1982

Equipment for local hyperthermia therapy of cancer

Charles F. Babbs
Purdue University, babbs@purdue.edu

James R. Oleson

John A. Pearce

Equipment for local hyperthermia therapy of cancer

Charles F. Babbs, M.D., Ph.D.

James R. Oleson, M.D., Ph.D.

John A. Pearce, Ph.D.[1]

From the Biomedical Engineering Center, Purdue University, West Lafayette, Indiana 47907; and the Division of Radiation Oncology, The University of Arizona Health Sciences Center, Tucson, Arizona 85724.

Abstract

Rapid improvements in hyperthermia apparatus are being achieved by industrial and university-based research groups that have already led to the marketing of a variety of commercial systems for heat therapy of malignancy. These tissue heating systems employ microwaves, capacitively or inductively coupled radiofrequency current, or high intensity ultrasound to produce controlled local heating of tumor tissues. No single system is superior to others in all applications; each has its limitations.

Key words: cancer; heat therapy; hyperthermia apparatus; microwave therapy; radiofrequency therapy; solid tumors; tissue heating; ultrasound therapy

[MEDICAL INSTRUMENTATION 1982:16(5);245-248]

Charles F. Babbs is supported in part by Research Career Development Award HL-00587, from the National Heart, Lung, and Blood Institute, U.S. Public Health Service. The research was supported by PHS Grants CA32691 (Purdue) and CA17343 (Arizona) awarded by the National Cancer Institute, and by a grant from the Purdue Cancer Center.

[1] Charles F. Babbs is associate research scholar, Purdue Biomedical Engineering Center, and clinical instructor in family medicine, Indiana University School of Medicine. He received his B.A. from Yale University in 1968; his M.D. with honor from Baylor College of Medicine, Houston, in 1974; his M.S. in anatomy from Baylor in 1975; and his Ph.D. in pharmacology from Purdue University in 1977.

James R. Oleson is assistant professor of radiology, the University of Arizona.

John A. Pearce is currently assistant professor of electrical engineering, the University of Texas at Austin. At the time this paper was written, he was research associate, Purdue Biomedical Engineering Center.

Local hyperthermia therapy refers to application of heat to a limited region of the body in such a way that core body temperature and arterial blood temperatures do not change appreciably. Under certain circumstances, such local application of heat can be highly effective in causing selective destruction of tumor tissue (Hahn and Kim 1980; U et al. 1980). Most notably, when blood flow to the tumor is significantly less than that in surrounding normal tissues, heat energy absorbed from an external source is carried away less rapidly from the tumor than from adjacent normal tissues; and as a result the tumor temperature rises to a higher steady-state level (Babbs 1982; Song et al. 1980).

There are four major modalities for producing local heating of tissues by external means: microwave radiation, capacitively coupled radiofrequency current, inductively coupled radiofrequency current, and high intensity ultrasound. This paper briefly reviews the principles and limitations of each modality and identifies for the reader some of the university based research groups and corporations developing each technology. (Further details can be found in the research reports cited in the list of references.) The present paper focuses on noninvasive hyperthermia apparatus, although local hyperthermia approaches using invasive means, including capacitively coupled radiofrequency with interstitial electrodes (Manning et al. 1982), interstitial microwave antennas (Strohbehn et al. 1979), and inductively heated ferromagnetic seeds (Straffer 1979), are also under active investigation.

Microwave Heating

Microwave generators operating between 30 MHz and 30 GHz generate waves of electromagnetic energy that propagate through air or other coupling media such as de-ionized water. The generators are connected to applicators (antennas of various shapes) placed near the skin surface. When excited by high frequencies, these applicators produce approximately plane waves that pass into the tissue. The incident energy is absorbed by molecules that make up the tissue. At microwave frequencies of the order of 100 MHz the mechanism of power absorption includes both translational movement of charge carriers and rotational movement of middle-size molecules. As the frequency is increased, the larger molecules are successively less able to follow the rapidly changing fields until at 2456 MHz the absorption mechanism is dominated by the rotational movements of water molecules.

Most tissues are good microwave absorbers--especially water containing tissues like skin and muscle. However, the specific absorption rate (SAR) is strongly dependent on the depth. For a plane wave normally incident on a thick homogeneous medium, the energy absorption diminishes exponentially with depth in the medium. Hence, a fundamental limitation of microwave heating is the difficulty of depositing power at depths of more than several centimeters from the skin surface, without excessive heating of overlying skin and fat.

Much of the energy incident on the skin surface is in fact reflected because the skin's electrical properties (characterized by the complex dielectric constant) are so much different from those of the air in which the wave was propagating. For the same reason, there is also reflection at the skin/fat and fat/ muscle interfaces. The reflected waves are generally different in phase from the incident waves and further complicated by the non-planar shapes of the tissue structures. The relative intensity and phase of the reflected waves depend on frequency, as does the wavelength of both the incident and reflected waves. Because of the relative phase differences, there may be regions of constructive and destructive interference between incident and reflected waves (i.e., standing wave patterns) which, in turn, create peaks and valleys in the heating patterns generated in the tissue (Johnson and Guy 1972). The exact heating pattern in any given target, therefore, is determined by the tissue properties and dimensions, antenna characteristics, and the frequency of the incident wave. In general, bulk absorption tends to dominate and the SAR falls off rapidly with depth. Because microwaves are effective for superficial heating, a large number of reports describe the use of microwave techniques for treatment of superficial tumors (Hornback et al. 1979; U et al.; Luk et al. 1981).

Deep-lying tumors are usually difficult to heat with microwaves because the overlying tissues absorb and reflect the incident microwave beam. One approach to the problem of inadequate deep heating with microwaves, developed by P.F. Turner with the BSD corporation in Salt Lake City, Utah, utilizes an annular phased array of microwave applicators (Short and Turner 1980). This device operates between 55 and 110 MHz. A ring of applicators encircles the patient, and diametrically opposite applicators are phased in such a way as to produce constructive interference of the plane waves in the center of the target. The interference patterns tend to mitigate undesired surface heating and to counteract attenuation of SAR with depth. An approximately uniform power deposition pattern can be produced in biological loads using this approach. However, because this approach tends to heat large volumes of tissue, a corresponding disadvantage is that the aggregate applied power may cause systemic hyperthermia that limits the duration of any one treatment--especially if the target tissues are well perfused.

To avoid electromagnetic interference with other electronic devices and to avoid possible hazards to hospital personnel of chronic low level exposure, microwave heating must be done in an electrically shielded room. A relatively low cost copper screen cage can be constructed for this purpose. More elegant shielded facilities require alteration and renovation of treatment rooms at significant expense. Most instrumentation within the shielded area cannot be used when the microwave apparatus is on, and accurate online temperature measurement is difficult during microwave treatment. In particular, thermistors are difficult to use because of field-thermometer interactions during application of power (Cetas and Connor 1978). Even low resistance thermocouple junctions may self heat sufficiently to produce errors of over 2°C (R.E. Shupe, personal communication, 1982). The BSD system endeavors to employ non-interacting thermometers based upon gallium arsenide fluorescence, together with fiber optical coupling to circumvent such problems. This system is currently undergoing field tests at many institutions, including the University of Utah (Gibbs et al. 1982).

Hornback, Shupe, and their coworkers (1979) at Indiana University Medical School in Indianapolis have considerable clinical experience with microwave hyperthermia. They use arrays of Erbe 434 MHz diathermy units to produce regional and whole-body hyperthermia. As the patient's body temperature rises during the initial stages of heating, reactive superficial vasodilation occurs, improving blood flow to the skin. Continued microwave heating of the skin tends to produce whole-body hyperthermia, since warmed blood is returned via the venous circulation to the heart. These investigators have thus found large aperture microwave heating to be useful for producing whole-body hyperthermia. Indeed any localized hyperthermia device that deposits power in a relatively large volume will tend to produce whole-body heating (Gibbs et al.). If such systemic hyperthermia is not desired, it is necessary to cool untreated regions of the body with fans, ice packs, temperature controlled blankets, or other means.

Capacitively Coupled RF Heating

Capacitively coupled radiofrequency (RF) heating is accomplished at frequencies of 0.5-30 MHz with contact electrodes. Many of the problems of dealing with propagating electromagnetic waves are obviated, and heating patterns are similar to those which would be generated by direct current in a complex bulk conductor. These frequencies are high enough, however, to avoid electrical stimulation of muscle and nerve tissue. Capacitively coupled radiofrequency heating of tumors has been employed in the clinic by Le Veen and coworkers (1976; 1980) at the Medical University of South Carolina and by Brezovitch and colleagues (1981) at the University of Alabama.

Capacitively coupled RF, like microwave energy, tends to cause excessive heating of surface tissues, albeit by a different mechanism. In order to heat deeper lying target tissue such as a tumor, the RF current must penetrate the subcutaneous fat. Fat has significantly higher resistivity than most other tissues (roughly 2000 ohm-cm for fat vs. 600 ohm-cm for skin, and 400 ohm-cm for viscera); so that much greater resistive heating of fat occurs when a given current is passed through it, as would be expected in a series circuit. Also, the current density distribution in a volume conductor (tissue) converges to maximal values immediately under the electrodes on the skin surface. Because resistive heating is proportional to both the tissue resistivity and the square of the current density, the power deposition beneath the electrodes is certain to be greater than elsewhere in the bulk conductor. For this reason, virtually all practical capacitively coupled electrodes are water cooled to dissipate excess heat at the skin surface.

A controversial scheme to provide a focusing effect with capacitively coupled RF has been proposed by LeVeen (LeVeen et al. 1980), and is under commercial development. This so-called "cross-fire" system works by activating alternate pairs of conductive electrodes that surround the target. In work in progress at the University of Arizona, one of us (JRO) measured power densities during RF heating in phantoms having typical human dimensions in cross section. With 15 cm x 15 cm electrodes on either side of a 22-cm-wide homogeneous load with conductivity and dielectric constant similar to muscle, the ratio of superficial to mid-plane power deposition was 8.3. The decreasing power density with depth in this case is explained by divergence of the electric field between the electrodes. Since the current flow is approximately perpendicular to major tissue interfaces in heterogeneous loads (e.g., skin/fat, fat/muscle, and muscle/viscera), the power density in superficial fat relative to midplane viscera will be equal to the above power deposition ratio multiplied by the ratio of conductivities of fat to viscera. The resulting unfavorable ratio of power densities (18. 7) reveals the fundamental difficulty of achieving power deposition at depth with capacitively coupled RF.

Inductively Coupled RF Heating

Inductive techniques for elevating tissue temperatures have been used in diathermy practice for many decades, but interest in the application of these techniques to human cancer therapy has been more recent. Storm and coworkers (1979a; 1979b) at Henry Medical Electronics in Los Angeles have reported on the use of a cylindrical electrode encircling large body regions (thorax, abdomen, or pelvis) for inductive heating of visceral tumors. The principle of this technique is that an alternating magnetic field is produced in the space encompassed by a coil carrying an alternating electric current. Faraday's law states that an alternating magnetic field passing through the torso will be associated with an induced electric field. In the case in which the coil surrounds the thorax or abdomen of the patient, this induced electric field can then produce current flow ("eddy currents") and, in turn, joule heating within the body. The general pattern of eddy current flow in a human patient surrounded by a current carrying coil follows concentric cylindrical surfaces about the longitudinal body axis. Moreover, there is a strong radial dependence of the magnitude of current flow that leads to a power density P_v within body tissues that in a strictly cylindrical load is given by the expression

$$P_v(r) = \frac{1}{8}\sigma(\omega r \mu H)^2,$$

where

σ = the electrical conductivity of the tissue (mho/m),
ω = the radian frequency of the alternating magnetic field (radians/sec),
r = the radius of the tissue element from the axis of the cylindrical load (m),
μ = the magnetic permeability of the tissue (Hy/m), and
H = the amplitude (phasor) of the applied magnetic field (amp/m) (Oleson, in press; Bottomley and Andrew 1978).

The most relevant feature of this expression for cancer therapy is the dependence of the absorbed power density on the square of the radius. This fundamental physical principle tends to make inductive radiofrequency heating--like microwave heating and capacitively coupled RF--much more effective in superficial tissues than in deep tissues, at least as long as cylindrical symmetry is maintained.

Experimentally, investigation of the power density patterns in cylindrical and heterogeneous loads has been reported by Paliwall and colleagues (1982) and Oleson (in press) in the case of an electrode encircling the load. Bioheat transfer modeling of temperature distributions in this case has been done by Halac and coworkers (in press) and by Hand and coworkers (1982a; 1982b) in the case of a flat "pancake coil" held over the skin surface. The essential features of the inductive heating seem to be that because eddy current flow is generally parallel to tissue interfaces, there is some sparing of the subcutaneous fat layer from excessive temperature rise in comparison to the capacitively coupled RF technique. However, because of the quadratic dependence of power density on radius, there is still a fundamental difficulty in achieving sufficiently high power densities at depth for therapeutic heating of tumors, while maintaining applied power levels that do not damage superficial tissues. Of course, cooling of surface tissues can be done as with any deep heating device, but the depth at which excessive heating can be reduced by various surface cooling techniques is limited to about 3 cm (Hand et al. 1982a). In practice, surface cooling may or may not be sufficient to overcome the problem of superficial hot spots in specific cases.

Another way of using the inductive method to heat deep seated tumors is to place a current loop on either side of the body (Helmholtz coils), such that the common axis of these two loops is perpendicular to the longitudinal body axis. This approach has been developed at the M.D. Anderson Hospital by P.M. Corry et al. (1982a), and at the University of Arizona and Purdue University by the authors and their coworkers (Oleson, in press; Oleson et al., in press; Voorhees and Babbs, in press). Power deposition with this technique still varies approximately quadratically with distance measured perpendicularly to the common electrode axis, but in contrast to the circumferential electrode power deposition pattern, there are points on the midplane between the electrodes where the power deposition does not vanish. The total volume of superficial tissue receiving power deposition is also less than with the circumferential electrode, thus reducing somewhat the problem of excessive whole-body heating. There are complementary features to the non-uniform power deposition patterns in the case of the circumferential electrode vs. the coaxial electrode pair, and in some circumstances alternating the two electrode arrangements may reduce the volume of tissue that is inadequately heated by one electrode arrangement alone. However, the power deposition pattern with this technique is very difficult to analyze and control in the case of heterogeneous loads with differing geometries.

Ultrasound

There is a vast literature available on the biomedical uses of ultrasound (Clark et al. 1980), both in diagnostic and therapeutic applications. Heating is produced as ultrasound vibrations are absorbed in tissue. Focusing and/or pulsing of ultrasound can lead to markedly increased absorption in limited regions because of nonlinear effects--perhaps to great advantage in hyperthermia applications (Dunn et al. 1982). In addition to the tissue heating, another effect of ultrasound is that of cavitation, and it is possible that this process may produce non-thermal injury in biological tissues (Apfel 1982).

In any application, it is important to recognize that ultrasound is poorly transmitted across air spaces, because strong reflection of the incident beam occurs within the soft tissue side of any tissue/air inlet face. Also, ultrasound is strongly absorbed within bone, and strongly reflected at tissue/bone interfaces. Hence presence of bone may interfere with the desired use of ultrasound. The absorption of ultrasound in soft tissue diminishes as frequency decreases, so that there is an optimal range of frequencies providing both adequate penetration and adequate absorption (Barber and Grifface 1981; Hill 1982). Near 1 MHz, wavelengths in soft tissue (approximately 1 to 3 mm) are short enough to enable beams to be focused using various lens designs. The possibility of sharply focused power deposition at depth sets ultrasound apart from external microwave or radiofrequency techniques, where physics seems to dictate that little focusing at depth is possible. On the other hand, poor acoustical transmission across air prevents ultrasound from being used for tumors surrounded by aerated lung. Accordingly, ultrasound has been most frequently used to treat superficial lesions, extremity lesions, or deep lesions in the abdominal cavity.

Clinical investigations of "plane wave" and focused ultrasound have been reported by Lele and Parker (1982) and by Marmor and coworkers (1979a; 1979b). Corry and associates (1982b) also have considerable experience in hyperthermia produced by plane wave transducers. Lele and Parker at M.I.T. and Fessenden and colleagues (1982) at Stanford are investigating the use of focused approaches for heating deep visceral tumors. At Stanford, a system developed jointly with Hewlett- Packard Corporation in Palo Alto, California, is under trial. In the near future it will be possible to make a preliminary judgment as to whether the theoretical promise of ultrasound hyperthermia for achieving focused, deep heating can be easily translated into clinical practice.

Summary and Conclusions

Technology for local heat therapy of cancer is evolving rapidly at a number of technologically diverse and geographically scattered institutions and companies. No single technology is superior to others in all applications, and no single company, laboratory, or research group has all the answers. An ideal system would provide focused heating at depth in a predictable fashion, with little probability of generating undesired hot spots in normal tissues and little interference with monitoring equipment. Existing systems approximate this ideal to different degrees, depending on the anatomy and geometry of the tumor and its surrounding tissues.

In the foregoing discussion the important problem of measuring temperatures in tumors and normal tissues has been slighted. At the present time, all thermometry is necessarily invasive, and there are limitations to the number of points at which temperatures can be measured utilizing percutaneously placed catheters as conduits for thermometers. However, further advances in the art, the science, and the technology of local heat therapy are likely to be forthcoming in the next few years from a diverse community of investigators and young companies, who are following an interesting variety of approaches. Continued research and development in the spirit of constructive, rather than destructive, competition will certainly advance the field substantially--much to the benefit of patients. At present, however, clinical engineers should realize that hyperthermia therapy for cancer is still experimental. Despite the flurry of commercial activity, considerable caution should be exercised in the purchase and use of hyperthermia equipment.

References

Apfel, R.E. 1982. Acoustic cavitation; a possible consequence of biomedical uses of ultrasound, Br. J. Cancer (Suppl. V) 45:140-146.

Babbs, C.F. 1982. Biology of local heat therapy for cancer. Med. Instrum. 16:23-26.

Barber, F. E., and C.P. Grifface. 1981. Power deposition for ultrasound hyperthermia. Paper presented at the 1981 AAPM Summer School on Physical Aspects of Hyperthermia, August 3-7.

Bottomley, P.A., and E.R. Andrew. 1978. RF magnetic field penetration, phase shift and power dissipation in biological tissue: Implications for NMR imaging. Phys. Med. Biol. 23:630-643.

Brezovich, T.A., et al. 1981. A practical system for clinical radiofrequency hyperthermia. Int. J. Radiat. Oncol. Biol. Phys. 7:423-440.

Cetas, T.C., and W.G. Connor. 1978. Thermometry considerations in localized hyperthermia. Med. Phys. 5:79-91.

Clark, G., et al. 1980. Bibliography of biomedical ultrasound from 1 January 1971. Ultrasound Med. Biol. 6:385-405.

Corry, P.M., et al. 1982a. Treatment of bulky human neoplasms with a magnetic induction system (abstract). Paper presented at North American Hyperthermia Group Annual Meeting, April17-19.

Corry, P.M., et al. 1982b. Combined ultrasound and radiation therapy treatment of human superficial tumors. Radiology 145:165-169.

Dunn, F., et al. 1982. Nonlinear ultrasonic propagation in biological media. Br. J. Cancer (Suppl. V) 45:140-146.

Fessenden, P., et al. 1982. Experience with a deep heating ultrasound system (abstract). North American Hyperthermia Group Annual Meeting, April 17-19.

Gibbs, F. A., et al. 1982. Preliminary experience with induction of deep regional hyperthermia using the BSD annular phased array applicator system (abstract). Paper presented at North American Hyperthermia Group Annual Meeting, April 17-19.

Hahn, E.W., and J.H. Kim. 1980. Clinical observations on the selective heating of cutaneous tumors with the radiofrequency inductive method. Ann. N.Y. Acad. Sci. 335:347-351.

Halac, S., et al. In press. Magnetic induction heating of tissue: numerical evaluation of tumor temperature distributions. Int. J. Radiat. Oncol. Biol. Phys.

Hand, J.W., et al. 1982a. Considerations of radiofrequency induction heating for localized hyperthermia. Phys. Med. Biol. 27:1-16.

Hand, J.W., et al. 1982b. Temperature distribution in tissues subjected to local hyperthermia by RF induction heating. Br. J. Cancer (Suppl. V) 45:31-35.

Hill, C.R. 1982. Ultrasound biophysics: a perspective. Br. J. Cancer (Suppl. V) 45:46-51.

Hornback, N. B., et al. 1979. Radiation and microwave therapy in the treatment of advanced cancer. Radiology 130:459-464.

Johnson, C.C., and A.W. Guy. 1972. Nonionizing electromagnetic wave effects in biological materials and systems. Proc. IEEE 66:692-718.

Lele, P.P., and K.J. Parker, 1982. Temperature distributions in tissues during local hyperthermia by stationary or steered beams of unfocused or focused ultrasound. Br. J. Cancer (Suppl. V) 45:108-121.

LeVeen, H.H., et al. 1976. Tumor eradication by radiofrequency therapy: response in 21 patients. JAMA 235:2198-2200.

LeVeen, H.H., et al. 1980. Radio-frequency therapy; clinical experience. Ann. N.Y. Acad. Sci. 335:362-371.

Luk, K.H., et al. 1981. Clinical experiences with local microwave hyperthermia. Int. J. Radiat. Oncol. Biol. Phys. 7:615-619.

Manning, M.R., et al. 1982. Clinical hyperthermia; results of a phase I trial employing hyperthermia alone or in combination with external beam or interstitial radiotherapy. Cancer 49:205-216.

Marmor, J. B., et al. 1979a. Tumor eradication and cell survival after localized hyperthermia induced by ultrasound. Cancer Res. 39:2166.

Marmor, J.B., et al. 1979b. Treatment of superficial human neoplasms by local hyperthermia induced by ultrasound. Cancer 43:188-197.

Oleson, J.R. In press. Hyperthermia by magnetic induction I: Physical characteristics of the technique. Int. J. Radiat. Oncol. Biol. Phys.

Oleson, J.R., et al. In press. Hyperthermia by magnetic induction II: Clinical experience with concentric electrodes. Int. J. Radial. Oncol. Biol. Phys.

Paliwall, B.R., et al. 1982. Heating patterns induced by a 13.56 MHz radiofrequency generator in pig abdomen and thorax. Int. J. Radial. Oncol. Biol. Phys. 8:829-835.

Short, J.G., and P.F. Turner. 1980. Physical hyperthermia and cancer therapy. Proc. IEEE 68:133-142.

Song, C.W. et al. 1980. Blood flow in normal tissues and tumors during hyperthermia. J. Nat. Cancer Inst. 64:119-124.

Stauffer, P.R. 1979. A magnetic induction system for inducing localized hyperthermia in brain tumors. Thesis. University of Arizona, Tucson, Arizona.

Storm, F.K. et al. 1979a. Normal tissue and solid tumor effects of hyperthermia in animal models and clinical trials. Cancer Res. 39:2245-2250.

Storm, F.K., et al. 1979b. Human hyperthermia therapy: Relationship between tumor type and capacity to induce hyperthermia by radiofrequency. Amer. J. Surg. 138:170-174.

Strohbehn, J.W., et al. 1979. An invasive microwave antenna for locally induced hyperthermia for cancer therapy. J. Microwave Power 14:339-350.

U, R., et al. 1980. Microwave-induced local hyperthermia in combination with radiotherapy of human malignant tumors. Cancer 45:638-646.

Voorhees, W.D., and C.F. Babbs. In press. Hydralazine-enhanced selective heating of transmissible venereal tumor implants in dogs. Europ. J. Cancer.