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HYPERTHERMIA THERAPY

The normal range of body temperature of human beings is maintained at a relatively stable temperature near 37°C. Organs and tissues function most efficiently at this range. Temperature elevation even a few degrees above this norm is associated with varying levels of biological responses. Hyperthermia is the term used to describe significant departure of tissue temperature from the usual limit (40°C) encompassed by thermoregulatory activity. Its use for therapeutic purposes has expanded in recent years to include a variety of abnormal conditions. Investigations to date have shown that while hyperthermia can produce whole-body (regional) and local tissue modifications for effective therapy, temperatures at which the desired tissue response occurs vary over a wide range. Moreover, final tissue temperature is a complex function of energy deposition, blood flow, and heat conduction in tissue.

Hyperthermia has been used therapeutically very early in human history. However, aside from a few well-established medical applications, hyperthermia is still in a relatively early stage of development. Current medical applications fall into three broad categories: musculoskeletal conditions, cancer treatment, and coagulative ablation therapy. An important aspect of its development is the production of adequate temperature distribution in the target tissue, superficial or deep-seated. Moreover, successful hyperthermia therapy requires not only a suitable energy source for heat production, but also an understanding of the underlying pathological condition being treated to define the critical target temperature as well as the ability to reach that tissue with the heating modality. Energy sources that can be used for hyperthermia include ultrasonic wave and electromagnetic field and radiation as well as conducted heat or convection.

Diathermy for Musculoskeletal Conditions

Therapeutic heating of musculoskeletal tissues by conversion of electromagnetic and ultrasonic energies in deep-lying tissues without excessive heating of the skin is known as *diathermy* (through heat). It has been the dominant clinical application until the 1970s. Diathermy modalities in use include spot focus ultrasonic transducers that operate at 1 MHz. In the United States, the most prevalent electromagnetic modalities are the shortwave inductive-coil diathermy operating at 27.12 MHz and the microwave (corner reflector or aperture) diathermy operating at 2450 MHz. The frequency of 433 MHz is used extensively in many European countries.

In practice, clinical diathermy is guided by patient report of pain and warmth sensation. Since local elevation of tissue temperature is apparently the most significant factor in physiological response to diathermy, objective measures of subcutaneous tissue temperature in real time would enhance both its efficacy and safety. While accurate and reliable noninvasive sensing of subcutaneous temperature must await further technological advance, the combination of multiple invasive sensors and computational estimates can provide some useful information.

Therapeutic indications are based on local elevations of tissue temperature brought about by volume heating (1,2). In particular, diathermic heating to 41°C to 45°C produces hyperemia-enhanced blood perfusion to the body part under treatment. The augmentation in blood flow is accompanied by elevations in capillary

pressure, in membrane permeability, and in the rate of metabolism. These increases can facilitate tissue healing and can also facilitate clearance of metabolites, debris, and toxic substances from diseased tissue under treatment. Diathermic heating of deep tissues promotes relaxation in muscles, reduces pain, and provides relief from muscle spasms (2,3). Heating can also produce greater extensibility in fibrous collagen tissues, which is significant in the management of joint contractures due to tightness of the capsule, fibrosis of muscle, and scarring.

Hyperthermia Treatment for Cancer

Hyperthermia cancer therapy is a treatment procedure in which tumor temperatures are elevated to the range of 40°C to 45°C. The rationale for hyperthermia therapy is related to the ability of elevated temperature to selectively destroy malignant cells. While tumor cells exhibit inherent hyperthermic sensitivity, their response is characterized by the acidic, hypoxic, and nutritionally deprived environment often found in the interior of various tumors (4,5,6). Poor blood perfusion in the interior of a tumor also facilitates heat buildup. Moreover, the cytotoxic effects of some autitumor drugs are enhanced and the cell-killing ability of ionizing radiation is potentiated by hyperthermia serving as a sensitizing agent. Hyperthermia also increases blood–brain barrier permeability (7). The synergism of hyperthermia and ionizing radiation is particularly poignant since it is accomplished by thermal killing of hypoxic cells and cells in S phase (DNA synthesis), which are resistant to ionizing radiation.

Clinical and laboratory results from various countries have indicated a promising future for hyperthermia (8). Its efficacy depends on the induction of sufficient temperature rise throughout the tumor volume. A recent assessment of superficial breast cancer has indicated that local complete response with hyperthermia and ionizing radiation is about 60% compared to 40% with irradiation alone (9). Currently, hyperthermia is still an experimental treatment in the United States for late-stage patients with advance tumors, but it has gained some acceptance in Europe and Japan (10,11,12).

While beyond the scope of this article, whole-body hyperthermia has been employed in some cases to enhance the effectiveness of chemotherapy for patients with systemic metastatic cancer. A variety of conductive and convective heating techniques such as warm air, water, and wax are used (13,14,15). Mild whole-body hyperthermia at 40°C for as long as 10 hours in rats has shown promising therapeutic potentials on primary tumor. Temperature up to 41.8°C is found to be safe and is well-tolerated by human patients for up to 60 min (16,17). While clinical results still remain guarded, they provide a foundation for further exploration.

Monitoring and control of tumor temperature in real time during hyperthermia treatment is essential for effective therapy. While progress in temperature sensing in vivo has been dramatic, considerable advance is needed prior to widespread clinically application of hyperthermia for cancer. Among approaches that may impact this outcome include invasive multipoint sensing (18) and noninvasive magnetic resonance imaging and diagnostic ultrasound temperature mapping (19,20,21).

A prominent problem in hyperthermia treatment for cancer is the generation of heat and control of temperatures in tumors. Ultrasonic and electromagnetic energies are the commonly used sources for regional and local hyperthermia. A large number of external and implanted antennas and applicators have been designed to produce therapeutic heating of localized tumors of different volumes in a variety of anatomical sites. Clearly, each modality has its own liabilities. Recently, there was a comparison of temperature distributions obtained in the same tumors, and there was also a comparison of acute and subacute toxicities in patients that were treated with both external ultrasound and electromagnetic applicators (22). It was concluded that there is no preferred modality. The type of applicator should be selected on the basis of specific site and type of the tumor.

Ultrasonic Heating. Absorption of ultrasonic pressure wave in biological tissue is determined by ultrasound frequency, velocity, and tissue density. Several frequencies between 0.5 MHz and 3.5 MHz have been used for hyperthermia cancer treatment. At these frequencies, ultrasound can penetrate deep inside the body

while maintaining the ability to focus energy into the tumor to raise the temperature tumor volume to above the minimum therapeutic temperature. Its clinical application is constrained by the available ultrasound window between the transducer and target tumor, as well as by the presence of bone and soft tissue interfaces in the propagation pathway. Differences in tissue density can give rise to excessive temperature elevation resulting from accumulation of reflected power at these interfaces. For a given set of anatomic and physiologic parameters, temperature distribution in a tumor is determined by transducer design, scanning pattern, scanning speed, and output power.

Ultrasonic modalities for noninvasive hyperthermia cancer treatment include spot focus transducers and phased arrays. By mechanically scanning a focused transducer around a treatment volume, uniform temperature distribution with a sharp falloff outside the treatment volume may be obtained (23,24,25). However, for large, deep-seated tumors, scanning transducers often produce hot spots proximal to the tumor along the central axis ahead of the focal plane (26). It should be mentioned that frequency sweeping and transducers with a nonvibrating center can be used to reduce the central hot spot (27). There are two classes of phased arrays that do not require physical movement of the transducer elements (28,29,30,31,32). The class of phased arrays with geometric focusing and spot scanning has features and limitations similar to those of mechanically scanned spot focus transducers (28). In this case, the transducer array is fixed in position and electrical spot scanning is accomplished through adjustment of array element phases which maximize constructive interference at each focal plane.

Alternative array element configuration and phase excitation can avoid hot spots that result from constructive interference along the array's central axis (29,30,31,32). Several phased array configurations have been proposed. They include the concentric ring, sector vortex, spherical section, and the square arrays. With proper selection of array element phases, these phased arrays can be operated to directly synthesize, without scanning, ultrasonic power deposition patterns for improved localization of heating within the tumor volume. Phased arrays offer another advantage over single focused transducer: They enable electronically programmable treatment planning (33). Pretreatment analysis can provide strategies aimed at satisfying therapeutic requirements for individual patients and specific tumor sites and spare other sensitive anatomic structures. It is noted that recently ultrasonic applicators have been tested for interstitial hyperthermia (34).

Electromagnetic Heating. Various frequencies of electromagnetic energy within the range of 0.05 MHz to 2450 MHz have been used for hyperthermia treatment of cancer. The interaction of electromagnetic fields and waves in biological tissue is governed by (1) source frequency and intensity, (2) antenna or applicator design and polarization, (3) tissue structure, and (4) dielectric permittivity (35,36,37). In thermal therapeutic applications, the final temperature is affected also by tissue blood flow and heat conduction. However, the time rate of heating and spatial distribution of electromagnetic energy at any given moment in time are direct functions of specific absorption rate (*SAR* or power deposition), which are functions of antenna or applicator design.

At frequencies below a few hundred megahertz [i.e., radio frequencies (*RF*)], wavelengths in tissue are 100 cm or longer (see Table 1). Power deposition for local tissue heating is characterized by quasistatic displacement or conduction currents, and heating comes about through tissue resistance to current flow. At microwave frequencies, wavelengths are much shorter, radiated power dominates, and dielectric loss gives rise to heat production. Power coupling from air into tissue is substantial and can exceed 50%. In addition, the effective depth of penetration can provide useful insight into the performance of various applicators. For example, because of both the focusing ability and the depth of energy penetration, single-contact applicators operating at 915 MHz or 2450 MHz have been used to heat well-localized superficial tumors extending to a depth up to 3 cm to 6 cm.

RF Heating. For noninvasive subcutaneous tissue heating by RF energy, simple capacitive plates and inductive coil applicators have been used. Tissues are positioned between the plates and are heated by displacement currents (38,39). A water bolus is often placed between the plate and skin to prevent superficial burns from large electric field concentration near the edges. A limitation of the capacitive applicator is that the

Table 1. Propagation Characteristics of RF and Microwave Fields and Waves in Planar Model of Biological Tissues of High- and Low-Water-Content Biological Tissues at 37°C[a]

Frequency (MHz)	Dielectric permittivity		Conductivity (S/m)		Wavelength in tissue (cm)		Effective depth of penetration (cm)		Power coupling coefficient from air	
	High	Low	High	Low	High	Low	High	Low	High	Low
27	113	20.0	0.61	0.03	68	241	14.3	77	0.14	0.56
40	97	14.6	0.69	0.03	51	187	11.2	58.8	0.17	0.62
100	72	7.5	0.89	0.05	27	106	6.7	34.4	0.22	0.74
433	53	5.6	1.43	0.08	8.5	28.2	3.6	18.3	0.36	0.82
915	51	5.6	1.60	0.10	4.4	13.7	2.5	12.8	0.40	0.83
2450	47	5.5	2.21	0.16	1.8	5.2	1.7	8.1	0.43	0.84

[a] From Ref. 35.

electric field is predominately normal to the interface between fat and other tissues. Overheating by as much as 20 times that in muscle can occur in subcutaneous fat greater than 2 cm in thickness. Note that it is possible to treat tumors of patients with subcutaneous fat as thick as 3 cm by precooling the fat prior to the initiation of heating (40).

The common inductive applicator consisting of a planar or "pancake" coil with a small number of turns when placed parallel to the body surface can avoid the excessive heating problem in fatty tissue. Since the induced electric fields form eddy currents that flow parallel to the tissue interface, heating is highest in muscle instead of fat. The heating pattern is toroidal with a null along the axis of the applicator (41). Some recent designs have SARs that do not include a null in the center and are considerably more uniform than that of the planar coil (38,42,43). While inductive applicators are used predominately for superficial treatment, some of the newer applicators can produce effective heating up to a depth of nearly 7 cm.

Several RF applicators have been invented to provide noninvasive heating of deep-seated tumors. These include the large capacitive applicator mentioned previously (44,45) as well as the ridged waveguide (46), helical coils (47,48), and multielement arrays (49,50,51,52). The helical coil applicator is simple in construction, and it provides SAR patterns that vary slowly with radial distance. However, the region to be heated must be located near the center since the axially directed electric field has a maximum near the center of the coil structure. Its performance may be improved by judicious selection of the diameter-to-length ratio and incorporation of external tuning. The multielement array concept has gained considerable utility in the clinic. A primary advantage of multielement array systems is the ability to steer the heating pattern electronically by varying the amplitude and phase of each element, thereby allowing phased arrays operating at RF to be used for selective heating of deep-seated tumors in a variety of anatomic sites.

In particular, the annular phased array system is utilized to heat large anatomical regions such as the thorax, abdomen, and pelvic area (49,50,53). Regional heating is frequently complicated by systemic

hyperthermia and hemodynamic compensation and by excessive heating or adjacent normal tissue structures, especially the bone–tissue interface. However, recent advances using feedback algorithms and adaptive software modifications to control the amplitude and phase of each element showed that it is possible to maximize the SAR at a target tumor position in a complex anatomy and simultaneously minimize or reduce the power deposition at locations where undesirable hot spots may occur.

A novel noninvasive or minimally invasive concept using ferro- or paramagnetic compounds for intracellular hyperthermia treatment of both primary and metastatic cancers was first proposed in the late 1950s. Earlier studies have demonstrated both the preferential accumulation of submicron-sized magnetic particles (magnetites) in tumors and the feasibility of selective heating using 0.24 MHz to 80 MHz RF magnetic fields. Current investigations (54,55,56) are directed toward cellular uptake of fluidized magnetic particles, bounding of magnetite with targeting activity towards cancer cells, and the hyperthermic effects of fine magnetic particles on tumor cells in vitro. It is expected that a magnetite-labelled antibody may soon be available clinically as a therapeutic agent for hyperthermia treatment of cancer.

A related technique for RF hyperthermia involves implanted ferromagnetic seeds activated by externally applied 0.05 to 2 MHz magnetic fields. Heating is produced by eddy currents induced on the surface of the implant and is therefore dependent on the permeability of the thermoseed material (57,58,59,60,61,62). Using Curie temperatures close to the maximum temperature desired in the tissue, the ferromagnetic seeds can be designed to provide thermal self-regulation so that a constant tumor temperature can be maintained throughout the treatment regime. Since volume tissue heating is by passive thermal conduction, these 0.1 mm to 1.0 mm diameter thermoseed of various length must be implanted closely. Nevertheless, under certain conditions this invasive seed implant method like the interstitial RF electrodes and microwave antennas to be discussed later may be preferable for local hyperthermia of deep-seated tumors. It is noteworthy that ferromagnetic seed hyperthermia in combination with other modalities are used in the control of ocular tumors in animals (63,64). Recently, multifilament seeds such as the palladium–nickel (PdNi) thermoseeds have gained interest because of a more effective power deposition than solid seeds (65).

For some deep-seated tumors or tumors of large volume, interstitial techniques have been employed to generate the desired hyperthermic field. RF electrodes operate in the frequency range of 0.5 MHz to 1 MHz (66,67,68,69). The advantages of interstitial techniques are safe (without skin burn) and more uniform heat distribution within the tumor. RF current flowing between pairs of needle-like bare electrodes is dissipated by the ohmic resistance of tissue and is converted to heat. The temperature distribution produced is strongly dependent upon blood flow in the tissue and spacing between electrodes. Most clinical applications require an array of these electrodes spaced at 1.0 cm to 1.5 cm intervals in parallel for optimal temperature uniformity. Excessive or inadequate heating could be minimized by independent control of RF currents and by varying the lengths of electrodes.

Microwave Heating. For superficial tumors, single-contact applicators operating at 433 MHz to 2450 MHz have been used. The shorter wavelength at these frequencies allows microwave radiation from a small applicator some focusing ability in tissues for selective hyperthermia. Because of the limited depth of energy penetration, these antennas have been applied to heating well-localized tumors extending to depths of up to 3 cm to 6 cm depending on the particular applicator (39,44,69,70).

The types of external applicators that have been reported for cancer hyperthermia include horns, microstrip applicators, and circular, rectangular, and ridged waveguides (71,72,73,74,75,76,77,78,79). These applicators are used with a high-permittivity, dielectric material to match them to tissue. In the case of a water-like bolus, it serves also to provide surface cooling of the skin and to avoid the problem of burns and blisters. Microstrip applicators are lightweight and have a low profile. They offer efficient energy coupling and are easier to use clinically (77,78,79). One limitation of a single applicator is its small area of tissue coverage. Another is that the SAR distribution cannot be modified during use, making it difficult to improve the nonuniform temperature distribution that are inevitably produced during patient treatments. One approach to overcome this problem is to scan the applicator over the tissues (80).

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A favorable external system to treat tumors of wide area (tumors that exceed several cm in diameter) is the phased array consisted of multiple microstrip applicators. The primary advantage of the multielement array system is the ability to control electronically the SAR distribution by varying the amplitude and relative phase of each element, independently. Moreover, a planar or quasiplanar phased array operating at microwave frequencies can be used to improve depth of penetration for selective heating of deep-seated tumors in a variety of anatomic sites (81,82,83,84,85,86). A further advantage is that the SAR distribution can be adjusted during treatment, enabling it to enhance the homogeneity of temperature distribution in the target region. The added sophistication needed for controlling a multitude of array parameters is well within the capability of current electronic technology. Although a bolus of cooling fluids can be used to prevent undesirable heating of superficial tissues, tissue layers and curvatures in the near field of the applicator present considerable challenge to quality control in patient treatments. In practice, the commonly accepted SAR variation is 50% throughout the entire treatment region.

Intracavitary techniques can be used for certain tumors at hollow viscera and cavity sites such as the esophagus, cervix, bladder, prostate, and rectum (69,87). Properly designed intracavitary applicators and antennas can lead to a highly targeted heating of tumors and a reduced risk of unwanted heating of normal tissues. There are several reports of devices designed for various tumor sites (88,89,90,91). Clinical applications may require the antennas to be equipped with an integrated cooling system.

The technical difficulty in heating deep-seated tumors without overheating adjacent normal tissue confronted by external applicators has enabled interstitial array techniques to become a viable treatment modality (67,69,92,93,94,95). The technique has the capacity to adapt its SAR distribution to an irregularly shaped tumor volume and to provide uniform temperature in deep-seated tumors. Also in combination with brachytherapy, interstitial hyperthermia renders a treatment modality for malignancies with little additional risk to the patient (69,95,96).

The efficacy of interstitial microwave heat treatment of soft-tissue tumors is predicated on a sufficient temperature distribution throughout the tumor. A major determinant is the catheter antenna. Recent designs have provided microwave interstitial array systems capable of inducing uniform temperature distribution throughout the entire tumor volume without the need for insertion of the tip of the antenna well beyond the tumor boundary (97,98,99,100). That requirement was a major drawback of many older catheter antennas which had the tendency to produce a cold spot or low-heating zone near the distal tip of the antenna (67,101, 102,103), which creates an unnecessary situation for damage to normal tissue. A desirable feature of some of the newer catheter antenna designs, especially those with integral sleeves or coaxial chokes, is that the SAR distribution is independent of insertion depth (90,104,105). These antennas have also managed to alleviate the common problem of excessive heating of the skin from current accumulation at the insertion point. In the clinic, interstitial microwave antennas are inserted into plastic catheters implanted into the tumor. Computational and experimental studies have shown that SAR distributions vary with antenna design, catheter size and material, and air space between the antenna and the catheter (100,105,106).

Array configurations (i.e., geometry and antenna spacing) would also dictate the performance of the interstitial array treatment modality. Current microwave interstitial array systems rely mostly on equilateral triangle and square arrays of catheter antennas operating at 433 MHz to 2450 MHz and use element spacings of 10 mm to 20 mm. Theoretical and experimental results have shown that uniform power deposition and temperature distribution can be attained from both triangular and square arrays. However, power deposition and temperature elevation are higher for the triangular configuration at a given level of delivered microwave power. Moreover, for coherent phase excitations, constructive interference can provide SARs at the array centers an order of magnitude higher than those corresponding to a single interstitial microwave antenna. A flexibility afforded by an array of interstitial antennas is that the point of maximum SAR may be shifted from location to location by changing the amplitude and phase of each antenna. This would avoid low SAR spots during treatment and would ensure uniform tumor temperature over the entire treatment session. Nevertheless, it should be noted that ideal operating conditions are difficult to assure in the clinical setting.

Coagulative Ablation Therapy

The development of coagulative ablation therapy over the past decade has revolutionalized the practice of cardiology, gynecology, and urology. For many of the diseases, surgical intervention has been the principal method of treatment, although alternatives to surgery have been sought in an effort to reduce the cost and morbidity of treatment (107,108,109,110,111,112,113,114). Minimally invasive catheter ablation offers several potential benefits: Long incisions are replaced with a puncture wound, major cardiac and pulmonary complications from general anesthesia are side-stepped, and the need for postoperative intensive care is significantly reduced and, in many cases, offers a complete or lasting cure. It also has important advantages over drugs that are merely palliative. It avoids the side effects, expense, and inconvenience of chronic drug therapy, often with only partial success.

Energy sources that can be used for ablation therapy include RF, microwave, laser, and ultrasound. Before describing the RF and microwave technology, a brief discussion of laser interactions with tissue is given since it is used for the thermal therapy.

The effect of lasers on tissue is related to fluence (the product of power density and duration of irradiation). Thermal ablation involves the delivery of laser power for periods lasting tens to hundreds of seconds. The temperature can easily reach 100°C, depending on the delivery system. The desire to limit excessive tissue damage (myocardium, uterine wall, etc.) has led to several innovative technologies for laser thermal intervention. However, the complication of perforation or dissection is a cause for special attention in laser sources (115,116,117,118,119,120,121,122,123). Nevertheless, laser catheter irradiation (e.g., Nd:YAG, 1064 nm, 15 W to 50 W, spot diameter 2.0 mm to 2.5 mm) has been shown to produce lesions selectively in the targeted segment of the right ventricular conduction system in dogs, and the method can be performed in a controllable manner (120). Endometrial ablation techniques using laser coagulation under direct hysteroscopic control have been attempted with varying success (115,116,117,118,119). The variability arises principally from the unpredictable nature of induced thermal injury and perforation of the uterine wall. Laser coagulation prostatectomy is used to improve urinary flow rates (121,122,123). While results are comparable to standard electrocautery resection, the procedure can be enhanced by modifying the laser regimen and the spatial distribution of lesions. Since medical applications of laser are discussed elsewhere, it will not be addressed further in this section.

RF and Microwave Ablation. In RF thermal ablation therapy, the current flows between a small electrode inside the body to a large grounded electrode on the surface. The current rapidly diverges from the small electrode, so that current density is the highest at the electrode–tissue interface. The tissue's resistance to current flow results in termal lesions: desiccation and coagulation of tissue in direct contact with the electrode. The desiccated and coagulated tissue would raise the resistance to current flow, impede effective tissue heating, and limit the size of RF-induced lesions. Lesion beyond the immediate vicinity of the electrode–tissue interface occurs as a result of passive heat transfer from the thin high-temperature region. Investigations have shown that RF-induced lesions increase rapidly in size during the initial period of power application; then the rate of increase diminishes rapidly as the resistance at the electrode–tissue interface rises and the current flow falls (124,125,126,127). For this and reasons described below, studies comparing the power deposition patterns of RF and microwave catheters have shown that the absorbed microwave energy could be 10 times higher than RF at the same tissue depth (128,129).

The frequencies of most interest to microwave ablation are 915 MHz and 2450 MHz. Typical values of microwave dielectric permittivity and conductivity at 37°C are given in Table 2. The biological tissues of interest to ablation therapy can be classified into three major groups according to their water content. The group with very high water content includes blood, uterine lining, or physiological fluids. The second group is of moderately high water content and includes muscle or cardiac wall. The third group is made up of tissues with low water content such as bone, fat, or desiccated tissue. It can be seen that there is a modest change in dielectric constant and conductivity as a function of frequency. However, differences among the tissues are

Table 2. Dielectric Constant and Conductivity of Blood, Muscle, and Fat Tissues at 37°C for 915 and 2450 MHz–Two Frequencies of Most Interest to Coagulative Ablation Therapy[a]

	Dielectricconstant			Conductivity (S/m)		
Frequency (MHz)	Blood	Muscle	Fat	Blood	Muscle	Fat
915	60	51	5.6	1.4	1.6	0.10
2450	58	49	5.5	2.1	2.2	0.16

[a] From Ref. 36.

quite large. The higher 2450 MHz frequency is chosen because at this frequency the dielectric constant for blood is 20% higher than that for muscle, and the dielectric constant muscle is about 800% higher than that for fat. While conductivities of blood and muscle are approximately the same, they are about 300% higher than that of fat. As the microwave radiates into the tissue medium, energy is absorbed and converted to heat by dielectric loss. This absorption will result in a progressive reduction of the microwave power intensity as it advances in the tissue. The time rate of heating and spatial distribution of radiated microwave energy at any given moment in time are direct functions of SAR and antenna radiation pattern, respectively.

The reduction is quantified by the depth of penetration; a measure of the distance through which the intensity of a plane wave field is reduced to 13.5% of its initial level in a medium. At 2450 MHz, the depths of plane wave penetration for blood, muscle, and fat are 19 mm, 17 mm, and 81 mm, respectively (35,36,37). For microwave catheter antennas which do not have plane wavefronts, the penetration depth is reduced according to the specific antenna design. Nevertheless, these values clearly suggest that microwaves can deposit energy directly into distant tissues. Furthermore, the difference in the dielectric permittivity yields a depth of penetration for tissues with low water content about four times deeper for muscle or higher water content tissue at 2450 MHz. This means that a microwave field can propagate more readily through and be absorbed less by low water content tissues than that of high water content. It also implies that microwaves can propagate through intervening desiccated tissue or fat to deposit energy directly into more deeply-seated tissue.

Cardiac Ablation for Tachyarrhythmia. For a significant portion of patients suffering from tachyarrhythmias, available drug therapy has been found unsatisfactory because of a lack of meaningful response or unacceptable side effects (107,108,109). In some cases, these patients can be meanaged by open-heart surgery. Percutaneous catheter ablation of arrhythmogenic foci inside the heart is a potentially curative mode of treatment. Indeed, RF ablation has emerged as an effective therapy for many supraventricular tachycardias and has become accepted as the standard treatment for arrhythmias associated with the Wolf–Parkinson–White syndrome (107,108,130). Typically, the catheter is inserted percutaneously into the femoral vein and, under the guidance of a fluoroscope, is then advanced to inside the heart chamber. The cardiac conducting tissue responsible for the tachycardia is identified with the aid of endocardiac electrograms. A burst of RF energy is delivered through the electrodes to thermally ablate the cardiac conducting tissue responsible for the tachycardia and restores the heart to its normal rhythm.

Rapid and reliable mapping of the endocardiac electrogram for identification remains a technical challenge. Also, the lesions induced by RF current is quite small and shallow (125,127,131). Increasing the output

power to heat tissue at a distance often results in excessive temperatures at the electrode–tissue interface without the desired enlargement of lesion size (126,132). Note that temperature-guided RF catheter ablation with very large distal electrodes can be used to improve lesion size (133). The impedance of the ablating electrode would rise due to poor coupling between the electrodes and adjacent tissue; desiccated and coagulated tissue raises the resistance to current flow, thwarts effective tissue heating, and limits the size of RF-induced lesions.

There is a need for energy sources that can produce larger and deeper lesions than RF currents. Large lesions are required for certain types of cardiac ablation to cure ventricular tachycardias secondary to coronary artery disease, for example, and arrhythmias due to reentry located deep in the myocardium in particular. The radiating and dielectric heating features of microwave energy theoretically may be useful for ventricular ablation. The interaction of microwaves as mentioned earlier can result in a greater volume distribution of energy and deeper penetration. The feasibility of ablating the atrioventricular (*AV*) junction in dogs with microwave catheter antennas has been shown both in vitro (134,135,136) and in vivo (137,138,139,140). Furthermore, using fresh bovine hearts and closed-chest dogs, the feasibility of a larger (4 mm long) split-tip catheter antenna has been demonstrated for ablation treatment of ventricular tachycardia (141,142). The results suggest that if the lesion size is sufficiently large, it would be possible to ablate a ventricular tachycardia focus using this split-tip microwave catheter antenna system. In addition to the split-tip catheter antenna, microwave antennas reported for cardiac ablation include monopole, helical coil, cap-slot, and cap-choke designs (134,135,136,137,138,139,140,141,142,143,144,145,146). A drawback of some catheter antennas is that a considerable amount of microwave energy is reflected by the antennas to the skin surface and is deposited at the point of antenna insertion into the blood vessel. The problem has been addressed by integrating a sleeve or choke in the antenna design (134,135,136,139,141,142,143,144).

It is noted that the feasibility of using ultrasound for cardiac ablation was investigated and a catheter mounted transducer has been reported (147,148).

Endometrial Ablation. Hysterectomy is performed to surgically remove the uterus in order to stop intractable bleeding or menorrhagia (149,150). Endometrial ablation is a relatively new treatment for menorrhagia and is a reliable alternative treatment for patients with dysfunctional uterine bleeding (151,152,153). It is superior to hysterectomy in terms of operative complication and postoperative recovery. While still in the beginning stages, RF and microwave thermal ablation of the endometrium have been reported as efficacious procedures for treatment of abnormal uterine bleeding (154,155,156,157). The technique is easier and quicker to perform than current alternatives. Quantitative measures and patients' subjective responses suggest that a meaningful fraction of patients treated with RF and microwave ablation experience significant flow reduction. Investigations with microwave energy indicate that a treatment temperature of 55°C is related to significant reduction or complete elimination of menstrual flow (156,157). Besides the difference between microwave and RF approaches mentioned already, the use of high-intensity RF power (500 W) could produce burns at points where electrocardiographic (*ECG*) electrodes come in contact with the body (158). Considerably more investigation is needed before microwave or RF ablation can become a safe and efficacious clinical modality.

Treatment of Benign Prostate Hyperplasia. Benign prostatic hyperplasia or hypertrophy is a major cause of morbidity in the adult male. At present, open surgery and transurethral resection of the prostate are the gold standards for treatment of benign prostatic hypertrophy. They can provide immediate relief of obstructive symptoms that remain fairly to extremely durable (159). A new, less invasive procedure uses thermal energy delivered by microwaves (160–165). An early report of a thermal microwave technique from 1985 employed a transurethral microwave applicator. It showed coagulation of the prostate in mongrel dogs and some salutary effects in an initial six patients treated with this device (160). An ensuing study used 2450 MHz microwave energy to treat 35 patients and compared transurethral resection alone to preliminary microwave coagulation followed by transurethral resection of the gland (161). Significant reduction in blood loss by initial treatment with microwave thermal therapy was observed. Numerous reports have appeared since that time on various

aspects of both transrectal and transurethral microwave therapy of the prostate using 915 MHz and 2450 MHz energy (162,163,164,165,166,167).

Most of the research in human subjects to date has focused on methods of delivery. Initial attempts to deliver the energy transrectally have not been effective, and injury to the rectal mucosa has occurred due to the difficulty of interface cooling of this organ (166,167). Recent investigations have focused on transurethral delivery of the energy with cooling systems within the catheter to ensure urethral preservation (143,144, 162,163,164,165,168,169). Sensors placed in the microwave antenna maintain temperature on the urethral surface between 43°C and 45°C. It is noted that while the number of treatment sessions and the temperature attained are extremely important predictors of response, sufficient hyperthermia volume is crucial for enhanced efficacy. Virtually no data clearly demonstrating reduction in prostate volume in human subjects have been reported, although most investigators have shown improvement in measured urinary flow rates compared to preoperative studies. Randomized studies comparing microwave thermotherapy to transurethral resection conclude that microwave hyperthermia treatment had a definite therapeutic effect on symptomatic prostatic hypertrophy (169,170,171,172). Thus, microwave thermal ablation of prostatic tissue and enlargement of the urethra with minimal clinical complications offers a therapeutic alternative to surgery in select patients with benign prostatic hyperplasia.

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