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Physical and Engineering Aspects of Hyperthermia

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1. Introduction

Heating of cancer cells together with other means of radiational or chemical therapy is now considered as one of the most promising methods of practical treatment. Heating of tissue as a means of therapy is a technique which has a very long history. The technique of hyperthermia, however, has to be a far more elaborate one because of the following reasons.

(i) The temperature must be accurately controlled within some ±0.5 deg.

(ii) Discrimination between normal and pathological cells has to be made(spatial resolution).

(iii) In view of the behavior of the cell such as heat tolerance, the time-course of heating should also be designed in combination with other treatment(temporal design).

There have been conceived of several means of heating the patient. Whole body (systemic) heating by circulation, electromagnetic energy and ultrasound are presently three major streams of heating techniques.

All of those contains difficult probelms in terms of physical and physiological basis as well as engineering and technical aspects due to the complicated nature and structure of the human body.

Monitoring the internal status of the patient during heating is also a difficult problem. Among those, temperature measurement is the most essential. Since no technique at present can cope with the requirement in heating and monitoring in a satisfactory way, the actual means of measurement and control must be backed-up with theoretical considerations.

2. Heating Techniques

(1) Electromagnetic Energy

Heating by electromagnetic energy is the technique which is most widely utilized at present. A number of commercial systems are available. The technique can roughly be divided into capacitive(electrode), inductive (coil) and electromagnetic wave heatings. It can also be divided into extracorporal and intracorporal heatings.

Physical properties of tissues have been studied for many years, and presently a complete knowledge is available about the electrical constants. Fortunately, there is no remarkable variation of those constants in the range of interest in hyperthermia. For simplicity, one can assume the following constants.

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* 대한의용생체공학회 주최 Hyperthermia Semina에서 발표한 내용을 발췌한 것임.

Tissue with high water content(brain, muscle, etc.)

conductivity 0.5~1 S/m,
dielectric constant 50

Tissue with low water content(fat, bone, etc.)

conductivity 0.1~0.25 S/m,
dielectric constant 10

It should be noted that fat and bone have relatively low conductivities(high resistance), which has sometimes a serious effect in low-frequency heating. Because of the high relative dielectric constant in soft tissue, one can assume that, as a rough measure, the wavelength inside of the body is one order of magnitude less than in the air.

Using the presently available knowledge, heating in the body was studied for various kinds of models. As the first approximation, the electromagnetic heating can be divided into low-and high-frequency heatings because of the following three reasons.

(i) Wavelength inside of the body is longer or shorter than the typical size of organ.

(ii) Extraordinary heating of fat layer or skulp is produced at low frequency.

(iii) Reaction of the magnetically-induced current to the original field can be ignored at low frequency, which is a very favorable situation in visualizing the heat generation.

In the low-frequency range, the situation is simple from theoretical point of view. In other words, one can calculate or visualize the current produced by the impressed voltage or magnetic field, and estimate the heat generation.

The phenomenon is simple, but in actual situation, difficult problems are the extraordinary heatings in fat and near pelvis or cavities. The extent of those overheatings can be estimated by theoretical models, and it is important that the clinician actually applying the energy has some knowledges about the phenomena.

It is also possible to some extent to perform theoretical estimations on the heat generation based on actual data such as x-ray CT. Although the computation is restricted to two-dimensional, the finite-element method can be applied to provide useful suggestions. It is still outside of the present-day small-scale computers to present the result in a short time, but the summary of various but typical situations will be helpful.

The frequency below several tens of MHz can be considered as low, and the frequency above 1 GHz can be considered as high. At high frequency, the electromagnetic field should be considered as a wave. Usual reasoning of waves such as in optics can be applied to estimate the field inside of the body, as in discussing the focussing. It should be noted, however, that the patient is always placed in the "near field" of the applicator, and usual reasoning of "far field" or plane wave cannot apply. For example, the notion of skin depth is not applicable, and there have been proposed several applicators that can convey energy far deeper than the skin depth.

The frequency range between several tens of MHz and 1 GHz contains very complex phenomena. A concentration of field, called resonance or hot spot, is easily produced. The generation of a hot spot may or may not be desirable from the viewpoint of hyperthermia, but the situation is very difficult to estimate. Consequently, this frequency range should not be used unless one is skillful in anticipating the field or has a theoretical tool for estimation.

(2) Ultrasound

Properties of tissues for ultrasound propagation have also been extensively studied, and there is already a sufficient knowledge about constant. As a rough measure, one can assume that the speed of propagation is 1.5 km/s, except for bone and air. Consequently, the wavelength inside of the body is 1.5mm/f, where f is the frequency in MHz. At frequency around 1 MHz, which is usually used in hyperthermia, the wavelength is sufficiently short and one can consider the propagation as a wave. On the other hand, it may be useful to try the hyperthermia at low frequencies.

Ultrasound propagating through the tissue suffers from attenuation with the attenuation constant proportional to the frequency. The attenuation constant is 0.5~2dB/MHz·cm, which is fairly large at 1 MHz. When a focussing technique is used, the point of maximum heat generation is a little closer to the surface than the geometrical focus because of the attenuation. By the same reason, focussing is needed to produce the maximum inside of the body.

Bone and air have the acoustic impedances which are greatly different from other tissues, and the wave is strongly reflected at the boundary. This is a prohibiting factor for hyperthermia and restricts the application. If a very low frequency is used, one way be able to get around the obstacle. This, however, complicates the design of therapy and has not been tried.

(3) Probe and Implant

Inserting a small sized probe into tracts such as esophagus or bladder, the energy can efficiently be applied to the site. At present, only electromagnetic heating is considered, which can be divided into monopolar and bipolar types. In either case, a problem is that the heat generation rapidly decays as one goes away from the applicator. Cooling of the surface is absolutely necessary. In some cases, in UHF range, it is possible to use an array of antennas to realize a somewhat deeper heating.

Lossy material can be implanted for a long term to absorb the impressed energy and concentrate the heat generation. Ferromagnetic materials with strongly temperature-dependent property has interesting applications that the heat generation is remarkable only below 42 deg. When the loss of the material is not satifactory, a combination of conducting and ferromagnetic materials can also be used.

(4) Whole Body Heating

Using the technique of extracorporal circulation, the blood flow into the body can be heated to the desirable temperature. The technique is reliable since it can raise the body temperature to a certain level. The difficulty is the complication due to the high and long-term temperature rise. Various kinds of physiological indications, such as rectum and tympanal temperatures, EEG may be utilized for monitoring. Due to the difficulty of administering the condition of the patient, the whole body heating may be combined with the localized heating so that a better spatial heating discrimination can be achieved.

3. Temperature

(1) Temperature Rise

The heat produced by the applied energy must be carried away by conduction and circulation, and the temperature rise is determined by the balance of heat generation and disposal. In normal situation, however, the major portion of the heat generated is carried away by the blood flow. The heat transport by conduction is almost negligible. The heat resistance of the skin is also high, and the heat transport across the skin cannot be a large amount, although the surface cooling is quite important to keep the skin at low temperature.

It is theoretically possible to calculate the temperature rise from the distribution of heat generation. The computer program for arbitrary body cross section is available. The problem is the inaccurate estimation of the blood flow, which, furthermore, changes with temeperature. Consequently, the estimation for the temperature rise cannot be a very precise one, but remains to be a qualitative one.

The transient behavior in the heating process can also be discussed theoretically. It is concluded that in most cases the rise of the temperature follows an exponential, single-time constant, curve. The time-constant is of the order of ten minute. It should be noted, however that the time-constant depends strongly on the blood flow. If the blood flow is stopped in the model or in the experimental animal, etc., the time-constant may greatly change.

(2) Temperature Measurement

Since the control of the temperature of the object site is very crucial in hyperthermia, the measurement of temperature is of utmost importance. The accurate measurement, however, can be carried out only by invasive means, i.e., by inserting a small-sized sensor into the tumor.

The first requirement for the temperature measurement system is to avoid the interaction with the heating system. This is especially so in the case of electromagnetic heating. The impressed field may be disturbed or guided by the inserted sensor, or the leaked field may affect the operation of the measuring system. In other words, the interference may be produced in both ways.

The most usual sensors are thermocouples and thermisters. Other means, such as optical and crystal sensors, can also be used. Some commercial models are already available in the market with satisfactory accuracy. There are sometimes included elaborations to make the electrical sensor high impedance to avoid the interaction.

The non-uniform temperature distribution is one of the most serious problems in temperature measurement. Even within a cancer cell, if it is of considerable size, the temperature is not uniform, and it is difficult to evaluate the temperature rise of the cell as a whole. Multi-sensor probe has been devised, but there is a limitation in the number of sensors equipped on a single small probe. A theoretical model should be incooperated with the measurement to estimate the average or minimum temperature within the cell. This is especially one of the important point in the evaluation of the clinical results from the viewpoint of temperature rise.

Due to the cumbersome procedure and pain of the patient, it is highly desirable to develop a non-invasive means of temperature measurement. Nuclear magnetic resonance, ultrasound, electromagnetic radiation or transmission, change of dielectric constant, etc. are investigated at present by a number of researchers. Due to the difficult nature of the problem, it will not be possible to achieve a satisfactory temperature and spatial resolution.

Another possibility is the implanted sensor. It is possible to design an electronic circuit encapsuled and implanted near the site of heating. Or, a passive snesor such as coupled coils with the distance changing with temperature, ferromagnetic material with temperature-dependent permeability, or a diode with temperature-dependent nonlinearity are some of the examples. Those implants are in-between of the invasive and non-invasive methods in terms of the performance.

4. Related Techniques

(1) Phantom

Phantoms are used in basic study as well as in testing the heating systems. Electrolyte, jelling agent and metallic powder are appropriately mixed to simulate various properties of tissues. In most of those phantoms, however, blood flow is not included. Consequently, in making evaluation of particular heating method by phantom, one must be careful that the temperature rise will be higher than with blood flow. Metabolic heat generation is neither included in the phantom so that, when left as it is, the phantom will settle to the room temperature, which is another factor to be taken care of in the experiment.

There are many theoretical tools, such as computer simulation, to evaluate the effectiveness of the heating method. If the phantom experiment is designed in a very simple way, it will merely be a verification of calculation or checking of the completeness of experiment. If the effort of people doing such basic work with phantom is directed to a more practical consideration, it will be more meaningful.

On the other hand, when a heating system is actually constructed, there must be a means to verify its satisfactory operation. In such a case, a phantom is needed. The phantom for such a purpose need not be an exact simulation of the tissues. The measured temperature rise can be converted by calculation to the actual performance. More important is the standardization of the phantom so that performances of various kinds of heating systems can be compared by the test results. The QA (quality assurance) committees established in various countries will act toward such a goal.

(2) Cooling

Surfact cooling is almost mandatory in any heating system. The reason for this is that the point of maximum heat generation is frequently produced near the surface, rather than that the heat should be carried away through the skin. Due to the thermal resistance of the skin, the latter mechanism is hardly expected to work satisfactorily. Both water and air coolings are used at present, but other means such as heat-pipes and evaporation coolings may be used in the future.

There are less number of technically difficult problems in cooling. The noise produced by the cooling system is sometimes very embarassing to the patient. The electrical conductivity of the coolant, usually water, has sometimes an effect in the case of electromagnetic heating. In the intracorporal heating, for example, an undesirable heating near the surface may result, depending on the frequency and the conductivity.

5. Conclusion

It is almost certain that the technique of hyperthermia, when successfully applied, will be one of the most promising means to treat cancer, since it is almost independent of the cellular properties at molecular level. The problem is how to heat the cancer cell effectively without much heating the normal cells. In this respect, the cooperation of engineers and physicists is essential.

The formation of an academic socity on hyperthermia is very meaningful from such a viewpoint. The heating system for hypertermia cannot be so much refined that it automatically realizes the ideal temperature distribution just by switching-in. Rather, it requires some insight on the side of clinicians. Education of medical people to get an insight into the situation will be required. The engineers, on the other hand, must help medical people not only by designing heating and measuring systems, but also in providing theoretical basis to evaluate, design and complement the therapeutic procedure. The future hyperthermia system must include elaborations such as automatic corrections to temperature measurement, optimize the location and excitation of applicators, monitor and judge about the status of patient, and even help the doctor in evaluating the thermal dose and design the treatment cycle.

The present state of research is a little too much excited. Without waiting for the advent of complete system, clinical people have already started trials. It is still too early a stage to discuss advantages and disadvantages of individual heating systems, but to evaluate the merits and demerits of individual heating methods. The author hopes that the enthusiusm at present will continue still for several years until we arrive at a reasonable view about the heating and measuring systems, applicators, therapy design procedure, education of people, evaluation of therapy, etc.