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SUSTAINED 35-GHz RADIOFREQUENCY IRRADIATION INDUCES CIRCULATORY FAILURE

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ABSTRACT—The objective of this study was to determine the thermal distribution and concomitant cardiovascular changes produced by whole-body exposure of ketamine-anesthetized rats to radiofrequency radiation of millimeter wave (MMW) length. Rats (n = 13) were implanted with a flow probe on the superior mesenteric artery and with a catheter in the carotid artery for the measurement of arterial blood pressure. Temperature was measured at five sites: left (T_{sl}) and right subcutaneous (sides toward and away from the MMW source, respectively), colonic (T_c), tympanic, and tail. The animals were exposed until death to MMW (35 GHz) at a power density that resulted in a whole-body specific absorption rate of 13 W/kg. During irradiation, the T_{sl} increase was significantly greater than the T_c increase. Heart rate increased throughout irradiation. Mean arterial pressure (MAP) was well maintained until T_{sl} reached 42°C, at which point MAP declined until death. Mesenteric vascular resistance tended to increase during the early stages of irradiation but began to decrease at $T_{sl} \geq 41$°C. The declines in both mesenteric vascular resistance and MAP began at $T_c < 37.5$°C; death occurred at $T_c = 40.3 \pm .3$°C and $T_{sl} = 48.0 \pm .4$°C. These data indicate that circulatory failure and subsequent death may occur when skin temperature is rapidly elevated, even in the presence of relatively normal T_c.

INTRODUCTION

In mammals, a primary mechanism of heat loss during thermal stress is dilation of the cutaneous vasculature. In mild to moderate heat stress, arterial blood pressure is maintained at normal levels despite the marked cutaneous vasodilation by both an increase in cardiac output and a redistribution of blood flow from the viscera to the skin. That is, cutaneous vasodilation is normally accompanied by a compensatory vasoconstriction in visceral vascular beds that is primarily mediated by increased sympathetic nervous system activity (1–4).

Severe hyperthermia, however, may result in heat stroke, a condition characterized by a precipitous fall in arterial blood pressure. Heat stroke may, in turn, lead to a state of circulatory shock, in which tissue hypoperfusion occurs. Although the mechanism(s) responsible for this circulatory dysfunction is still in question, it now appears that a significant loss of vasoconstrictor tone occurs in vascular beds that were previously constricted. Adolph and Fulton (5) first suggested that circulatory failure contributes to heat-induced circulatory shock. Subsequently, Daily and Harrison (6) demonstrated that, during severe hyperthermia in humans, hypotension and decreased cardiac output were the result of peripheral pooling of blood. Kielblock et al. (7) later proposed that fatal heat-induced shock resulted from cardiac failure due to a marked decline in vascular resistance after the loss of compensatory vasoconstriction.

Kregel et al. (8) directly measured the sequence and nature of vascular responses to environmental heat stress in both conscious and anesthetized rats. In these models, mean arterial pressure (MAP) increased until core temperature reached approximately 41.5°C, at which point MAP decreased precipitously. Mesenteric vascular resistance increased during the early stages of heat stress but dropped sharply before the sudden decline in MAP. Thus, a selective loss of compensatory visceral vasoconstriction appears to trigger the circulatory collapse associated with severe hyperthermia. The sudden visceral vasodilation, combined with continued cutaneous vasodilation, produces hypotension by decreasing both total peripheral vascular resistance and venous return; the latter ultimately results in decreased cardiac output.

The recent development of hardware systems capable of generating radiofrequency radiation of millimeter wave (MMW) length, as well as the increased use of MMWs for military and civilian purposes, has spawned considerable interest in the possible bioeffects of exposure to these waves. Previous studies of MMW bioeffects have generally employed models such as bacterial, yeast, and animal cell cultures (9). To date, cardiovascular responses to heating produced by whole-body MMW exposure have not been reported in laboratory animals.

Theoretical calculations suggest that all of the MMW energy absorption in animals will occur in the cutaneous region; the depth of penetration of 30-GHz radiofrequency radiation has been calculated to be .78 mm (9, 10). This study therefore sought to determine the following: 1) the thermal distribution produced by MMW (i.e., 35 GHz) exposure in anesthetized rats; 2) whether this pattern of heat distribution is sufficient to produce circulatory failure; and, if so, 3) whether visceral

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vasodilation accompanies the onset of hypotension during MMW exposure.

MATERIALS AND METHODS

Animals and instrumentation

All experiments and animal care were approved by the Institutional Animal Care and Use Committee of Armstrong Laboratory and were conducted according to the National Institutes of Health "Guide for the Care and Use of Laboratory Animals."

Thirteen male Sprague-Dawley rats (Charles River Laboratories) weighing between 388 and 528 g (mean ± SE = 433 ± 15 g) were used in this study. Before experimentation, animals were housed in polycarbonate cages with free access to Purina rodent chow and water and were maintained on a 12 h light/dark cycle (lights on at 0600) in a climatically controlled room (ambient temperature = 24.0 ± .5°C).

Ketamine-HCl (Vetalar; 150 mg/kg i.m.) was administered, with supplemental doses provided during experimentation. Ketamine administration at this dose level has been shown to produce prolonged surgical anesthesia in Sprague-Dawley rats (11); use of this anesthetic has recently been fully discussed (12). A Teflon catheter was placed into the left carotid artery for measurement of arterial blood pressure. This catheter was attached to a pre-calibrated blood pressure transducer (Century, Model CP-01) that was connected to a pressure processor (Gould, Model 13–4615-52). Via a laparotomy, a 1.0 mm blood flow probe (Biotronix Laboratory, Inc., Model BL 7010-H36) was placed around the superior mesenteric artery and connected to a pulsed-logic flowmeter (Biotronix Laboratory, Inc., Model BL610). Before experimentation, the flow probe was calibrated *in situ* using an arterial preparation attached to a saline-filled Harvard programmable pump (Model 44) with a digital readout in mL/min. Output from the flowmeter was inputted into the system computer, which was programmed to convert the flowmeter voltage output into mL/min. As a result, the system was calibrated to measure blood flow in the range of 5–35 mL/min. A Lead II ECG was obtained by use of nylon-covered fluorocarbon leads attached to a shielded cable placed outside the radiofrequency field; this cable was then attached to a Gould ECG/Biotach amplifier (Gould, Model 20–4615-65). Respiration was monitored by a pneumatic transduction method employing a piezoelectric pressure transducer (Narco Biosystems, Model 320-0109-B) interfaced to an electrosphygmograph coupler (Narco Biosystems, Model 7211), a Narco Type 7070 channel amplifier and, subsequently, a DC amplifier (Gould, Model 57–1340). All measured variables were recorded continuously throughout experimentation on a Gould 2600S recorder.

The animals were also instrumented to monitor temperature at five sites: 1) left subcutaneous (lateral, mid-thoracic, side facing the MMW antenna; T_{sl}); 2) right subcutaneous (lateral, mid-thoracic, side facing away from the MMW source; T_{sr}); 3) right tympanic (T_t); 4) colonic (5–6 cm post-anus; T_c); and, 5) tail (subcutaneous, dorsal, 1 cm from base; T_{ta}). All temperature measurements were obtained via thermistor probes (BSD Medical Corporation) attached to a precision thermometry system (BSD Medical Corporation, Model BSD-200). These temperature probes have a conductivity similar to biological tissue, are biologically inert, and produce no alterations in either the radiofrequency radiation field or in tissue energy absorption rate (13). Temperature and cardiovascular data were A/D (analog-to-digital) converted by an IBM-compatible custom-designed Physiological Monitoring System (14) with real-time graphics display and data analysis capabilities.

MMW equipment

Continuous-wave 35-GHz fields were generated by a Millimeter Wave Exposure System (Applied Electromagnetics, Inc.) and were transmitted through a Model 3–28-725 standard gain horn antenna (Macom). Irradiation was conducted under far-field conditions with the animal centered along the boresight, 110 cm from the antenna. The incident power density of the field was determined at the exposure site with an electromagnetic radiation monitor (Model 8616, Narda Microwave Corporation, employing a Model 32029 probe). The generator power output was monitored throughout exposure with a Model 4–32-B power meter (Hewlett-Packard) and recorded by a Gould 2600S recorder. Irradiation was conducted in an Eccosorb RF-shielded anechoic chamber (Applied Electromagnetics, Inc.) at the Radiofrequency Radiation Facility at the USAF Armstrong Laboratory, Brooks Air Force Base, TX. Chamber temperature and relative humidity were maintained at 27.0 ± .5°C and 20 ± 5%, respectively, during experimentation.

Experimental procedure

After surgery, the animal was placed on a holder consisting of seven .5 cm (O.D.) Plexiglas rods mounted in a semicircular pattern on 4 × 6 cm Plexiglas plates (.5 cm thick). Each animal was exposed in E orientation (left lateral exposure, long axis of body parallel to electric field and perpendicular to magnetic field) to 35-GHz radiofrequency radiation at an incident power density of 75 mW/cm^2. This power density resulted in a whole-body specific absorption rate (SAR) of 13.0 W/kg, as determined before experimentation on six rat carcasses using the calorimetric method of Padilla and Bixby (15).

Irradiation was continued until a lethal temperature was attained. Previous studies have shown that the lethal event occurring in response to both radiofrequency radiation (16) and environmental (17) heating is cessation of respiration.

Data analysis

Because the body weights of the animals varied, the MMW exposure time to death also varied. Temperature data were therefore normalized for percent time-to-death to make valid comparisons of temperature changes among animals with varying durations of MMW exposure. To compare changes in temperature and heating rates among the five sites of measurement, a one-way analysis of variance (ANOVA) was applied, followed by Tukey's Honest Significant Difference test (18).

Because of the extremely rapid and linear rate of rise of T_{sl} during MMW exposure, readings of cardiovascular data were obtained at .5°C increments of T_{sl} and analyzed accordingly. Mesenteric vascular resistance (MVR) was calculated by dividing values for MAP by mesenteric blood flow (MBF) values. Changes in MVR and MBF are expressed as percent change from the initial value to account for differences in baseline values among animals. To compare values of each cardiovascular variable at increasing T_{sl} to initial (pre-MMW) values, a one-way ANOVA was applied, followed by the Dunnett's test (18). In all statistical tests, significance was considered to be obtained when $p < .05$. All data presented in RESULTS are mean ± SE.

RESULTS

The period of MMW exposure required to elicit death ranged from 32–69 min, with an average of 49.8 ± .8 min. Because of this large range of exposure times, group data for thermal variables are expressed as percentage of total exposure time.

Fig. 1 shows temperatures at each of the monitored sites during exposure to MMW. At the onset of MMW exposure, T_{sl} began to increase immediately and continued to increase steadily and rapidly (.25 ± .02°C/min) throughout the period of exposure. Increases in T_c, T_t, and T_{sr} were not concurrent with the onset of MMW exposure, but instead lagged behind (3–11 min) the increase in T_{sl}. Furthermore, the increase in T_{sl} produced by MMW exposure was significantly greater than that occurring in T_c, T_t, and T_{sr} (Table 1). It is important to note that death occurred at a relatively low T_c (40.3 ± .3°C). At the point of death, however, T_{sl} had reached 48.0 ± .4°C, an 11.8°C elevation from baseline. T_{ta} remained virtually unchanged during irradiation.

Absolute values of T_c, MAP, and heart rate (HR) as well as percent changes from control in MBF and MVR during irradiation are depicted in Fig. 2. MAP tended to increase during the initial ($T_{sl} < 41.5$°C) phase of irradiation but this increase did not reach statistical significance. MAP subsequently began to decline when T_{sl} and T_c increased to ≥ 42.0°C and >37.5°C, respectively. From this point, MAP continued to decrease, reaching values statistically lower than control (pre-

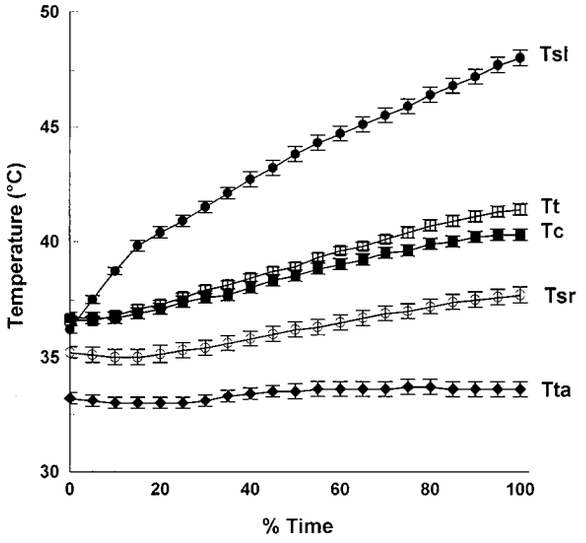

FIG. 1. **Thermal responses to exposure to 35-GHz radiofrequency radiation in ketamine-anesthetized rats (n = 13).** Exposure time is represented as a percentage of total time to account for differences in duration of individual experiments. T_{sl}, left subcutaneous; T_{sr}, right subcutaneous; T_t, right tympanic; T_c, colonic; T_{ta}, tail.

exposure) values at $T_{sl} \geq 45.0°C$. In contrast, HR increased continuously throughout the period of MMW exposure. The baseline respiratory rate was 102 ± 6 breaths/min and MMW exposure did not significantly alter this value ($p > .68$; data not shown).

Baseline values of MBF and MVR were 18.5 ± 2.2 mL/min and 6.4 ± .7 mmHg·mL/min, respectively. During the initial period of irradiation ($T_{sl} \leq 40.5°C$), MBF did not change while MVR tended to increase (Fig. 2). MBF tended to increase at $T_{sl} \geq 41.0°C$ but this trend did not reach statistical significance ($p < .06$). Concomitantly, MVR peaked at $T_{sl} = 40.5°C$ and subsequently began to decline thereafter. Levels of MVR at $T_{sl} \geq 45.0°C$ were statistically lower than the pre-exposure level.

DISCUSSION

The major findings of this study are twofold. First, localized heating of the skin is sufficient to produce circulatory failure and subsequent death in anesthetized rats exposed to MMW radiation. Second, mesenteric vasodilation accompanies the onset of MMW-induced circulatory failure.

Theoretically, most of the MMW energy absorption *in vivo* should occur in the cutaneous region (9, 10). Two observations in the present study confirm this prediction: 1) the extremely high subcutaneous temperature on the animal side facing the MMW source (T_{sl}); and, 2) the significant period of time (3–11 min) between the onset of the T_{sl} increase and the onset of the T_c increase. These findings suggest that actual energy absorption occurred very superficially and that deep body heating was achieved through circulatory heat transfer from the periphery to the core. As a result, terminal levels of T_{sl} (48.0°C) were much greater than those for T_c (40.3°C). Sustained exposure to 35-GHz radiation thus yields a large difference in heating rates between skin and colonic sites and a significant skin-to-core thermal differential.

Despite the moderate increase in T_c, MMW irradiation resulted in circulatory failure and subsequent death. The onset of hypotension in MMW-exposed animals was accompanied by a loss of compensatory vasoconstriction in the mesenteric vascular bed. In a previous study, Kregel et al. (8) demonstrated that the onset of hypotension in rats exposed to environmental heating was clearly preceded by a dramatic fall in MVR. Although the advent of the decline in MVR appeared to occur at a lower T_{sl} ($\geq 41°C$) than did the onset of hypotension ($\geq 42°C$) in the present study, this trend did not reach statistical significance because of animal variability. It is therefore unclear whether mesenteric vasodilation actually preceded the decrease in MAP in MMW-exposed animals. However, it is clear that a loss of compensatory vasoconstriction in the mesenteric vascular bed occurred during sustained MMW exposure and that this visceral vasodilation was associated with a decrease in MAP.

Interestingly, the onset of all of these cardiovascular events occurred at a T_c of approximately 37.5°C and death ensued at a T_c of only 40.3°C. This finding contrasts with observations of heat stroke induced by environmental heating, in which mesenteric vasodilation and hypotension occurred only when T_c exceeded 41.5°C (8). Nevertheless, MMW exposure produced much larger and more rapid increases in subcutaneous and, by inference, skin temperature (on the side facing the MMW source) than would be found during environmental heating. These results suggest that input from cutaneous thermoreceptors (19) may be responsible for the initiation of circulatory failure during such extreme peripheral heating.

Several lines of evidence support the suggestion that cutaneous thermoreceptors might play a prominent role in triggering an integrated response to MMW exposure. First, sudden warming of the skin in the absence of an increase in core temperature produces immediate (within 2 min) alterations in the activity of sympathetic nerves subserving thermoregulatory reflexes in anesthetized cats (20). Second, it is well-established that the control of thermoregulatory responses is extremely sensitive to the rate of temperature change (21); that is, increases in HR (22), evaporative heat loss (23), and heat loss from the rodent tail (24) are related not only to the absolute increase in temperature but also to the rate of heating. In this study, thermoregulatory reflexes activated by cutaneous thermoreceptors would therefore be expected to respond to the dramatic rate of cutaneous temperature increase. Finally, we

TABLE 1. **Temperatures at monitored sites before RFR exposure (initial) and at death (final)**

Temperature-monitoring site	Initial temperature (°C)	Final temperature (°C)	Increase in temperature (°C)	Heating rate (°C/min)
Colonic (T_c)	36.7 ± .3	40.3 ± .3	3.6 ± .2	0.08 ± .01
Tympanic (T_t)	36.6 ± .2	41.4 ± .3	4.8 ± .2	0.10 ± .01
Subcutaneous, left (T_{sl})	36.2 ± .2	48.0 ± .4	11.8 ± .5*	0.25 ± .02*
Subcutaneous, right (T_{sr})	35.2 ± .3	37.7 ± .4	2.5 ± .2	0.05 ± .01
Tail (T_{ta})	33.2 ± .3	33.6 ± .4	0.4 ± .2*	0.01 ± .01*

*$p < .05$ compared with T_c value; n = 13.

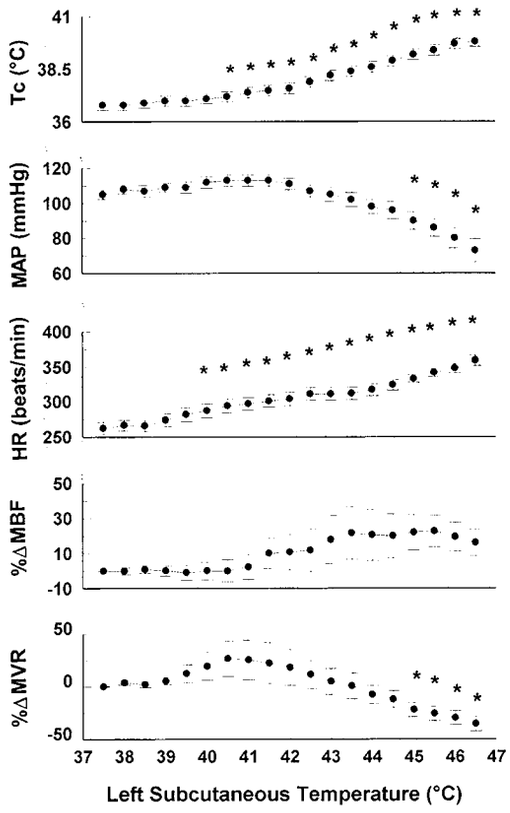

FIG. 2. **Cardiovascular responses to exposure to 35-GHz radiofrequency radiation in ketamine-anesthetized rats (n = 13).** Colonic temperature (T_c), mean arterial pressure (MAP), heart rate (HR), and left subcutaneous temperature (T_{sl}) are absolute values, while mesenteric blood flow (MBF) and mesenteric vascular resistance (MVR) are presented as percent change from initial values. *Significantly ($p < .05$) different from initial value.

(25) have previously shown that HR increases in response to radiofrequency irradiation are directly related to the frequency of radiation utilized. Because depth of energy penetration is inversely proportional to frequency, larger HR changes are elicited at frequencies that produce greater peripheral heating and, therefore, greater cutaneous thermoreceptor stimulation (25). Taken together, these observations suggest that stimulation of cutaneous thermoreceptors by MMW irradiation may trigger the attendant cardiovascular responses, even in the presumed absence of marked activation of core thermoreceptors.

An alternative explanation for these results is that the extreme skin heating may have produced localized thermal injury, leading to cardiovascular responses secondary to tissue injury rather than cutaneous thermoreceptor discharge. It should be noted, however, that the onset of mesenteric vasodilation occurred at a T_{sl} of 41°C, which is not yet in the range that would acutely produce traditional burn injury (26). Furthermore, cardiovascular responses to MMW exposure differ significantly from those associated with established experimental models of burn (27, 28). We therefore suggest that MMW exposure does not produce thermal injury akin to that produced by scalding or other immersion models. Although we cannot eliminate the possibility that vasoactive humoral substances are released as the skin was heated (i.e., before thermal injury), the release of such substances following thermal injury occurs only after a significant time delay (29) and is therefore not a probable mediator of MMW-induced circulatory failure.

Another possibility is that heat stress induces direct thermal injury to temperature regulatory centers in the central nervous system, thereby resulting in a failure of thermoregulatory control and subsequent cardiovascular collapse (30). In rabbits, heat stroke induced by environmental heating has been shown to result in central nervous system damage (31). In this study, the onset of heat stroke was taken to be the point at which coma occurred; at this point, rectal temperature was 43.5°C and MAP was dramatically reduced from control (31). From the data, it is unclear as to whether hypotension preceded the comatose state, or vice versa. Although it is possible that a central failure of thermoregulatory control occurred in MMW-exposed animals, it is doubtful that the level of brain heating was sufficient to produce neural damage and consequent cardiovascular collapse. This conclusion is based on the observation that the onset of cardiovascular changes occurred at a T_c and T_t of approximately 37.5°C, which is much lower than the value shown to induce neural damage in heated rabbits (31).

As noted previously, a decrease in MVR accompanied the decline in MAP. This fall in vascular resistance may have contributed to the decrease in MAP by lowering total peripheral resistance. Because the splanchnic circulation contains ~20% of the total blood volume and receives ~25% of the cardiac output at rest, any change in arterial resistance in this bed can significantly influence the maintenance of MAP (4). Kregel and his colleagues (8) suggested that the decline in MVR during the latter stages of environmental heating results in the further accumulation of blood in this vascular bed, thereby producing a reduction in functional blood volume. Such an effect would likely result in a decrease in venous return and stroke volume, which would further contribute to the reduction in MAP. This scenario could occur in animals exposed to sustained MMW irradiation as well, because HR increased continuously while MAP fell. Confirmation of this supposition awaits actual measurement of cardiac output during circulatory failure induced by either environmental heating or MMW exposure.

In conclusion, sustained exposure to 35-GHz radiation resulted in large and rapid increases in skin temperature and only moderate increases in colonic temperature. This thermal distribution was sufficient, however, to produce a state of hypotension and circulatory failure. Unlike heat stroke produced by environmental heating, circulatory failure in MMW-exposed animals occurred at a $T_c < 40$°C. In circulatory failure induced by either MMW exposure or environmental heating, a loss of compensatory mesenteric vasoconstriction occurs with the decrease in MAP, suggesting that visceral pooling of blood and subsequent loss of functional blood volume may contribute to the hypotensive state in both models. Sustained exposure to MMW may thus be a useful model for future investigation of circulatory failure induced by thermal stress. Moreover, this animal model may be of use for continued evaluation of safety

standards for human exposure to MMW. Current studies are directed toward determining the physiological mechanism(s) underlying this phenomenon.

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