

(REVIEW ARTICLE)



Hyperthermia

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Abstract

There is scientific support for the concept of a temperature set point that is, maintenance of an optimal temperature for the metabolic processes that life depends on. Nervous activity in the preoptic-anterior hypothalamus of the brain triggers heat losing (sweating, etc.) or heat generating (shivering and muscle contraction, etc.) activities through stimulation of the autonomic nervous system.

The pre-optic anterior hypothalamus has been shown to contain warm sensitive, cool sensitive, and temperature insensitive neurons, to determine the body's temperature setpoint.

As the temperature that these neurons are exposed to rises above 37 °C (99 °F), the rate of electrical discharge of the warm-sensitive neurons increases progressively.

Keywords: Hyperthermia; Temperature; HSP-70; Chemotherapy; Radiotherapy; Thermodox

1. Introduction

Definition: It is a type of treatment in which body tissue is heated to as high as 133F to help damage and kill cancer cells with little (OR) no harm to normal tissue.

- Hyperthermia to treat cancer is also called Thermal Therapy, Thermal Ablation (OR) Thermotherapy.
- Different types of techniques may be used to create heat for hyperthermia treatment. These techniques include:
 - Radio waves,
 - Lasers,
 - Ultra sound,
 - Heating fluids such as blood (or) chemotherapy drugs and putting them into body (Perfusion),
 - Placing the entire body in heated chamber.

2. Types of hyperthermia

- Local Hyperthermia
- Regional Hyperthermia
- Whole body Hyperthermia

2.1. Local Hyperthermia

Doctors apply heat to a small area. This type of local hyperthermia used depends on where the tumour is located.

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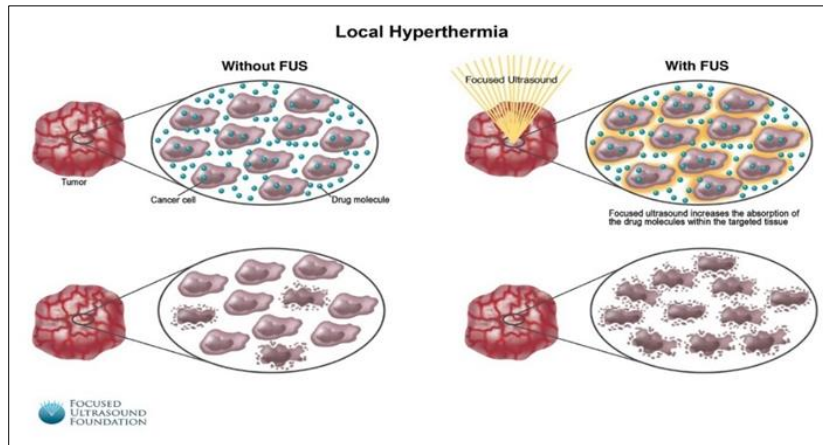


Figure 1 Local Hyperthermia

2.2. Regional hyperthermia

This type of hyperthermia is used to treat tumour that are on (or) just below the skin. Create heat around (or) near the treatment area.

2.3. Whole body Hyperthermia

This is used to treat tumours deep within the body, such as in the brain.

- The doctors will insert the probes (or) needles into tumour imaging techniques, such as ultrasound, probe is in the right place. The heat source is then inserted into the probe.

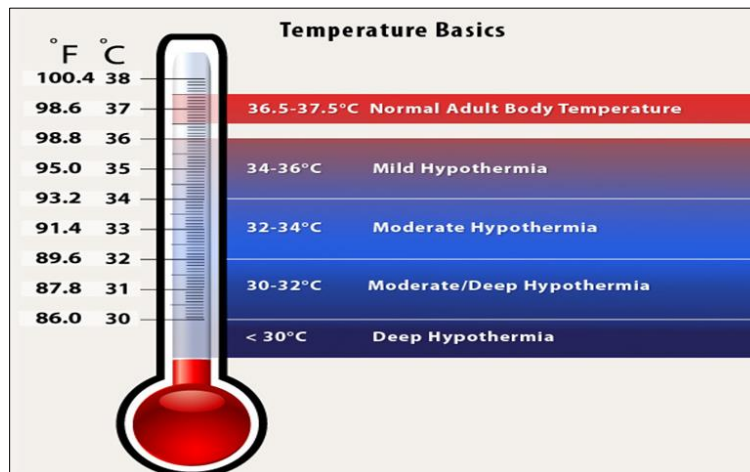


Figure 2 Basic temperatures

3. Pathophysiology

A fever occurs when the kernel temperature is set higher, through the action of the pre-optic region of the anterior hypothalamus.

Example: In response to a bacterial infection, certain white blood cells within the blood will release pyrogens which have a direct effect on the anterior hypothalamus, causing body temperature to increase, much like raising the temperature setting on a thermostat.

In contrast, hyperthermia occurs when the body temperature rises without a change in the heat control centres. Some of the gastrointestinal symptoms such as acute exertional heatstroke, vomiting, diarrhoea and gastrointestinal bleeding, may be caused by barrier dysfunction and subsequent endotoxemia.

Ultraendurance athletes have been found to have significantly increased plasma endotoxin levels.

Endotoxin stimulates many inflammatory cytokines, which in turn may cause multiorgan dysfunction.

Experimentally, monkeys treated with oral antibiotics prior to induction of heat stroke do not become endotoxemic.

There is scientific support for the concept of a temperature set point that is, maintenance of an optimal temperature for the metabolic processes that life depends on. Nervous activity in the preoptic-anterior hypothalamus of the brain triggers heat losing (sweating, etc.) or heat generating (shivering and muscle contraction, etc.) activities through stimulation of the autonomic nervous system.

The pre-optic anterior hypothalamus has been shown to contain warm sensitive, cool sensitive, and temperature insensitive neurons, to determine the body's temperature setpoint.

As the temperature that these neurons are exposed to rises above 37 °C (99 °F), the rate of electrical discharge of the warm-sensitive neurons increases progressively. Cold-sensitive neurons increase their rate of electrical discharge progressively below 37 °C (99 °F).

4. Diagnosis

Hyperthermia is generally diagnosed by the combination of unexpectedly high body temperature and a history that supports hyperthermia instead of fever. Most commonly this means that the elevated temperature has occurred in hot, humid environment (or) in someone taking a drug for which hyperthermia is known side effect .

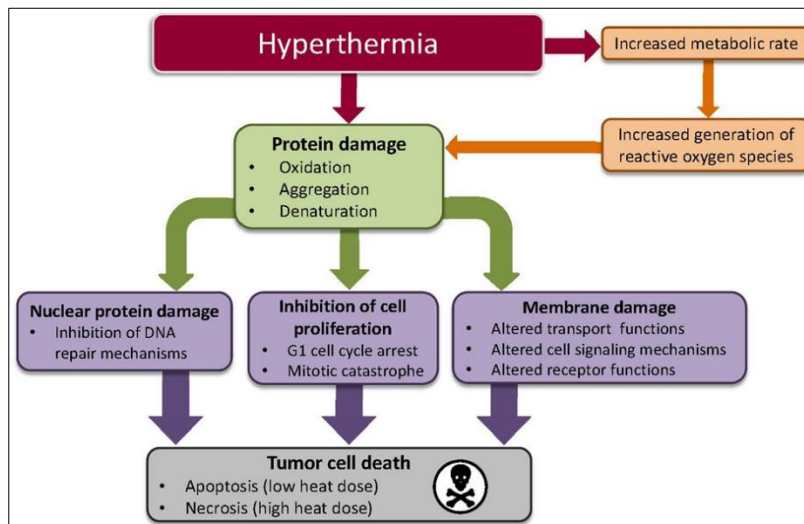


Figure 3 Pharmacology of hyperthermia

The presence of signs and symptoms related to hyperthermia syndrome, such as extrapyramidal symptoms characteristic of neuroleptic malignant syndrome, and the absence of signs and symptoms more commonly related to the infection related fevers, are also considered in making the diagnosis.

(7). Hyperthermia is an adjuvant local anticancer treatment using temperatures exceeding the physiologically optimal level, typically 40-43 degree centigrade for approximately one hour. Hyperthermia applied as radiosensitizer or chemosensitizer has shown great results in over four decades and is presently successfully applied in combination with radiotherapy or chemotherapy for treatment of many tumours types, including recurrent breast cancer, bladder cancer, cervica carcinoma, head and neck cancer, soft tissue sarcoma, and melanoma (1). To further improve the effectiveness of hyperthermia delivery in the clinic, clinical trials and preclinical hyperthermia research aim at even better exploiting the pleiotropic effects of hyperthermia, and technical research is performed into better controlled and more effective forms of heat delivery. Hyperthermia affects cells and tissues in various ways (2). It can directly alter the physical properties of cellular components, but it can also influence cellular responses. Hyperthermia affects multiple intracellular processes, like e.g., DNA repair pathways, as well as systemic immune responses. Furthermore, hyperthermia can target cancer cells in hypoxic and nutrient-deprived tumour areas where ionising radiation and

chemotherapy are least effective. Hyperthermia can also modify factors that are essentials for tumour survival and growth, such as the environment, immune responses, vascularisation, and oxygen supply (3). Thus, the effects of hyperthermia are multifactorial, as addressed in the contributions in this issue. Hyperthermia inhibits the homologous recombination (HR)DNA repair pathway by inducing proteasomal degradation of BRCA2(4). Van den Temple et al. investigated the mechanisms driving hyperthermia-induced BRCA2 degradation, finding that BRCA2 degradation is evolutionarily conserved, BRCA2 stability is dependent on HSP90, ubiquitin might not be directly involved, and BRCA2degradation might be modulated by oxidative stress and radical scavengers (5). Mei et al. investigated the impact of temperature(37-42^oc), sequence and time interval (0 up to 4h) for ionizing radiation combined with hyperthermia on different HPV-positive and HPV- negative cervical cancer cell lines, demonstrating that shorter time intervals were associated with more unrepaired DNA damage and more tumour cell kill, radio especially at higher temperatures (6). Hyperthermia at 42^oc was also demonstrated to have a marked potential in inducing an immune response in an in vivo mouse model of colon adenocarcinoma, where intravenous administration of a human CCL3 variant carrying a single amino acid substitution after mild local hyperthermia treatment not only induced significant tumour growth inhibition but also inhibited metastasis Hader et al. investigated the impact of the heating method on changes in the immune phenotype of tumour cells, comparing the effect of warm-water bath versus 2.45 GHZ Microwave heating on cell death, the release of HSP70, and the expression of immune checkpoint molecules(ICMs) on br4east cancer cells. They observed released of HSP70 after hyperthermia at a range of temperatures and independently of the heating method, but microwave heating was more effective in cell killing, and microwave heating with and without radiotherapy increased subsequent HSP70 concentrations(8). Presently commercially available hyperthermia devices are available that are capable of ensuring effective heat delivery in many Tumour sites (9). Further progress is ongoing to develop dedicated equipment for specific sites, improve tumour control or facilitate a more effective work flow during treatment. Reproducibility of applicator shape and position is needed for accurate planning of superficial hyperthermia treatments, present a fast reconstruction method for bendable superficial hyperthermia applicators suitable for routine clinical patient-specific treatment planning (10). Magnetic resonance thermometry (MRT) is emerging as a clinical non-invasive 3D-temperature measurement method. Curto et al. found good MRT accuracy for MR-hyperthermia hybrid systems at five European institutes while heating a centric or eccentric target in anthropomorphic phantoms with pelvic and spine structures(12). Establishing antenna phase and amplitude settings resulting in optimal tumour heating is challenging and time-consuming for modern multi-antenna systems, a contribution of Kuehne presents an elegant and fast solution for establishing global optimality, automatically determining optimum application RF frequencies and time-multiplexed RF excitations for desired target regions, desired power deposition patterns and constraints (13). Advanced applicator design and test of a novel 32-channel modulator signal source for heating deep-seated tumours. The large number of coherent RF channels, wide frequency range, and accurate phase shift provided by this source from a sound basis for well controlled, magnetic resonance(MR) guided hyperthermia treatment delivery(14). A step further is a Thermal magnetic resonance (Thermal MR) feasibility study using an integrated RF applicator accommodating ratio frequency (RF)-induced temperature modulation, thermometry, anatomic and functional imaging using 7.0-tesla whole body MR scanner, and molecular probing, aiming at controlled release at the tumour site of therapeutics from thermos responsive nanogels (15). Encapsulating drugs in temperature-sensitive liposomes is a novel method to enhance the distribution and concentration of drugs in tumours. Besse et al. investigated effectiveness and tumour drug distribution after treatment with different doses of different liposomal doxorubicin formulations of in mice bearing a human fibrosarcoma. Results indicate that tumour drug distribution is important for effective treatment and Thermodox combined with hyperthermia resulted in the highest tissue drug levels (16). Photothermal tumour ablation can serve as an alternative to classic surgery in tumour treatment. Kim et al. numerically analysed optimal conditions for laser-tissue interactions in gold nanoparticle (GNP)-enhanced photothermal therapy resulting in good tumour control while preventing overheating.

5. Conclusion

Generally, Hyperthermia is considered as a disease state but Hyperthermia is used as a treatment method in the cancer. Presently commercially available hyperthermia devices are available that are capable of ensuring effective heat delivery in many tumour sites. Further progress is ongoing to develop dedicated equipment for specific sites, improve tumour control or facilitate a more effective work flow during treatment.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest in publishing this paper.

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