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Studies on Microwaves in Medicine and Biology: From Snails to Humans

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This d'Arsonval Medal acceptance presentation highlights several research themes selected from Dr. Lin's published works, focusing on the microwave portion of the nonionizing electromagnetic spectrum. The topics discussed include investigation of microwave effects on the spontaneous action potentials and membrane resistance of isolated snail neurons, effects on the permeability of blood brain barriers in rats, the phenomenon and interaction mechanism for the microwave auditory effect (the hearing of microwave pulses by animals and humans), the development of miniature catheter antennas for microwave interstitial hyperthermia treatment of cancer, the application of transcatheter microwave ablation for treatment of cardiac arrhythmias, and the use of noninvasive wireless technology for sensing of human vital signs and blood pressure pulse waves. The paper concludes with some observations on research and other endeavors in the interdisciplinary field of bioelectromagnetics. Bioelectromagnetics 25:146–159, 2004. © 2004 Wiley-Liss, Inc.

Key words: **action potential; auditory effect; blood brain barriers; blood pressure pulses; cardiac arrhythmia; interstitial hyperthermia; membrane resistance; microwave ablation; vital signs**

INTRODUCTION

As I mentioned during the d'Arsonval Award presentation, words are insufficient on an occasion like this. I am humbled by the selection. Frankly, I am very excited about it also. Metaphorically, I hope that the humble rocks for which I am being recognized today, would seed the process by which jade-like gems are unearthed in the days to come.

I would like to take this opportunity to thank the Board of Directors, the Awards Committee, and all members of the Bioelectromagnetics Society for the Award. I also wish to thank my family for their love and their faith. Thank you all for coming to share this honor with me.

Professionally, there are two individuals whom I would like to especially acknowledge. The first is Professor Akira Ishimaru, the advisor of my PhD dissertation on ''wave propagation in discrete random media.'' Dr. Ishimaru is one of those professors who is genuinely appreciated by his students. His example of blending rigorous analysis with imaginative research, and his willingness to pay close attention to the works of his students have been a tremendous influence on my academic career. He not only launched me into university teaching and research, he started a tradition that set the tone for my intellectual pursuit and service to my profession.

The second is Dr. Arthur W. Guy. I had the privilege of working with Bill as a junior faculty member in the Rehabilitation Medicine Department at University of Washington, immediately after receiving my PhD degree in 1971 from the electrical engineering department at the same university. In a little more than 3 years, we had established the Bioelectromagnetics Research Laboratory, with Bill Guy as the director and me the assistant director. We worked really hard and got a lot done. It was a very exciting time and I learned a great deal from having worked with him as well. Some of the research conducted during that period has been covered by Bill Guy in his d'Arsonval lecture [Guy, 1988].

In deciding on a title for the d'Arsonval Award presentation, the default approach would have been a physical one, given the background of my formal education, though there was a diversion into anatomy and physiology. The paper might have included section titles such as dosimetry, modulation, temperature, near field, plane wave, electromagnetic pulse, and transient exposure. Instead, I settled on a subtitle based on

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biological objectives and experimental subjects for the simple reason that they have helped associates and me to pursue answers to some very interesting questions and propositions. Accordingly, this paper will include discussions on microwave effects on the spontaneous action potentials and membrane resistance of snail neurons, the blood brain barriers (BBBs) in rats, interstitial hyperthermia treatment for cancer, the hearing of microwave pulses by humans and animals, microwave ablation for cardiac arrhythmias in dogs, and the monitoring and sensing of vital signs in humans. I regret that I will not be able to cite all the relevant and significant contributions made either by members of my research team or by other investigators, and I apologize for any error of omission.

SPONTANEOUS ACTION POTENTIALS AND MEMBRANE RESISTANCE OF SNAIL NEURONS

The interaction of microwave energy with the nervous system has been a subject of considerable interest, and it has been studied by many investigators, especially in the former Soviet Union and other Eastern European countries [Michaelson and Lin, 1987]. The studies have included experimental and theoretical methodologies, using preparations ranging from isolated axons, neurons, and intact animals. A large number of them imply a direct microwave interaction with the central nervous system (CNS) and peripheral nervous system of both humans and animals at incident power levels that are relatively low. However, most of these publications had reported only microwave exposure or incident fields on the experimental subject, with near-total absence of any indication of the absorbed energy or internal fields in these reports.

The realization that the absorption of microwave energy by biological subjects varies according to body size, configuration, and composition had aroused considerable controversy regarding the actual strength of incident fields at which the microwave effects can occur. The issue was further complicated by the fact the exposure systems and instrumentations involving metallic wire conductors, often used in the past, can produce induced fields in the tissue far greater than that expected from estimates made through incident power measurements. Consequently, it was difficult to ascertain a clear causal relationship between the incident fields and observed effects.

Several projects were initiated at the University of Washington, where specialized equipment, instrumentation, and protocols were designed and implemented to help quantify microwave interaction with the central and peripheral nervous systems [Johnson and Guy, 1972; Guy et al., 1975a; Courtney et al., 1975; Guy, 1988]. In particular, efforts were made to ascertain the distribution of absorbed energy in the brain, using the metric of specific absorption rate (SAR) and measurement of temperature in the target tissue. The electrophysiological investigations demonstrated that the effects of acute exposure to a continuous wave (CW) microwave energy on the central and peripheral nervous systems were thermally mediated [Guy et al., 1975a]. The observed electrophysiological responses were all accompanied by a concurrent temperature elevation of the targeted nervous tissues and could be duplicated in their entirety by methods employing conductive heating. Subsequently, the effects which occur at a measurable elevation of tissue temperature have been commonly accepted. However, microwave effects that occur in the absence of a measurable elevation of tissue temperature or at constant system temperature, remained controversial.

To help resolve this issue, we designed a series of studies to investigate the response of isolated nerve cells, ganglia of the land snail *Helix aspersa*, to CW and pulse modulated microwave energy, by using a microelectrode recording technique and a double-circulation exposure chamber [Arber and Lin, 1985a; Ginsburg et al., 1992]. Temperature in the recording chamber was measured in real time, with a nonfield perturbing thermistor probe (Vitek), located within a few mm of the neuron. Briefly, snail ganglia were placed on the center of the floor of a thin-walled plastic, Ringer's solution-filled chamber, positioned in a water-filled waveguide chamber. The waveguide chamber was linked by a dielectric matching plate to an air-filled waveguide-to-coax adapter, which was connected to a CW or pulse source of 2450 MHz microwaves [Arber and Lin, 1985b; Field et al., 1993]. The recording chamber was surrounded by water circulated through the waveguide chamber and maintained at constant temperature. It is noteworthy that the spontaneous activity and input resistance of snail neurons respond robustly and reversibly to temperature changes; higher temperatures tend to inhibit spontaneous activity and decrease membrane input resistance [Arber and Lin, 1985a; Ginsburg et al., 1992]. A threshold temperature increase of 0.38 °C was observed for changing the action potential time constant. The threshold increase for the input resistance was found to be 0.63 °C for neurons kept at a normal temperature of 21 °C.

The results showed that exposure of snail neurons to CW microwaves for 30–60 min at 13 W/kg at 21 °C tended to inhibit spontaneous activity, but not always [Arber and Lin, 1985a; Ginsburg et al., 1992]. Also, microwave exposure either reduced the input resistance during irradiation or increased it afterward. The latency or lag time observed with these changes suggested that the response may not be thermally mediated, since neurons were kept at a constant temperature (21 °C) throughout the entire experiment period. The precise mechanism of interaction for the input resistance depression during microwave exposure was obscure. It was hypothesized that a Ca^{++} dependent process may be involved, given the influence of Ca^{++} in cell function in general.

To test this hypothesis and to examine the role of extracellular calcium in triggering the microwave-induced decrease of membrane resistance of snail neurons, two sets of experiments were conducted [Arbor and Lin, 1985b]. In the first set, snail neurons were superfused using Ringer's solution with extra Cd^{++} (0.9 mM), which is a known blocker of calcium channels. In the second set, neurons were superfused with a low Ca^{++} (0.7 mM) Ringer's solution. It was found that lowering of Ca^{++} in bathing solution, as well as blocking of calcium channels in neuronal membrane by means of Cd^{++}, did not alter the fall in membrane resistance induced by microwave radiation. In fact, the observed changes in membrane resistance in these experiments were nearly equal to those observed for neurons superfused by normal Ringer's. Thus, these results ruled out the possible contribution of external Ca^{++} in the observed microwave effect. Experiments with high Ca^{++} concentrations also supported this conjecture.

Several studies were undertaken to ascertain the role of intracellular Ca^{++} in triggering the microwave response. Injection of EDTA, a Ca^{++} chelating agent, into the snail neuron, 1–2 min before microwave exposure, completely eliminated the microwave response; membrane resistance remained stable at control levels within at least 60 min. Thus, results from this well-known direct test of intracellular calcium unequivocally indicated that the microwave effect is triggered by intracellular free Ca^{++} [Arber and Lin, 1984]. Moreover, tetracaine has been shown to block Ca^{++} release from intracellular stores by either preventing Ca^{++} release from endoplasmic reticulum or binding of Ca^{++} to the plasma membrane. Indeed, microwave induced changes in membrane resistance was completely eliminated when irradiation was initiated following a 25 min treatment of the snail neurons with 0.2 mM of tetracaine. These results strongly supported the notion that intracellular free calcium is a possible trigger of snail neuron microwave response.

In an effort to help identify the intracellular source of free Ca^{++}, we employed electron microscopic and electron probe X-ray analysis to examine intracellular granules of snail neurons subjected to microwave treatment. It was found that intracellular granules are not sensitive to the microwave exposure. The percentage of granules in neurons did not significantly change after the microwave exposure [Arber et al., 1985]. Likewise, there was no significant change in calcium content in the microwave irradiated granules. However, the microwave exposure was observed to cause minor ultrastructural alterations in Golgi complexes and slight swelling of the endoplasmic reticulum [Arber et al., 1986]. Since snail neurons' endoplasmic reticulum is known to contain calcium deposits, the result seems to nominate the endoplasmic reticulum as the intracellular site of microwave interaction.

An investigation using pulse modulated 2450 MHz radiation showed that there was no apparent alteration in the behavior of spontaneous action potentials in snail neurons. There was no consistency in the direction of change of action potential's inter-spike intervals (ISIs); neurons exposed to pulse modulated microwaves were associated with either an increase or a decrease in the mean and standard deviation of ISIs at 82 or 174 W/kg (82 or 174 kW/kg peak) [Bernardi et al., 1991; Field et al., 1993]. Statistical comparison with sham irradiated neurons revealed a significant increase in the mean input resistance of neurons exposed to pulse modulated microwaves. Using a previously developed integrator model for spontaneously active neurons [O'Neill and Lin, 1984; O'Neill et al., 1986], we found the net input current to be marginally more variable in neurons exposed to pulsed microwaves [Field et al., 1993]. The mean input current was not affected. However, exposure at 174 W/kg significantly altered the threshold action potential voltage observed in snail neurons [Bernardi et al., 1991].

BLOOD BRAIN BARRIER (BBB) IN RATS

The BBB is an anatomic and physiologic complex associated with the cerebral vascular system. It is composed of a network of astrocytic pseudopodia, which envelope the tight junctions of the vascular endothelium. The cell layers constituting the barrier form a regulatory system that maintains the physiochemical environment of the brain within certain narrow limits that are essential for life. It functions as a differential filter that permits the selective passage of biological substances from blood to brain. For instance, amino acids, anesthetics, and glucose may gain access to brain cells, while carbohydrates, proteins, and most microorganisms and antibiotics are excluded from brain tissues by the BBB. Even so it is interesting to note that while the hydrophobic barrier is readily crossed by small, lipid-soluble molecules, certain other lipid-insoluble molecules, such as glucose, can also cross the barrier. The intact BBB protects the brain from damage, whereas a disrupted BBB may subject the CNS to assault from extraneous microorganisms and allow influx of normally excluded hydrophilic molecules into the brain tissue.

Since the first studies on the effect of microwave radiation on BBB of experimental animals [Polyaschuk, 1973; Frey et al., 1975], many investigators have reported on related studies with varied results. Microwave frequencies investigated range from 1 to 3 GHz. Studies showing or not showing a microwave-induced increase in rat BBB permeability have used both high and low levels of microwave exposure. Nevertheless, the reported microwave-induced disruption of BBB at lower levels of microwave exposure has captivated special attention [Lin, 2001]. A preponderance of the studies did not report local SARs inside the head. The relationship between incident power density and SAR was not defined in many cases. Also, the distribution and location of absorbed energy inside the brain were unknown. Since a given exposure, as determined from incident power measurements, can produce SARs in the tissue far greater than that expected, it is difficult to draw a definitive conclusion on the basis of incident power density from these studies. In addition, nearly all of the investigations used protocols which involved whole body exposure of the experimental animal.

To quantify the relationship between incident power density and SAR and to assess any correlation between BBB permeation and the distribution of SAR inside the rat brain, we implemented an experimental approach which employed partial exposure of one-half of the brain of the rat; using an antenna applied directly to the scalp of an anesthetized rat. The head of the rat was held in a stereotaxic head frame, which was constructed using a nonperturbing dielectric material (Delrin). A series of studies was performed in our laboratory using visual dye markers such as Evan's blue and sodium fluorescein. We found that 20 min exposures to 2450 MHz microwaves, if the average incident power ranged between 5 W/m^2 and 26 kW/m^2, and SARs between 0.04 and 200 W/kg, did not produce staining in the brain, except in regions that normally are highly permeable. The highest temperature measured in the brain was less than 42 °C in this case [Lin and Lin, 1980]. But the results indicated that when the applied microwave power was high enough to elevate the temperature of the brain to 43 °C or higher, BBB permeability increased for normally excluded Evan's blue dye [Lin and Lin, 1982]. Moreover, microwave hyperthermia induced BBB disruption was shown to be reversible within 30–45 min following microwave treatment. Subsequently, these observations were confirmed by using an assay technique that employed a radioactive tracer (^{86}Rhobidim), which offered a quantitative method to assess breaching of the BBB [Goldman et al., 1984].

To guide the delineation of a mechanism for the BBB-microwave interaction, we studied the combined effects of ethanol and microwaves on the permeation of Evans blue through the BBB in rats. We found that intravenous infusion of ethanol prior to microwave irradiation resulted in cooling of the brain, thereby mitigating against an excessive increase in brain temperature, and could attenuate the observed changes in BBB permeation [Neilly and Lin, 1986]. In particular, this result showed that as the quantity of alcohol was increased, the degree of staining was decreased or eliminated. The steady-state temperature of the irradiated area of the brain was highest in animals receiving saline or the smallest dose of alcohol. As the quantity of alcohol was increased, the brain temperature was reduced below 42 °C. These results indicate that ethanol inhibits microwave-induced permeation of the BBB through reduced heating of the brain. The above studies have helped to reach a general consensus that reliably demonstrable increases of BBB permeability are associated with intense, microwave-induced hyperthermia, and that the observed changes are not due to field-specific interaction.

The reliability and reversibility of microwave hyperthermia induced increases of BBB permeability had encouraged us to initiate an investigation to explore its potential as a modality using microwave selective hyperthermia to facilitate the chemotherapeutic treatment of brain tumors. For example, Methotrexate (MTX) is a widely prescribed antifolate, used in chemotherapy for a variety of neoplasms. It is the drug most often used for high dose chemotherapy, However, the BBB permeability of MTX is among the lowest among the agents that are currently in clinical use. In our study of the effect of selective microwave hyperthermia on the transport of MTX across BBB, we performed standard high pressure liquid chromatography (HPLC) analysis to determine the drug concentration in rat brain tissues [Lin et al., 1998]. We compared MTX concentration in brain tissue with or without microwave hyperthermia. Also, we correlated the amount of MTX uptake by the brain after microwave hyperthermia treatment as a function of time, post microwave hyperthermia treatment. The results indicated that MTX uptake was substantially increased (about 20 fold) in rat brains subjected to noninvasive microwave hyperthermia treatment. Furthermore, the increase was reversible within 45 min, post microwave treatment.

INTERSTITIAL HYPERTHERMIA TREATMENT FOR CANCER

Hyperthermia cancer therapy is a treatment procedure in which the tumor temperature is elevated to the range of 43–45 °C. The technique is mostly used in conjunction with radiotherapy and chemotherapy, since the ability of ionizing radiation to kill tumor cells and the anticancer action of drugs are enhanced by hyperthermia [Watmough and Ross, 1986; Lin, 1986a,b, 1999a]. As noted above, microwave hyperthermia also can increase BBB permeability to certain anticancer drugs. Clinical and laboratory results have indicated a promising future for hyperthermia [Lin, 1999a]. Its efficacy depends on the production of temperatures in excess of 42 °C throughout the tumor volume, without overheating the adjacent normal tissue, i.e., maintaining the surrounding area's temperature at or below 42 °C to avoid thermal damage.

Interstitial microwave techniques are used to produce localized deposition of electromagnetic energy in subcutaneous and deep seated tumors. For treatment regions that are large compared to the field penetration depth at 915 and 2450 MHz, the required SAR uniformity throughout a tumor volume cannot be achieved with a single antenna, and arrays of antennas are then employed. Indeed, interstitial array techniques can be optimally configured to heat irregularly shaped tumor volumes. In combination therapies involving brachyradiotherapy, interstitial hyperthermia renders a treatment modality for malignancies with little additional risk to the patient, since antennas can be inserted in the tumor tissue by using the same catheters prepared for the insertion of radioactive implants.

Clearly a major component for the successful application of interstitial microwave hyperthermia treatment of cancer is the antenna. Several antennas have been designed and studied in our laboratory, aimed at overcoming some major drawbacks of conventional center-fed antennas [Lin and Wang, 1987a,b]. The center-fed or helical antennas produce a cold spot or low heating zone near the distal tip of the antenna, therefore necessitating the need to insert the antenna beyond tumor boundaries and creating a potential situation of damage to normal tissue [Lin, 1999a]. For example, a sleeved-slot antenna was configured to have two circumferential slots and a second outer conductor, which serves as a current-restricting choke to prevent reflected current from flowing up the transmission line and returning to the air–tissue interface [Lin and Wang, 1987a]. The choke-sleeve is short-circuited at the proximal end to the coaxial outer conductor. The miniature interstitial antenna is mounted on a semi-rigid coaxial cable (0.86 mm, OD). For 2450 MHz operation, the antenna is 20 mm in length and about 1 mm in diameter. The experimentally measured and numerically calculated SAR distributions in a homogeneous tissue phantom agreed well and showed, away from the antenna surface, a light-bulb-shaped SAR pattern, about 25 mm in length, with enhanced power deposition near the slots toward the distal end of the antenna. Moreover, the SAR produced by the sleeved-slot antenna was independent of insertion depth, so long as the depth was greater than the antenna length.

We have investigated the use of equilateral triangular arrays of interstitial sleeved-slot microwave antennas and larger arrays formed by using the basic triangle configuration as "building blocks." The SAR distributions of three element arrays in tissue-equivalent phantom models have been studied both experimentally, by measuring the rate of temperature change caused by the radiated power, and theoretically, by using approximate and finite-difference, time-domain (FDTD) numerical algorithms [Lin et al., 2000; Pisa et al., 2003]. The results were in excellent agreement. For equilateral triangles of 10, 15, and 20 mm antenna spacings, the results showed that SAR distributions were mainly concentrated inside the volume bound by the antennas. The shape of the high SAR region was strongly dependent on the antenna spacing, while a rapid decay was evident outside the array. Moreover, SAR variation was the most uniform for the 15 mm array spacing; and a 15 mm array produced comparable SAR distributions over most cross sections, including the array center and near the antenna surface.

In clinical hyperthermia, a parameter of interest is the distribution of temperature elevation inside the tumor, with SAR distribution providing the driving power responsible for tissue heating. Accordingly, we have employed graded-mesh FDTD computer modeling, coupled to a three-dimensional, alternate-direction-implicit finite-difference (ADI-FD) solution of the bioheat equation, to study the optimal array spacing and input power for achieving an efficacious tumor heating [Pisa et al., 2003]. By varying the blood flow rate from 5 to 200% of its nominal value and holding the input power fixed at 8 W for a 15 mm array, the heat removal mechanism was found to be less efficient as blood flow was diminished. Consequently, the effective region of hyperthermia therapy was enlarged. For a 50% reduction in blood perfusion rates; typical in the core of large tumors, results from computer simulation showed that the region where temperatures were above 43 °C, was enlarged by about 40% for a given input power. Moreover, outside the tumor region, the temperature decayed quickly to 37 °C in normal tissues, and the necrotic core region was heated to 43 °C with less power. Thus, a reduced blood flow in the necrotic core of a tumor and an increase in blood flow in normal tissue would have a facilitative effect on hyperthermia.

Also, our analyses have indicated that deep-seated tumors, from 10 to 40 mm in diameter, can be treated by using equilateral triangular arrays of 10, 15, and 20 mm antenna spacings for input powers that range from 2 to 32 W. There was a minimum input power for each array spacing, below which the region above 43 °C actually consisted of three separate regions surrounding the three antennas. Once this power was exceeded, a simply connected domain was observed. Thus, there appeared to be an optimal combination of array spacing and input power for these sleeved-slot antennas in heating deep-seated tumors without damaging superficial tissues.

However, for tumor sizes that exceed 40 mm in diameter, arrays of more than three antennas would be required to achieve a ΔT of 6 °C, the temperature differential between 37 and 43 °C. This situation was simulated by computing the SAR distributions in homogeneous tissue models of six or seven antenna hexagonal arrays, formed by replicating the 15 mm equilateral triangular arrays [Lin et al., 2000]. In the case of a six element array, the central antenna was left out of the catheter. The computed SAR patterns at transverse cross sections, including sections through the antenna slots, showed elevated SARs near the center of the array. Interestingly, there were additional peaks at the centers of each of the six virtual equilateral triangles formed by the interstitial antennas, even without the central antenna in the hexagonal array. The addition of a 7th antenna at the center gave rise to computed SAR patterns that were similar to those obtained for six element arrays, except for a higher SAR surrounding the central antenna. A comparison of SAR distributions produced by a six or a seven element configuration suggested that the average SAR at the array center and the range of its variation produced by the six element array were slightly lower than that produced by the seven element array. While these observations have been confirmed by measurements using homogeneous tissue phantoms, their validations in animal models are continuing at present.

HEARING OF MICROWAVE PULSES BY HUMANS AND ANIMALS

The microwave auditory phenomenon, known as the microwave hearing effect, pertains to the hearing of short pulse, modulated microwave energy at high peak power by humans and laboratory animals [Frey, 1961, 1962; Guy et al., 1975a,b; Lin, 1978, 1980]. The effect can arise, for example, at an incident energy density threshold of 400 mJ/m^2 for a single, 10 μs pulse of 2450 MHz microwave energy, incident on the head of a human subject. It has been shown to occur at an SAR threshold of 1.6 kW/kg for a single 10 μs pulse of 2450 MHz microwave energy. A single microwave pulse can be perceived as an acoustic click or knocking sound, and a train of microwave pulses to the head can be sensed as an audible tone, with a pitch corresponding to the pulse repetition rate.

The hearing of microwave pulses is a unique exception to the airborne or bone-conducted sound energy normally encountered in human auditory perception. The hearing apparatus responds to acoustic or sound pressure waves in the audible frequency range, but the hearing of microwave pulses involves electromagnetic waves whose frequency ranges from hundreds of MHz to tens of GHz. Since electromagnetic waves, e.g., light, are seen but not heard, the report of auditory perception of microwave pulses was at once astonishing and intriguing. Moreover, it stood in sharp contrast to the responses associated with CW microwave radiation. Initially, the microwave auditory effect had been interpreted to imply a direct microwave interaction with the neurophysiological system [Frey, 1961, 1962, 1971; Frey and Messenger, 1973].

At many sites along the auditory neural pathway, small electrodes may be inserted to record electrical potentials that arise in response to acoustic-pulse stimulation. If the electrical potentials elicited by a microwave pulse exhibited characteristics akin to those evoked by conventional acoustic pulses, this would vigorously support the argument that pulsed microwaves are acoustically perceptible. Furthermore, if microwave-evoked potentials were recorded from each of these loci along the auditory neural pathway, this would lend further support to the contention that the microwave auditory phenomenon is mediated at the periphery, as is the sensation of a conventional acoustic stimulus.

An early study showed that the classical components of the action potential from the auditory branch of the eighth cranial nerve and the round window of the cochlea appeared in both the microwave and the acoustic pulse cases [Taylor and Ashleman, 1974]. This suggested that the site of initial interaction of pulse-modulated microwave radiation with the auditory system is at or outside the cochlea of the inner ear.

A peripheral interaction should involve displacement of tissues in the head, with resultant dynamic effects in the cochlear fluids, hair cells, and CNS; these auditory activities have been well described for the acoustic case. In fact, the cochlear microphonic response, a signature of mechanical disturbances in the cochlear hair cells, has been demonstrated in cats and guinea pigs subjected to microwave pulse exposure [Chou et al., 1975, 1976].

Furthermore, evoked-potential recordings have been obtained from the vertex of the head and from the central auditory nervous system of cats. Specifically, responses recorded from the vertex represent volume-conducted electrical events that occur in the auditory brainstem nuclei within the first 8 ms after the onset of an acoustic stimulus [Lin et al., 1978, 1979a,b,c]. Indeed, essentially identical microwave and acoustic pulse evoked neural electrical activities were recorded from five levels of the central auditory system: the primary auditory cortex, medial genicular nucleus, inferior colliculus nucleus, lateral lemniscus nucleus, and the superior olivary nucleus [Lin et al., 1979a,b,c]. Thus, the same pathway through the central auditory nervous system is activated by both microwave and acoustic pulses.

This interpretation was augmented by observations made in systematic studies of the loci involved through production of coagulative lesions in ipsilateral auditory nuclei and bilateral ablation of the cochlea, the known first stage of transduction for acoustic energy into nerve impulses [Chou and Galambos, 1979]. Also, successive lesion production in the inferior colliculus, lateral lemniscus, and superior olivary nuclei resulted in a drastic reduction of the recorded response amplitude [Lin et al., 1978, 1979]. The consequence of cochlear disablement was abolishment of all potentials recorded from three levels of the auditory nervous system, the primary auditory cortex, brainstem nucleus, and the eighth nerve, evoked by both microwave and acoustic pulses. These data indicate that peripheral site of initial interaction of pulse-modulated microwave radiation with the auditory system was, indeed, distal to the cochlea of the inner ear.

These results confirmed that the microwave auditory effect was mediated by a physical transduction mechanism, initiated outside the inner ear, and involve mechanical displacement of biological tissues. Concurrent with the electrophysiological research activities, an intense effort was devoted to identifying the physical transduction mechanisms responsible for microwave hearing. Among the several physical transduction mechanisms suggested that involve mechanical displacement, the thermoelastic expansion emerged as the most effective mechanism.

Although not directly related to microwave hearing, two earlier publications, one by White [1963] and another by Gournay [1966], had described the conversion of electromagnetic (laser) energy to acoustic energy by surface heating of fluids. By extension, Foster and Finch [1974] had observed that microwave pulses in water produced acoustic pressure transients with peak amplitudes that were within the auditory frequency range of 200 Hz to 20 kHz, and were well above the expected threshold for perception by bone conduction. They presented the observation as evidence for thermoacoustic auditory stimulation by pulse microwaves. After examining the forces generated by electrostriction, radiation pressure, and thermoelastic stress in brain tissue, we found that the thermoelastic pressures are one to three orders of magnitude greater than the other candidate mechanisms [Lin, 1976a,b].

We then embarked on a series of detailed mathematical analyses, where we combined the electromagnetic and thermoelastic formulations, using spherical head models of animals and humans [Lin, 1976c, 1977a,b,c]. The analyses showed that the minuscule ($\sim 10^{-6}$ °C), but rapid rise (1–10 μs) in temperature as a result of the absorption of pulse microwave energy, creates a thermoelastic expansion of tissue matter, which then launches an acoustic wave of pressure that travels to the cochlea: and there it is detected by the hair cells and then relayed to the central auditory system. Specifically, the thermoelastic theory of auditory perception of pulsed microwave radiation delineated the acoustic waves' frequency, pressure, and displacement, generated in the head, as functions of head size and the characteristics of impinging and absorbed microwave energies. In addition to the expected dependence of sound pressure on the strength of microwave pulses, it prescribed the dependence of induced sound pressure (or loudness of perceived sound) on pulse width and the dependence of induced sound frequency on head size. For example, the thermoelastic theory predicted a fundamental sound frequency that varies inversely with head radius: the smaller the radius, the higher the frequency. For rat-size heads, it predicted acoustic frequencies in the ultrasonic range of 25–35 kHz, which rats can perceive. For the size of human heads, the theory predicted frequencies between 7 and 15 kHz, which are within the audible range of humans.

To acquire biophysical confirmation of the predicted thermoelastic pressure and frequency, we conducted a series of measurements using a hydrophone transducer (3 mm in diameter), implanted in the brains of cats, rats, and guinea pigs and in brain-equivalent, spherical head models. The results showed sound or pressure frequencies as expected from that predicted by the thermoelastic transduction theory [Olsen and Lin, 1981, 1983; Su and Lin, 1987]. Moreover, we measured a speed of thermoelastic pressure wave propagation of 1523 m/s in the brain of cats irradiated with pulsed microwaves [Lin et al., 1988].

The thermoelastic mechanism had given rise to a rather surprising prediction, a sound pressure or loudness that initially increases with pulse width but soon reaches a peak and then with a further increase in pulse width, gradually oscillates to a lower value [Lin, 1977a,b,c]. While some indirect experimental evidence had come from the measured amplitudes of evoked auditory responses of animal subjects [Lin, 1980], a direct measure of the sound pressure or loudness which would verify the prediction had to come from another direction. There was a study conducted in Moscow which had been reported to disprove the thermoelastic theory [Tyazhelov et al., 1979]; and yet, in the end, the data provided in that paper supported the theory [Lin, 1981, 1990]. The Tyazhelov et al. study investigated the variation of loudness perception with pulse width on human subjects exposed to microwave pulses. The experimental data were presented as curves of the subject's sensitivity to microwave-induced auditory sound, the inverse of perceived sound loudness or pressure. When viewed properly, the results showed remarkably similar loudness characteristics to the predictions of the thermoelastic theory. Thus, instead of disproving it, the report from Moscow actually furnished direct evidence in support of the thermoelastic theory.

We now know that the microwave auditory phenomenon does not arise from an interaction of microwave pulses directly with the auditory nerves or neurons along the auditory neurophysiological pathway of the CNS. Instead, the microwave pulse, upon absorption by soft tissues in the head, launches a thermoelastic wave of acoustic pressure that travels by bone conduction to the inner ear. There, it activates the cochlear receptors via the same process involved for normal hearing [Lin, 1990, 2002]. The microwave auditory effect is the most widely accepted biological effect of microwave radiation, aside from tissue heating, with a known mechanism of interaction: the thermoelastic theory of the microwave-induced acoustic pressure waves in the head. A thorough discussion of the phenomenon and mechanism of microwave hearing is given in a book [Lin, 1978], an invited review paper [Lin, 1980], and an invited book chapter [Lin, 1990], on the subject.

Our thermoelastic theory for hearing microwave pulses was developed on the basis of bulk absorption of pulsed microwave energy in the brain, which was assumed to be spherical for analytically clarity and simplicity [Lin, 1976c, 1977a,b,c]. Recently, a numerical analysis was presented by a group from Tokyo, using the FDTD computational algorithm, which is capable of detailed anatomic modeling of the brain and head structure [Watanabe et al., 2000]. In addition to confirming the characteristics of microwave pulse induced acoustic waves, such as sound frequency and pressure amplitude, that were previously obtained using a homogeneous spherical head, the recent numerical computation graphically illustrated the sequence of pressure wave propagation inside the head following absorption of pulse microwave energy. It is noteworthy that the pressure wave initially reverberated and then focused near the center of the head.

ABLATION FOR CARDIAC ARRHYTHMIAS IN DOGS

An arrhythmia is any kind of abnormal heart rate or rhythm. There are several causes of arrhythmia. However, they all prevent the heart from pumping enough blood to meet the body's needs. Atrial fibrillation develops when a disturbance in the electrical signals causes the two upper atrial chambers of the heart to quiver, rather than pump efficiently. Supraventicular tachyarrhythmias are caused by abnormal electrical pathways inside the heart. It is often associated with the Wolff–Parkinson–White syndrome, where there is an accessory atrioventricular (AV) conduction pathway. The extra pathway allows the electrical signal to bypass the normal conduction delay of the AV node and causes supraventricular tachyarrhythmia [Huang and Wilber, 2000]. Ventricular tachycardia is the most severe and life threatening arrhythmia. It affects the contraction of the ventricles, the main pumping chambers of the heart.

Until recently, the treatment of patients with cardiac arrhythmias was mostly palliative, involving lifelong dependence on medication. However, in a significant portion (10–15%) of these patients, available drug therapy has been found unsatisfactory because of a lack of meaningful response or unacceptable side effects. Surgical intervention has been the principal method of treatment in these cases. During the past decade, minimally invasive cardiac ablation has become a widely used procedure for the treatment of cardiac arrhythmias. Minimally invasive intervention offers many benefits: long incisions are replaced with a puncture wound; major cardiac and pulmonary complications are sidestepped; and the need for postoperative intensive care is significantly reduced. In the case of cardiac ablation, minimally invasive intervention offers a "cure" without major surgery. In addition, it replaces chronic drug therapy and reduces its accompanying side effects and inconvenience.

In cardiac ablation, electromagnetic energy is delivered to the myocardium via a catheter to create thermal lesions, in order to disrupt or eliminate conduction pathways supporting the arrhythmia, instead of using a surgical blade [Huang and Wilber, 2000; Lin, 2000]. The procedure involves introducing a small catheter into the vein of an anesthetized patient and placing the catheter at the responsible heart muscle substrate with the aid of radiographic and electrophysiologic monitoring. A pulse of electromagnetic energy is then delivered through the same catheter until an irreversible conduction block is achieved. This commonly would require an average power of 30–50 W, applied for 30–60 s, for the tissue temperature to reach 60–70 °C. The temperature is kept below 100 °C to prevent induction of coagulation at the tip of the catheter.

While several energy sources have been used for cardiac ablation, the two sources of electromagnetic energy of most interest are radio frequency (RF) or microwaves. In RF ablation, 500–750 kHz currents are induced to flow in radial paths through tissues between the intracardiac electrode tip and a large dispersive electrode on the body surface. Lesions are produced by resistive heating of the cardiac tissue. Despite its success, especially for supraventicular tachyarrhythmias, RF ablation has some significant disadvantages. RF power deposition in the heart tissue decays as the fourth power with distance; thus, lesion sizes are limited. Also, necrotic lesions occur at the electrode–tissue interface from coagulated tissue. As a consequence, approaches such as increasing the output power to heat tissue at a distance often result in excessive temperature elevation at the electrode–tissue interface without the desired enlargement of lesion size.

Microwave energy was first used as an ablative energy source for the experimental treatment of cardiac arrhythmias in a canine model in 1987 by our research group [Beckman et al., 1987]. The properties of microwave ablation which make microwaves advantageous include: (1) microwave antennas radiate electromagnetic waves into the surrounding heart tissue, (2) a dispersive electrode on the skin is not required, and (3) power deposition follows a second-power law with distance and thus can heat tissue at greater depth than RF currents. We have developed several catheter antennas, using flexible coaxial cable, 2 mm in diameter, for percutaneous cardiac ablation. Some design advantages of these catheter antennas, compared to conventional monopole or helical antennas are that they produce high SARs in the tip region of the antenna, low SAR along the transmission cable, and minimize reflected power or unwanted tissue heating. These catheter antennas also serve as bipolar electrodes for sensing endocardiac electrograms.

Briefly, the cap-choke catheter antenna was a matched-dipole type antenna, designed by connecting an annular cap to the enlarged inner conductor and by connecting a coaxial choke to the outer conductor [Lin and Wang, 1996]. The coaxial choke was used to match the antenna to the coaxial transmission line for greater efficiency. The entire assembly measured 6 mm in length and 2.5 mm in diameter and was mounted on the flexible cable. The proximal end of the coaxial choke serves as an open circuit to prevent any reflected power from flowing up the transmission line. Also, the combination of an enlarged inner conductor and annular cap increased the antenna's tip capacitance, which in turn enhances microwave radiation emitted from the tip of the catheter antenna.

The split-tip catheter antenna was designed to provide an ellipsoidal split-tip catheter antenna. The hemi-ellipsoidal tip was formed by connecting the two arms of a dipole to the inner and outer conductors of the coaxial cable and a coaxial choke to the outer conductor [Lin et al., 1996]. A junction separated the dipole and the choke sleeve. The antenna measured 2.5 mm in diameter. The two arms of the split-tip, hemi-ellipsoidal dipole are used also as electrodes for bipolar endocardiac electrogram recording.

The cap-slot catheter antenna consisted of a protruding inner conductor enlarged in the form of a cap at the catheter tip, and a flexible coaxial choke connected to the outer conductor [Lin and Wang, 1995]. A cylindrical Teflon dielectric film separated the second outer conductor from the outer conductor of the coaxial cable. A Teflon ring was placed between the cap and the termination plane of the coaxial outer conductor and choke. A second ring slot inside the coaxial choke was used to enhance microwave radiation in the forward (antenna tip) direction. The enlarged inner conductor and annular cap combination increases the tip capacitance and enhanced its radiation efficiency. The choke sleeve helped to match the antenna to the coaxial transmission. A prototype 2.45 GHz antenna, measuring 2.5 mm in diameter and 6 mm in length, is capable of handling up to 50 W of input power.

Our experimental studies and FDTD numerical simulations, using phantom tissue models, have shown that the SAR distributions for all three catheter antennas are light-bulb-shaped with a maximum toward the distal end (tip) of each antenna [Lin, 1999b, 2003]. The SAR distributions for the cap-choke and split-tip catheter antennas were similar for the same antenna length. The cap-slot design had a much longer SAR distribution compared to the others. The longitudinal half SAR length; the length along the antenna over which the SAR is at least one-half of its peak value, was 16 mm for the cap-slot catheter antenna. However, a longer (4 mm) split-tip antenna can also produce larger lesions. Note that a larger lesion, that is, a greater volume distribution of energy and deeper penetration, makes microwaves an appropriate form of ablation energy for certain types of cardiac ablation, such as arrhythmias due to reentry located deep in the myocardium.

Indeed, these antenna features have been demonstrated not only in phantom, but also in vitro and in vivo for 2450 MHz microwave energy [Lin, 1999b, 2003].

For example, using these catheter antennas, microwave ablation of the AV junction has been investigated in healthy anesthesized open and closed-chest dogs, respectively during cardiopulmonary bypass and via the femoral vein. It was found that irreversible AV conduction blocks were consistently produced with 190 J of microwave energy delivered by a catheter antenna to the Bundle of His, a conduction pathway of excitable cardiac tissue between the AV node and the ventricles, in an open-chest dog model [Lin et al., 1995]. Tissue temperature recorded near the microwave catheter antenna tip increased with increasing amounts of delivered energy. The temperature recorded was correlated with lesion development and the appearance of AV blocks. Statistical analysis showed that the occurrences of irreversible AV conduction blocks were strongly correlated with temperature rises between 60 and 70 °C.

In the closed-chest protocol, microwave catheters were introduced percutaneously into the femoral vein and placed in the septal leaflet of the tricuspid valve. The number of microwave applications and the amount of energy delivered to the heart to cause a complete AV block, varied from dog to dog. It was found that an amount of microwave energy higher than 200 J was required to cause irreversible AV blocks [Lin et al., 1996]. Likewise, an endocardium temperature of 65 °C was required. Further, one or more applications of microwaves were necessary. These results indicated that the percutaneous, transcatheter microwave system is capable of inducing AV blocks consistently in dogs using the flexible, curved tip catheter antennas. Moreover, the results suggested that the lesion size was sufficiently large that it would be possible to ablate a ventricular tachycardia focus using these microwave catheter antennas.

HUMAN VITAL SIGN MONITORING AND PRESSURE PULSE SENSING

When microwaves impinge on a biological target, a strong reflection takes place, such that about 50% of the incident microwave is scattered by the target. Moreover, the scattered microwaves experience a Doppler effect, which shifts their frequency either up or down from the frequency of the impinging microwave, depending on the direction of the movement with respect to the microwave source [Lin, 1986c]. Because the chest, heart, and lungs are in continuous motion, microwaves bounced back from these organs provide an approach to remotely and noninvasively sense vital signs, such as the heart beat and respiration, without the need for cooperation by the subject or when conventional detection or monitoring is not possible. The advantage afforded by remote sensing suggests the potential use of this technology for monitoring frail and elderly patients or patients with premature development, monitoring of unrestrained persons in holding areas or cells, or detection of unauthorized personnel or intruders, as well as persons who fell prey to such hazardous scenarios as explosion, fire, chemical or nuclear contamination, and natural, terrorism, or other man-made disasters.

The use of microwaves in measuring respiratory movements in humans and animals has been documented in several reports [Lin, 1975, 1986c, 1989]. For example, the microwaves were employed to provide real-time sensing of the respiratory activity of a cat subjected to selective heating of its head, showing the microwave sensor is capable of registering instantaneous changes in respiratory activity. In this case, microwaves at 10 GHz, directed toward the upper torso of the cat, were able to register increases in the respiration rate and a period of hyperventilation, followed by intense tachypnea in real time [Lin, 1989]. The record also showed the ending of rapid panting and the return of respiration to normal about 15 min after brain heating. This approach is advantageous over more conventional techniques because it does not require any physical contact with the subject.

For remote sensing of vital signs, microwave frequencies between 2 and 10 GHz are preferable. Indeed, heart and respiratory rates have been detected and monitored at distances of a few to tens of meters from a subject, with or without intervening physical barriers [Chan and Lin, 1987]. Microwaves at these frequencies were able to penetrate layers of clothing and did not require direct sensor contact with the subject. Problems such as skin irritation, restriction of breathing, and electrode connections are eliminated. For longer distances, a higher sensitivity with low levels of radiated power can be achieved by using a directive and higher gain antenna and by minimizing various noise sources.

More recently, we have initiated an effort to integrate the remote vital sign monitoring function with existing telecommunications infrastructures, in order to made the remote vital sign monitoring technology applicable to a broad portion of the population in an efficient manner [Lin, 1999c; Lubecke et al., 2000]. Such an approach may be realizable through the use of personal wireless devices, cellular mobile handsets, or other wearable RF devices. The vital data can be channeled to a remote location through an existing telephone or wireless connections. Laboratory experiments performed by colleagues at Lucent Technologies, Inc., using a radio system with frequency and power similar to a typical mobile phone, silicon BiCMOS RFICs developed for DCS 1800/PCS1900 base station applications, showed that signals from such consumer electronics could provide readily extractable data on heart and respiration activity [Droitcour et al., 2001]. In the case of cellular mobile telephones, some of the microwaves transmitted by a phone's antenna bounce back to the phone from the chest, heart, and lungs of the person using it. The handset can then send this signal, picked up by its antenna to the base station, where further signal processing would detect the Doppler frequency shift in the reflected signal, and extract the user's heart beat and respiration rate.

In a slightly different manner, we have shown that noninvasive microwave systems, applied in direct contact or at close range, can provide the capability for continuous monitoring as well as quantifying time-dependent changes at various points along the cardiovascular tree. Potential applications include the sensing of blood pressure pulses, the monitoring of arterial blood flow both in the central and peripheral circulations, and the detection of ventricular movements, with minimal interference to the physical integrity of the physiological events from the measurement instrumentation.

The hemodynamic events, which take place in the left ventricle during a cardiac cycle, are echoed in the low frequency displacement of the precordium overlying the apex of the heart. Our development of microwave apexcardiography, noninvasive microwave measurement of the related movements in the left ventricle using microwaves, revealed that the microwave apexcardiogram has a close correlation to the hemodynamic events occurring within the left ventricle [Lin et al., 1979c]. The technique may be useful in delineating the architecture of ventricular activity. This noninvasive, noncontact method involved detecting the reflected Doppler component in the microwave signal using an antenna located a few cm from the chest, over the apex of the heart.

For centuries, physicians have used palpation of the arterial pulse as a diagnostic tool. In modern times, noninvasive recording of the arterial pulse has been used to evaluate cardiovascular function and monitor arterial pressure. We have developed a Doppler microwave technique to measure arterial wall movement and pulse wave characteristics. The Doppler microwave pulse wave sensor consisted of a low power, solid state source, a signal processing module, and a sensing head (probe) operating at 24 GHz. Experimental validations of the noninvasive Doppler microwave pulse measurement were conducted at a variety of arterial sites, including the carotid, brachial, and radial arteries from human volunteers [Lee and Lin, 1985; Lin, 1989, 1992]. The waveforms obtained by the microwave sensor favorably compared with invasively obtained arterial blood pressure waveforms.

We also have assessed the clinical efficacy of the noninvasive Doppler microwave arterial pulse wave sensor. In particular, the ability to detect pathological conditions in patients with known diseases was evaluated by obtaining microwave-sensed carotid pulse waveforms, using contact application of the noninvasive sensor along with simultaneously recorded intra-aortic pressure waves. The resemblance of the microwave-sensed arterial pulse wave and the invasively recorded pressure wave was remarkable. Specifically, the consistency of microwave pulse waves with respect to the intra-aortic pressure measurements, was evaluated in human patients. The recordings were used to calculate left ventricular ejection time (LVET) and time required for a pressure to reach one half of its maximum amplitude (T1/2). The results confirmed that a noninvasive Doppler microwave sensor can successfully and reproducibly detect pressure pulse waveforms of diagnostic quality [Papp et al., 1987]. In addition, the sensor has been evaluated on the ease of recording, the quality of the recording, and the reproducibility of the measurements from normal subjects. With minimal training, a technician using this microwave sensor can usually obtain a good quality pulse waveform within 1 min, as compared to an ultrasound system, which when used often requires much longer detection times.

CONCLUDING REMARKS

In closing, I would like to make three brief observations. While time and space do not permit excursions into my service toward safety standard-setting efforts, I believe that this is an effort that is of utmost significance. All sectors of society stand to benefit from the proper development, promulgation, and administration of safety guidelines or standards. This is the case for public health, industrial development, commercial exploitation, and for health care and safety. Flaws in this endeavor, perceived or otherwise, will not eliminate public opposition to siting of wireless communication facilities and costly litigations, nor will they mitigate against fears of personal injury and threat to public health. They may in fact, worsen such challenges.

Bioelectromagnetics research is a multidisciplinary endeavor. It thrives on collaborative efforts and insights among scientists. In fact, viewing it from a higher level, we should be vigilant in guarding against any inclinations directed otherwise. For without effective participation of biological and medical colleagues, the most skilled engineer or physical scientist can be like sheep that go astray. Without meaningful participation of engineers and physical scientists, the most expert biologist or physician can fare no better. The interdisciplinary approach would most definitely enhance the progress of bioelectromagnetics research.

The discipline of bioelectromagnetics is well established and most amazing. It exhibits the enormous attributes of self organization, renewal and transformation. It has reinvented itself nearly once every decade. When I first entered the field, more than 30 years ago, the driving forces were medical diathermy and microwave oven safety. Today, these topics are taken almost for granted because of the research effort and time spent in setting safety and performance standards. Hyperthermia for cancer treatment had followed suit in the 1980's. Exposure to ELF and power line fields was the rage in the 1990's. Today, a majority of the efforts are focused on wireless communication radiation. I believe if scientific research in this area is permitted to proceed, it will have the most far-reaching ramifications with regard to public health, given the ubiquity and rapid expansion of wireless applications in every aspect of human endeavor.

There has been a remarkable stream of medical applications of RF and microwave energy over the years. As one who has contributed modestly to these applications, I believe that even greater opportunities lie ahead for making contributions in biology and medicine, just as I believe is the case for the Bioelectromagnetics Society. I therefore congratulate all members of Society for your accomplishments and convey my best wishes for continued success.

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I thank my colleagues and students, both from the universities at which I have served and elsewhere around the world, for their participation, collaboration, and dedication. Instead of repeating their names that are included in the citations, I would like to direct the readers to the list of references. Also, I express my gratitude to all the sponsors of our research activity over the years. Clearly, a major part of the research summarized here could not have proceeded without their generous support.

I lost my brother, Chin Ming Lin, to an unfortunate accident during the preparation of this paper. I wish to offer this work in rememberance of him. I especially appreciate Editor Ben Greenebaum, for his patience and understanding.

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