Cerebral Blood Flow Changes During Localized Hyperthermia

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Abstract

Hyperthermia is becoming a potent therapeutic method for malignant brain tumors, either alone or in combination with radiation therapy. The heat response of organized tissues includes other factors besides the inherent cellular thermosensitivity, that is, tissue pH, PaO$_2$, and nutrient supply, all of which are largely influenced by the tissue blood flow. In this study, the regional cerebral blood flow (rCBF) changes in 15 Japanese normal monkey brains during interstitial microwave hyperthermia were investigated by the hydrogen clearance method. Under general anesthesia and controlled respiration, a parieto-occipital craniectomy, 4 × 4 cm, was performed. A microwave antenna was inserted into the brain to a depth of 2.0 cm, and the brain tissue was heated with 2450 MHz microwave irradiation. The intracerebral temperatures and rCBF were measured in the white matter 1 cm from the brain surface. During hyperthermia, the rCBF linearly increased at a rate of 10% per 1°C temperature rise. Heating at 42°C for 180 minutes resulted in a constant increase in rCBF. The perfusion rate returned to the control levels after the termination of heating. Above 45°C, the rCBF transiently increased and then started to decline during heating. No consistent results were obtained with heating at 43°C. These results show that normal monkey brain tissues respond to hyperthermia by an rCBF increase as long as the threshold values of tissue temperature (43°C) and exposure time (40–60 minutes) are not exceeded. Excessive heating may lead to irreversible damages to normal tissue and vasculature.

Key words: cerebral blood flow, heat toxicity, hyperthermia, malignant brain tumors, microwave

Introduction

It is now an established fact that an acidic, nutrient-poor environment greatly increases the thermosensitivity of tissue and inhibits the recovery from thermal injury and perhaps the development of thermotolerance. These environmental features are closely related to the tissue blood supply. The rise in tissue temperature during hyperthermia therapy mainly depends on the heat supply from the external heat source and the heat dissipation by the blood flow. Since current technology cannot accomplish the preferential delivery of heat energy to the tumor tissue, the selective heating and killing of tumor cells can only be expected when the heat dissipation by the blood flow is less in the tumor than in the surrounding normal tissue. Thus, a detailed knowledge of tumor and normal tissue vasculature is essential for the safe and effective use of hyperthermia.

Materials and Methods

I. Hyperthermic apparatus

We used a microwave hyperthermia device, HMS-020 (Aloka Co. Ltd., Tokyo) consisting of a 2450 MHz microwave generator, thermometry equipment, and a microcomputer with color display. A silicone-coated interstitial microwave antenna of 1.5 mm diameter, with a 4 cm-long radiating tip section (HTA-2450-5-5, Aloka Co. Ltd.), was also used. The intracerebral temperatures were measured by nonperturbing copper-constantan thermocouples having 10 recording channels, and the microwave
power could be automatically controlled to maintain one arbitrary thermocouple temperature constant. A microwave antenna-cooling system was employed to make the thermal field more uniform. The detailed structure and capabilities of the cooling system have been described elsewhere.\textsuperscript{13}

II. Hydrogen clearance apparatus

We used a PHG-203 (Unique Medical Inc., Tokyo) consisting of a head unit to detect the diffusion current and an amplifier unit connected to an analog printer. The hydrogen electrode was made of 200 μm-diameter platinum wire insulated by epoxy resin except for the 1 mm tip section, which was plated with platinum black to increase the sensitivity. Ag/AgCl dish electrodes were used for the reference electrode.

III. Animal preparation

Under anesthesia with ketamine hydrochloride (10 mg/kg, i.m.) and induced paralysis with pancuronium bromide (0.2 mg/kg, i.m.), 15 adult Japanese monkeys (Macaca fuscata) were orotracheally intubated and mechanically ventilated. Catheters were inserted into the femoral artery and vein to monitor blood pressure, to sample arterial blood for the blood gas analysis, and to allow intravenous infusion of fluids. Body temperatures were measured by an esophageal thermocouple. The respiratory volume and rate were adjusted to maintain the arterial pH, PaO\textsubscript{2}, and PaCO\textsubscript{2} within the normal range. Care was taken to assure an adequate anesthetic depth throughout the experiment.

The animal's head was fixed in a stereotactic frame, and a parieto-occipital craniectomy, 4 x 4 cm, was performed. Following the dural incision, the microwave antenna with the cooling system was vertically inserted into the brain to a depth of 2.0 cm (Fig. 1). The thermosensors were placed in closed-end catheters (Insyte\textsuperscript{®}, Deseret Medical Inc., Sandy, Ut., U.S.A.) and inserted into the brain parallel to the antenna axis. The hydrogen electrodes were implanted immediately adjacent to the thermosensors (approximately 2 mm apart) at radial distances of 0.5 and 1.0 cm from the antenna. All the sensors and electrodes were inserted to a depth of 1.0 cm. An especially designed plastic frame was used to stabilize the depth and position of the antenna and thermosensors. The reference electrodes were implanted subcutaneously in the right thigh.

IV. Regional cerebral blood flow (rCBF) measurements during heating

rCBF was measured by the hydrogen clearance method. Hydrogen gas was delivered to the endotracheal tube for 3 minutes, with the flow rate adjusted to maintain the hydrogen concentration in the inhaled gas at approximately 5%. After the hydrogen gas supply was stopped, the diffusion current was recorded.

In five monkeys, the brain tissue was heated with 2450 MHz microwave irradiation until the tissue temperature reached 47°C (step-up heating). rCBF was measured before and during the heating, with one arbitrary thermocouple temperature (reference point) kept constant by computer control. The arterial blood gas was analyzed during each rCBF measurement.

In the other nine monkeys, the reference points were rapidly elevated to 42, 43, 45, or 50°C and maintained for 180 minutes (constant temperature heating). During the heating, rCBF measurements were repeated every 20 minutes. In one animal, the rCBF was measured under the same experimental conditions but without microwave irradiation (control).

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\textbf{Fig. 1} Experimental design. The interstitial microwave (MW) antenna with the cooling system was inserted to a depth of 2 cm, and the brain tissue was heated with 2450 MHz microwave irradiation. The thermocouples and hydrogen clearance electrodes were implanted to a depth of 1 cm at radial distances of 0.5 and 1.0 cm from the antenna.

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Results

I. Physiological parameters

The mean blood pressure during the experiments was 126.3 ± 20.2 (SD) mmHg, and the mean arterial pH, PaO₂, and PaCO₂ were 7.44 ± 0.06, 133.1 ± 25.5 mmHg, and 36.4 ± 6.0 mmHg, respectively. No significant changes in these parameters were observed during hydrogen gas inhalation and/or microwave irradiation.

II. rCBF changes during step-up heating

The majority of measurements roughly followed monoexponential decay curves of hydrogen clearance before and during heating (Fig. 2). The semilog plots of these curves were approximately linear (Fig. 3). The rCBF values calculated from the slopes in Fig. 3 were 37.7 ml/100 gm·brain/min before heating (35.9°C) and 82.1 ml/100 gm·brain/min during heating (44.7°C), that is, rCBF increased 2.2 times after an 8.8°C temperature rise. The relationship between the rise in temperature and the rCBF ratio (post/preheating rCBF) is shown in Fig. 4, in which the rCBF increased at a rate of 10% per 1°C temperature rise [correlation coefficient (r), 0.88]. The mean rCBF before heating was 18.6 ± 8.1 ml/100 gm·brain/min, which is in good agreement with the previously reported rCBF of cerebral white matter, so mechanical injury due to electrode insertion appears to be negligible.

III. rCBF changes during constant temperature heating

No significant change in rCBF was observed in the control animal (Fig. 5). Thus, the anesthetic and operative procedures did not appear to affect the rCBF measurements. Heating at 42°C caused an immediate increase in rCBF to 1.7 times the preheating value, which continued throughout the heating period of 180 minutes. With heating at 45°C, the
rCBF increased to a peak value of 2.6 times in 40 minutes and then progressively decreased to the preheating value at the end of the heating period. Heating at 50°C caused a peak increase in rCBF in a few minutes followed by a subsequent rapid decline. As shown in Fig. 6, no consistent results were obtained with heating at 43°C. The wide variation in results was probably due to combination factors as follows: 1) errors in the hydrogen clearance rCBF measurements (<10-15%), 2) temperature differences between the thermocouple and hydrogen electrode (located approximately 2 mm apart), and 3) differences in the thermosensitivity among vessels or animals. It was clear, however, that the threshold for the pathological vascular damage is around 43°C and 1 hour heating.

**Discussion**

Early clinical trials have provided the basis for the use of hyperthermia as a potent therapeutic method for malignant brain tumors.15,16,25,27 The reasons for the usefulness of hyperthermia against malignant brain tumors are twofold. First, there is likely to be an enhanced mechanism of heat-induced cytotoxicity in the tumor, which is resistant to radiation therapy or perhaps chemotherapy, because of the inferior blood supply as compared to normal tissue. Second, heat can be effectively used in combination with radiation therapy, chemotherapy, or perhaps even surgery.4,5,7,8,18,22

At temperatures higher than 42.0-42.5°C, heat acts as a cytotoxic agent, since mammalian cells die after heating in a time-temperature- and cell cycle-dependent manner.4,18,22 According to our present knowledge, one main target for hyperthermia is the cell membrane.4,18,22,23 In addition, hyperthermia inhibits deoxyribonucleic acid replication as well as ribonucleic acid and protein syntheses. Furthermore, heat usually leads to changes in physiological equilibria and to the modification of chemical reactions including metabolic processes.18,22,23

Recent in vitro studies indicate that the intrinsic thermal sensitivity of cells somewhat varies among cell lines, and is not clearly related to cell malignancy. In other words, there is no consistent evidence that neoplastic cells are more or less thermosensitive than normal cells.4,22,26 However, it has been demonstrated that neoplastic tissues can be damaged at temperatures innocuous to normal tissues. The differences in thermosensitivity between normal and neoplastic tissues are mostly attributable to physiological factors.5,7,8,20-22,26

In solid tumors, the blood flow is disorganized and sluggish compared to the normal tissues. This has two important consequences. First, the microenvironment of the tumor becomes hypoxic, acidic,
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and nutrient-poor; these features are known to sensitize tumor cells to hyperthermia therapy. Second, tumor tissues have a less effective cooling mechanism than normal tissues because the blood flow has a major role in heat dissipation. This will result in the preferential heating of tumor tissue by local application of heat energy. Song et al. introduced the concept of blood flow ratio (BFR: blood flow in tumor/blood flow in surrounding normal tissue) and stated that preferential heating of tumor tissue can be achieved when the BFR is less than 1.0. In addition, poorly developed tumor vessels are quite vulnerable to heat, so that irreversible damage tends to develop at temperatures innocuous to normal tissue vascularity. Therefore, further decreases in the BFR and selective tumor cytotoxicity can be expected by adopting suitable tissue temperatures and exposure times.

Heat-induced cytotoxicity in vivo is thought to involve immunological mechanisms. The tissue microcirculation is an important interface between the tumor tissue and the host immune system. Therefore, a detailed knowledge of heat-induced blood flow changes in both the tumor and adjacent normal tissue is essential for clinical use of hyperthermia.

The normal tissue most commonly used to study the effect of heat on the vascular function is the skin and muscle of rodents. Song et al. investigated blood flow changes in the skin and muscle of Sprague-Dawley rats. After heating at 45°C for 15 minutes, the skin blood flow increased to 15 times the preheating value, but prolongation of the heating time resulted in a rapid decrease to less than one half of the preheating value. With heating at 44°C, the skin blood flow increased to the peak value of 12 times in 30 minutes, from which it started to decline but remained about 5 times the preheating value after 120 minutes. Heating at 43°C caused a steady increase in the skin blood flow for 120 minutes. Similar results were obtained for muscle, excepting that the heating temperature at which the blood flow began to decrease was 45°C, 1°C higher than that for skin.

Dudar and Jain measured the blood flow in mature granulation tissue grown in a transparent rabbit ear chamber during heating. The blood flow increased with the rise in tissue temperature and remained high for 60 minutes, up to approximately 45.7°C of tissue temperature. At higher temperatures, the blood flow initially increased but eventually ceased due to vascular stasis and occlusion. Higher temperatures required less time for the vascular stasis. Vessel diameters also increased by up to 50% during heating at moderate temperatures but slightly decreased at higher temperatures (>47°C).

These data and others indicate that heat induces an immediate increase in blood flow in the normal tissues as long as the critical levels of tissue temperature and exposure time are not exceeded. This blood flow increase is due to the thermoregulatory mechanism and is accompanied by a similar increase in heat dissipation by convection to compensate for the potentially damaging heat load on these tissues. However, excessive heating progressively produces vascular stasis and endothelial damage. The magnitude of the flow increase and the threshold for pathological damage vary with the species studied, the tissues investigated, and the heating techniques employed.

Few reports have investigated the blood flow changes in the brain during hyperthermia. Bicher et al. demonstrated a blood flow increase in feline brains heated with microwave irradiation but presented no quantitative data. Salcman et al. heated canine brains with interstitial microwave irradiation and measured the rCBF by the hydrogen clearance method, in which the rCBF linearly increased with rise in temperature and nearly doubled after a 7°C rise. Oscar et al. also demonstrated an rCBF increase during systemic hyperthermia in rats.

This study demonstrated that normal monkey brain tissue consistently responds to hyperthermia by an rCBF increase at a rate of 10% per 1°C temperature rise. The threshold values of tissue temperature and exposure time for vascular damage, such as endothelial degeneration, thrombosis, and hemorrhage, appeared to be approximately 43°C and 40–60 minutes.

Several reports about heat toxicity in normal brain tissues have been published. Recently, Matsumoto histologically examined normal monkey brains 7 days after interstitial microwave irradiation and observed irreversible tissue damage in the region heated above 44°C for 60 minutes, which are slightly higher than the threshold values previously reported (42.2–42.5°C, 50–60 minutes). This small difference might be due to the uniform thermal field achieved by the cooling system. Matsumoto et al. studied heat toxicity in canine brains using sequential quantitative computed tomography, which detected heat-induced low-density areas corresponding to the tissues heated above 44°C for 30 minutes. The estimated temperatures of the enhanced areas surrounding the low density was 43–44°C.

These reports and our work show that heating above 43°C for approximately 1 hour can damage normal brain tissues either by the direct cytotoxic
effect or via vascular disruption. Therefore, during hyperthermia therapy, the temperature of the normal brain tissue should be kept below 43°C to prevent deleterious side effects. Further studies are necessary to identify the temperature range in which the brain tumor vasculature is preferentially destroyed.

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