses to MW-induced heating (Jauchem, Frei & Heinmets, 1984, 1985a,b, 1988). This area of research has been reviewed previously (Jauchem, 1985). In our previous studies (Jauchem & Frei 1994, Jauchem *et al*., 1984) of terminal exposure of rats to lower-frequency MWs (2.45 and 2.8 GHz), β-adrenoceptor antagonism with propranolol resulted in significantly decreased survival times and lower lethal colonic temperatures when compared to saline-treated animals. Cardiovascular and respiratory responses were altered in the propranolol-treated animals; decreases in MAP and increases in respiration rate occurred, relative to values in saline-control animals. Responses of this nature have not been studied in animals exposed to MWs of millimetre wavelengths. Mikolajczyk, Kamedula, Ruppe & Eggert (1991) speculated that

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different mechanisms could be involved in heat-stress responses at different frequencies of MWs.

β-adrenoceptors may be subdivided into β_1-adrenoceptors (chiefly at cardiac sites) and β_2-adrenoceptors (at other sites) on the basis of the relative selectivities of agonists and antagonists. Esmolol has been classified as a cardioselective β_1-adrenoceptor antagonist with negligible intrinsic sympathomimetic activity. Its rapid onset of action is of particular interest in experiments involving rapid heating (e.g. as a result of 35 GHz MW exposure, which causes a rapid increase in skin temperature), since the drug may, without delay, exert effects during essentially the whole period of heat exposure. A better preservation of skin blood flow after selective β_1-adrenoceptor blockade rather than non-selective β-adrenoceptor blockade has been reported (McSoley & Warren, 1978). Davies, Brotherhood & ZeidiFard (1978) showed that selective β_1 blockade caused a significant decrease in mean skin temperature in human subjects. Since skin blood flow plays an important role in heat dissipation, selective β_1 blockade may affect thermoregulatory responses to MW radiation differently than non-selective β blockade.

Possible protective or sensitizing effects of therapeutic pharmacological agents on MW-induced hyperthermia are relevant to the safety of military personnel or the general population potentially exposed to MWs. The purpose of this study was to examine effects of the β_1-adrenoceptor antagonist esmolol on HR, MAP, respiratory rate, localized body temperature changes, survival times, and lethal body temperatures that occur during the exposure of anaesthetized rats to 35 GHz MWs.

Methods

Animals and physiological monitoring

Forty male Sprague–Dawley CD-VAF/Plus rats (Charles River Laboratories, Wilmington, MA), weighing between 338 and 397 g (mean ± standard error of the mean (SEM), 350 ± 2 g) were used in this study. Formal approval was received from the Armstrong Laboratory Animal Use Committee to conduct these experiments. Prior to experimentation, animals were housed in polycarbonate cages with free access to Purina rodent chow and water, and maintained on a 12 h/12 h, light/dark cycle (lights on at 0600) in a climatically controlled environment (ambient temperature 27 ± 1°C).

Ketamine HCl (Vetalar), 150 mg kg^{-1} i.m., was administered as a general anaesthetic, with supplemental doses provided as necessary during experimentation. Administration of ketamine at approximately this dose provides adequate anaesthesia in Sprague–Dawley rats, and results in a stable animal preparation compatible with physiological monitoring (Jauchem & Frei, 1991). Ketamine exerts minimal effects on temperature regulation in rats (Refinetti & Carlisle, 1989), and is known for its lack of significant autonomic, cardiovascular, or respiratory effects. Use of ketamine in the rat has been discussed in detail previously (Jauchem & Frei, 1994).

HR, MAP and respiratory rate were measured and recorded as described previously (Jauchem & Frei, 1994; Jauchem, Frei, Chang & Berger, 1995). Briefly, a catheter was inserted into a carotid artery for measurement of MAP; HR was derived from a standard lead II EKG. Respiration was monitored by a pneumatic transduction method using a piezoelectric pressure transducer (model 320-0102-B, Narco Biosystems). In the present study, an additional catheter was placed into a jugular vein, to allow drug infusion during MW exposure. Temperature was monitored at five sites on each rat: (a) colonic (5–6 cm post-anus); (b) right tympanic; (c) left subcutaneous (lateral, midthoracic, side facing the antenna); (d) right subcutaneous (lateral, midthoracic, side away from MW source); and (e) tail (subcutaneous, dorsal, 1 cm from base). The probe for measuring tympanic temperature was inserted into the auditory meatus until the tympanic membrane was perforated. In other experiments performed under conditions similar to those in the current study, left and right tympanic temperatures differed by 0.5°C or less (Ryan *et al.*, 1996b). Temperature and cardiovascular data were converted from analog to digital signals by an IBM-compatible custom-designed Physiological Monitoring System with real-time graphics display and data analysis capabilities (described in more detail in Jauchem *et al.*, 1995).

Exposure conditions

First series: MW exposure until MAP of 75 mmHg. The temperature and relative humidity in the exposure chamber were held constant for all experiments (27 ± 0.5°C, 20 ± 5% RH). Other aspects of the exposure were as described previously (Frei *et al.*, 1995), with slight modifications. Animals were exposed to 35 GHz MWs at an incident power density of 75 mW cm^{-2} (whole-body average specific absorption rate, 13 W kg^{-1}). Since previous work involved two different procedures for heating using different durations of MW exposure, the present experiments were divided into two separate series. In the first series, MW exposure was continued until MAP decreased to 75 mmHg. In a previous study, this level of MAP had been defined, arbitrarily, as the point at which circulatory failure began (Ryan, Frei, Berger & Jauchem, 1996a). MW exposure was started when colonic temperature was at approximately 37°C. At the start of the exposure, esmolol (Brevibloc® Injection, Ohmeda Inc.) was infused, using a Harvard® infusion pump (model 55-1144), at a dose of 2 or 4 mg kg^{-1} body wt min^{-1}, in a total volume of 0.1 ml kg^{-1} body wt min^{-1}, until MW

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exposure was stopped (immediately after MAP dropped to 75 mmHg) ($n = 8$ in each group). An additional group of animals ($n = 8$) received saline infusions, in the same volume as listed above.

Altered levels of blood potassium may play a role in the pathology of heatstroke (Gisolfi *et al.*, 1991). In addition, stimulation of β-adrenoceptors can affect plasma potassium levels (Jauchem & Vick, 1979). Therefore, immediately before and after MW exposure, 0.5 ml samples of arterial blood were obtained for determination of serum potassium levels (using a Hitachi model 747 chemical analyser).

In contrast with other β antagonists, there is a relatively rapid disappearance of β blockade following discontinuation of esmolol infusion. Thus, by stopping the infusion when MAP decreased to 75, any changes in physiological parameters immediately prior to death would probably not be related to residual drug effects.

Second series: MW Exposure until death. In a second series of experiments, conditions were as in the previous series except that either saline or esmolol (4 mg kg^{-1} min^{-1}) were infused and MW exposure was continued until death occurred ($n = 8$ in each group).

Statistical analysis

For between-group comparisons of lethal temperatures and survival times, one-way analysis of variance (ANOVA) was applied. When repeated observations of physiological parameters were made at successive time points, ANOVA for repeated measures was performed to determine between-group differences. If statistical differences were found by ANOVA, the Tukey honest significant difference test was used to identify pairs of group means that were significantly different. A P value of less than 0.05 was considered to indicate significance in all cases. Results are expressed as mean ± SEM.

Results

First series: MW exposure until MAP of 75 mmHg

Figure 1 illustrates the time required for MAP to decrease to 75 mmHg (at which point MW exposure was stopped) and the subsequent time until death in each group of animals. The time for MAP to reach 75 mmHg was significantly shorter in the high-dose esmolol group than in the saline and low-dose esmolol groups. The time until death, however, was significantly longer in the high-dose esmolol group than in the other two groups.

Initial, 'MAP = 75 mmHg', and terminal values of colonic, tympanic, right and left subcutaneous, and tail temperatures are given in Table 1. The majority of temperatures at the point of MAP = 75 mmHg were significantly less in the high-dose esmolol group than in the saline-control group. The majority of terminal temperatures were significantly less in the high-dose esmolol group than in both other groups.

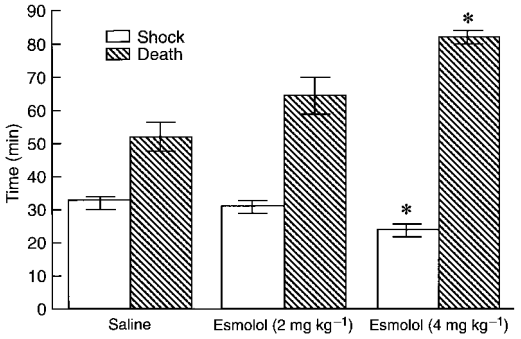

Figure 1 Effects of esmolol (2 or 4 mg kg^{-1} min^{-1}) on time until shock (from beginning of microwave exposure and drug infusion until mean arterial blood pressure decreased to 75 mmHg) and total time until death. $n = 8$ in each group. *Significantly different from saline and 2 mg kg^{-1} min^{-1} esmolol.

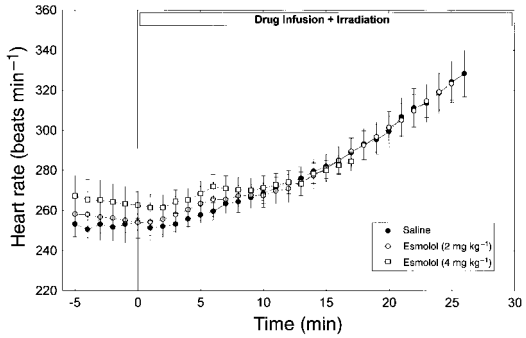

Figure 2 Effects of esmolol (2 or 4 mg kg^{-1} min^{-1}) on heart rate changes during exposure to microwaves. After a 5 min control period, microwave exposure and drug infusion were performed. $n = 8$ in each group.

HR changes, recorded each minute during MW exposure, are illustrated in Fig. 2. A continuous increase in HR occurred in each group for the entire period of exposure. There were no significant differences among the values in the different groups. (In Figs. 2–4, mean values are included only up to the time point at which the n size of each respective group becomes less than 8; i.e. one or more animals had reached the MAP endpoint and were no longer receiving drug infusion and irradiation.)

As shown in Fig. 3, MAP exhibited a biphasic response in each group, with an initial increase (peak values within 8–10 min) followed by a decrease. Esmolol-treated (both high- and low-dose) animals exhibited significantly lower values of MAP than saline-treated animals; this effect was dose-dependent. There were statistically significant main effects (ANOVA for repeated measures) of time of exposure and of drug treatment. An interactive effect of these two factors was present in each group (starting at minute 7 of exposure).

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Table 1 Initial temperatures, temperatures at point when MAP = 75 mmHg, and terminal temperatures (mean ± SEM) of rats exposed to 35 GHz microwaves in 'series 1'

Monitored area	Initial	75 mmHg	Terminal
Saline			
Colonic	36.9 ± 0.1	40.3 ± 0.2	40.1 ± 0.1
Tympanic	36.8 ± 0.1	39.9 ± 0.1	39.4 ± 0.3
Right subcutaneous	36.7 ± 0.2	38.9 ± 0.4	38.7 ± 0.4
Left subcutaneous	36.3 ± 0.2	46.1 ± 0.3	41.0 ± 1.0
Tail	30.5 ± 0.5	34.8 ± 0.4	31.5 ± 0.6
Esmolol (2 mg kg^{-1})			
Colonic	37.0 ± 0.1	40.4 ± 0.3	39.6 ± 0.5
Tympanic	36.6 ± 0.1	39.8 ± 0.2	38.7 ± 0.3
Right subcutaneous	36.2 ± 0.1	38.2 ± 0.2	38.1 ± 0.3
Left subcutaneous	36.4 ± 0.2	45.6 ± 0.3	39.5 ± 0.8
Tail	29.8 ± 0.4	34.0 ± 0.5	30.6 ± 0.5
Esmolol (4 mg kg^{-1})			
Colonic	36.9 ± 0.1	39.1 ± 0.2*†	37.2 ± 0.3*†
Tympanic	36.7 ± 0.1	38.9 ± 0.3*†	37.0 ± 0.3*†
Right subcutaneous	36.3 ± 0.1	37.2 ± 0.4*	36.3 ± 0.4*†
Left subcutaneous	36.6 ± 0.2	44.3 ± 0.9	36.3 ± 0.3*†
Tail	30.3 ± 0.3	33.2 ± 0.3*	29.6 ± 0.4*

*Significantly different from saline.
†Significantly different from 2 mg kg^{-1} esmolol.

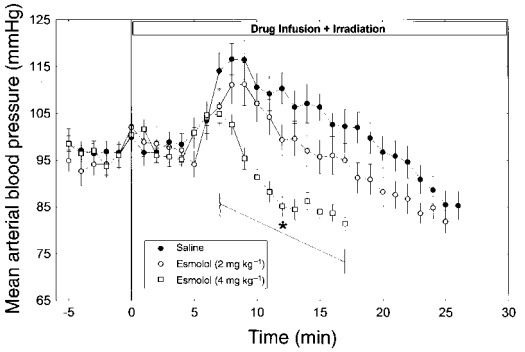

Figure 3 Effects of esmolol (2 or 4 mg kg^{-1} min^{-1}) on mean arterial blood pressure changes during exposure to microwaves. After a 5 min control period, microwave exposure and drug infusion were performed. n = 8 in each group. *Significant interactive effect of microwave exposure and of drug treatment (ANOVA for repeated measures).

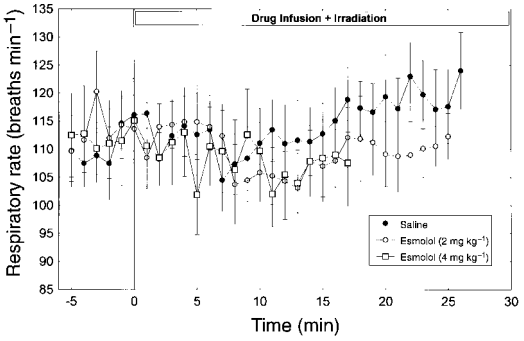

Figure 4 Effects of esmolol (2 or 4 mg kg^{-1} min^{-1}) on respiratory rate changes during exposure to microwaves. After a 5 min control period, microwave exposure and drug infusion were performed. n = 8 in each group.

No consistent patterns of change were observed in respiratory rate (Fig. 4) and there were no significant differences among groups.

Post-exposure values of serum potassium were significantly greater than pre-exposure values in each group (Fig. 5). There were no significant differences among groups. Pre- and post-exposure haematocrits were also measured; there were no significant changes in any groups.

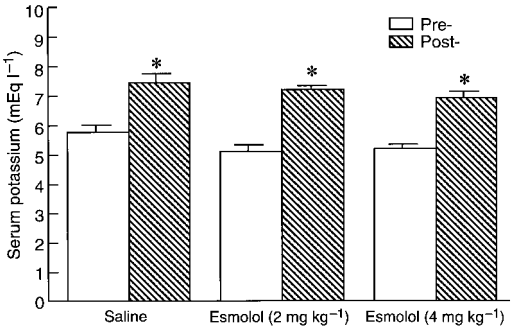

Figure 5 Serum potassium pre- and post-microwave exposure and drug infusion. *Significant difference in pre- and post-values.

Second series: MW exposure until death

Since the first series of experiments revealed a dose-dependent effect of esmolol, the high dose (4 mg

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Table 2 Initial and terminal temperatures (mean ± SEM) of rats exposed to 35 GHz microwaves in 'series 2'

	Saline		Esmolol	
Monitored area	Initial	Terminal	Initial	Terminal
Colonic	36.9 ± 0.1	41.0 ± 0.1	36.8 ± 0.1	39.4 ± 0.3*
Tympanic	36.7 ± 0.1	40.7 ± 0.2	36.5 ± 0.1	39.2 ± 0.2*
Right subcutaneous	36.1 ± 0.2	38.7 ± 0.2	35.7 ± 0.2	37.3 ± 0.3*
Left subcutaneous	35.8 ± 0.2	48.7 ± 0.2	35.5 ± 0.1	47.1 ± 0.5*
Tail	29.3 ± 0.5	34.3 ± 0.4	29.2 ± 0.3	33.5 ± 0.5

*Significantly different from saline.

kg^{-1}) was selected for use in the second series. In this series, esmolol infusion and MW exposure were continued until death occurred. Survival times were 43.5 ± 1.2 min and 30.2 ± 1.6 min in saline- and esmolol-treated animals, respectively. The difference was statistically significant. Initial and terminal values of colonic, tympanic, right and left subcutaneous, and tail temperatures are given in Table 2. Initial values were practically the same in the two groups. Terminal values of colonic, tympanic, and right and left subcutaneous temperatures were significantly lower in the esmolol group than in the saline-treated group.

HR gradually increased in both groups until death (Fig. 6). Esmolol-treated animals exhibited lower values of HR than did saline-treated animals. There were statistically significant main effects of time of exposure and of drug treatment. An interactive effect of these two factors was present in each group (starting at minute 21 of exposure). (In Figs 6–8, mean values are included only up to the time point at which the n size of each respective group becomes less than 8; i.e. death had occurred in one or more animals.)

As shown in Fig. 7, the initial increase in MAP seen in saline-treated animals, was blunted in esmolol-treated animals. Esmolol-treated animals exhibited lower values of MAP than did saline-treated animals. There were statistically significant main effects of time of exposure and of drug treatment. An interactive effect of these two factors was present in each group (starting at minute 7 of exposure).

No consistent patterns were observed in respiratory rate (Fig. 8); there were no significant differences between groups.

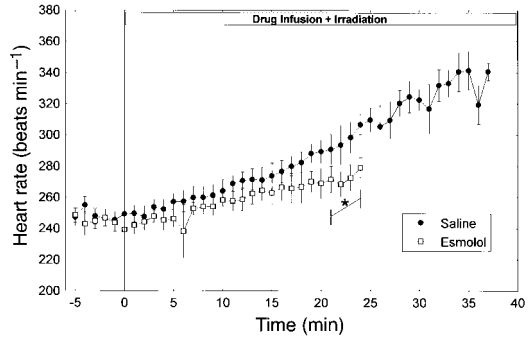

Figure 6 Effects of esmolol (4 mg kg^{-1} min^{-1}) on heart rate changes during exposure to microwaves. After a 5 min control period, microwave exposure and drug infusion were initiated and continued until death. n = 8 in each group. *Significant interactive effect of microwave exposure and of drug treatment (ANOVA for repeated measures).

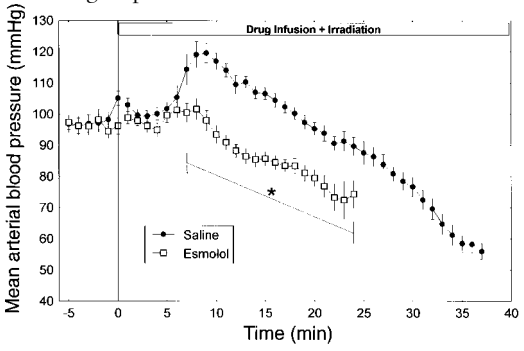

Figure 7 Effects of esmolol (4 mg kg^{-1} min^{-1}) on mean arterial blood pressure changes during exposure to microwaves. After a 5 min control period, microwave exposure and drug infusion were initiated and continued until death. n = 8 in each group. *Significant interactive effect of microwave exposure and of drug treatment (ANOVA for repeated measures).

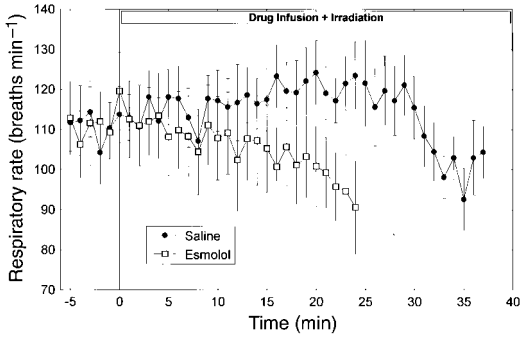

Figure 8 Effects of esmolol (4 mg kg^{-1} min^{-1}) on respiratory rate changes during exposure to microwaves. After a 5 min control period, microwave exposure and drug infusion were initiated and continued until death. n = 8 in each group.

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Discussion

Effects of esmolol on survival: relation to cardiovascular changes

The gradual rise in HR throughout the exposure period, and the biphasic change (initial increase followed by decrease) in MAP, were similar to changes observed by other investigators during experiments of lethal environmental heat stress in anaesthetized rats (Kielblock, Strydom, Burger, Pretorious & Manjoo, 1982; Kregel & Gisolfi, 1990). In our earlier studies of terminal exposures of anaesthetized rats to 2.45 GHz (Jauchem & Frei, 1994; Jauchem *et al*., 1995; Jauchem, Chang & Frei, 1996), 2.8 GHz (Jauchem *et al*., 1984) and 5.6 GHz MW (Jauchem, Frei & Heinmets, 1983; Jauchem *et al*., 1988), the pattern of HR and MAP changes was qualitatively comparable.

In the first series of the present study, drug infusion and MW exposure were continued until MAP decreased to 75 mmHg. Even though body temperatures decreased after MW exposure was stopped, death occurred approximately 20, 33 and 58 min later (in saline-, low-dose esmolol-, and high-dose esmolol-treated animals, repectively). This fact indicates that the mechanisms leading to death had already been irreversibly activated by the time of MW exposure cessation. The differences in times required for death to occur after halting MW exposure reflected the total exposure times that were necessary to result in MAP decreasing to 75 mmHg (lower exposure time would result in less overall heating).

Esmolol-treated rats exhibited a significant, dose-dependent decrease in MAP, compared to saline controls, but only a small attenuation of the heat-induced rise in HR. This finding of a lack of significant effects on HR may seem inconsistent with the classification of esmolol as a selective β_1 antagonist. These results, however, are consistent with clinical studies in which a dose-related hypotensive effect of esmolol was reported with only a small decrease in HR (e.g. Deegan & Wood, 1994). Reilly, Wood, Koshakji & Wood (1985) suggested that esmolol may exert a direct stimulant effect on vascular β_2 adrenoceptors. These investigators also mentioned the possibility that one of esmolol's metabolites may have direct vasodilating effects. Reynolds, Gorczynski & Quon (1986), however, reported that the major acid metabolite of esmolol possesses a β-antagonism potency 1500-fold lower than esmolol. Although another highly cardioselective β_1 antagonist, celiprolol, posesses some partial β_2 agonism (Prichard, 1992), this effect has not been shown for esmolol. Deegan & Wood (1994) suggested that the hypotensive effect of the drug could not be accounted for simply by β blockade. There was no evidence to support a direct vasodilatory effect of esmolol. Although chronic treatment with a β_1-adrenergic antagonist has been reported to stimulate vasodepressor-type prostaglandin generation in the rat (Hirawa *et al*., 1991), the effects of acute administration are unknown.

Most previous experimental studies of esmolol have used the dog or rabbit. The present investigation is one of the first studies reported to investigate *in vivo* effects of esmolol in the rat. (A search of the literature by using MEDLINE 1982–1995 and TOXLINE 1981–1995 revealed one previous report). Reynolds *et al*. (1986) suggested that there may be species differences in the peripheral vascular effects of esmolol at high doses. Clinically effective doses in humans are generally much lower than the doses used in our study. For example, in a group of patients with supra-ventricular tachyarrhythmias, the majority achieved therapeutic response at doses of 200 μg kg^{-1} min^{-1} or less (Sung *et al*., 1986). More recently, a single bolus of 4.4 mg kg^{-1} of esmolol was used to attenuate hypertension in other patients (Castelli *et al*., 1995).

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, Morimoto, Nose, Itoh, & Yamada (1983) 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 venous pressure decrement, along with an accompanying decrease in cardiac filling, may be the limiting factor in survival during heat stress. Kregel & Gisolfi (1990) suggested that hyperthermia may prevent vasomotor stimuli from exerting an effect on the contractile apparatus of blood vessels. Takamata, Nose, Mack & Morimoto (1990) 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 & Nose (1984) had shown that vascular compliance is lower during hyperthermia. Additional aspects of this phenomenon have been discussed previously (Jauchem *et al*., 1996).

A decreased cardiac output could result in less efficient dissipation of heat, which would lead to a decrease in survival time. Esmolol has been shown to decrease cardiac output (Ryan *et al*., 1993). Although cardiac output was not measured in the present study, the decreased survival time in esmolol-treated animals could have been related, in part, to effects on this parameter.

Serum potassium concentration was increased in each group at the end of the MW exposure period. This finding is consistent with previous work by Gisolfi *et al*. (1991), who exposed Sprague–Dawley rats to environmental heat and found that, at core temperatures of 41°C and above, plasma potassium was significantly elevated. In the present study, however, potassium levels in the two esmolol-treated groups were similar to that in the saline group.

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Comparison of 35 GHz with lower frequencies

Mikolajczyk *et al*. (1991) speculated that different mechanisms could be involved in effects of heat stress caused by exposure to different frequencies of MW (in particular, 2.88 GHz vs. 9.5 GHz). These authors proposed that heating caused by the lower frequency would affect primarily deep tissue, including the central nervous system and endocrine system, while heating from exposure to the higher frequency would affect primarily tissue on the surface, including the peripheral nervous system. Our previous studies are consistent with this hypothesis (Frei, 1995).

Possible mechanisms of physiological responses to 35 GHz MW exposure have been discussed previously (Frei *et al*., 1995), including sympathetic nerve activity associated with cutaneous receptor discharge and vasoactive humoral substances released from the skin as a result of localized tissue injury. Neugebauer & Lorenz (1988) noted that about 100 different mediators have been listed as being causally related to circulatory shock. Toxic factors produced in scalded or burned skin tissue have been characterized by Rosenthal, Harvey & Hakim (1972) and Schoenenberger (1975). Gisolfi *et al*. (1991) found that, during heating, splanchnic sympathetic nerve discharge gradually increases as core temperature rises from 37.0 to 41.0°C, whereas circulating catecholamines do not increase until core temperature is above 41.0°C. The role of nerve activity or humoral substances in the thermal/physiological responses of the present study is unknown.

Adair, Adams & Akel (1984) have shown that minor changes (<0.1°C) in hypothalamic temperature can influence thermoregulatory responses. Although hypothalamic temperature was not measured directly in the present experiments, tympanic temperature has been shown to be a reliable indicator for hypothalamic temperature in humans (Benzinger & Taylor, 1963) and brain temperature in rats (Robinson, Hutchison & Blatt, 1967; Dunscombe, Rail, Steinert, Ramsey & Rose, 1980). It is likely that, during the initial part of the MW exposure period, most input to the thermoregulatory centre of the hypothalamus would be via peripheral thermoreceptor discharge. Direct heating of the hypothalamus, however, would have occurred gradually (albeit at a lower rate of increase) because of circulating blood that was heated during its transit through the periphery. It is the total integration of all temperature signals (both central and peripheral) that controls the body's thermoregulatory responses directed by the hypothalamus (Boulant, 1986). Boulant (1994) found that, although warming of the skin will increase the firing rate of thermosensitive neurones in the hypothalamus, such heating will also decrease these neurones' sensitivity to their own (hypothalamic) temperature. This aspect may be important regarding exposure to MWs of millimetre wavelength.

The second series of experiments in the present study was performed in a manner similar to an earlier study of exposure to 2.8 GHz MWs (Jauchem & Frei 1994) (e.g. all exposures were continued until death occurred; each series included a group of animals infused or injected with saline; whole-body average specific absorption rates were similar). Mean left subcutaneous temperature (i.e. side toward the MW source) at death was much higher in saline-treated animals in the present 35 GHz MW exposures (48.7°C) than during exposure to 2.8 GHz MWs (43.6°C). There was less of a difference, however, between the mean lethal colonic temperatures (which would be more representative of the core body temperature) and mean lethal tympanic temperatures (which would be more representative of hypothalamic temperature) at the two frequencies. Despite the relatively large difference in lethal subcutaneous temperatures between the studies, the general pattern of HR and MAP changes were similar. The time course of physiological changes in the present study, however, was longer than the time course in the previous 2.8 GHz study (mean survival times of 43.5 min vs. 32.0 min).

Different mechanisms may be operating during exposures to different frequencies. For example, circulating or humoral factors may be more likely to be released from the skin during 35 GHz heating than during lower-frequency heating. The changes in HR and MAP, however, as mentioned above, appeared to be similar. It is possible that, once MAP has decreased to a certain level, the ultimate scenario leading to death follows a common pathway.

Summary

To summarize, in the present study, esmolol caused a significant, dose-dependent decrease in MAP (compared to saline controls), but only a small attenuation of the heat-induced rise in HR. These results are consistent with clinical studies in which a dose-related hypotensive effect of esmolol was reported with only a small decrease in HR. The lower blood pressure may have been related to shorter survival times in esmolol-treated animals. When comparing the results of these 35 GHz MW exposures with previous studies of exposure to a lower MW frequency, it appears that the pattern of HR and MAP changes occurring prior to death are similar.

Wenger (1983) has suggested that basic studies of cardiovascular responses during heat stress might be easier to perform with MW-induced heating than with conventional methods. The results of this study provide additional insight concerning the pathophysiology of heatstroke and effects of drugs on heat tolerance.

Acknowledgements

The authors wish to acknowledge the MW exposure support of the Sources and Measurements Branch,

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Radiofrequency Radiation Division, and the technical assistance of TSgt Raul Escarciga in performing serum potassium measurements. The animals involved in this study were procured, maintained, and used in accordance with the Animal Welfare Act and the *Guide for the Care and Use of Laboratory Animals* prepared by the Institute of Laboratory Animal Resources, National Research Council. The views and opinions expressed in this paper are those of the authors and do not necessarily state or reflect those of the US Government.

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(Received 22 July 1996
Revised 29 January 1997
Accepted 17 March 1997)