TABLE I
OPTICAL EXTINCTION AT 450 nm OF LIPOSOMES TREATED WITH GRAMICIDIN D

Liposomes containing K^+	E^1_{450} at 10 min	
	Na^+	Rb^+
Irradiated	0.72±0.03[2]	0.76±0.03
Heated	0.94±0.02	0.87±0.02
Room-temperature	0.95±0.02	0.88±0.02

1. Absorption range 0.3 full scale
2. Data are means of three experiments ±S.D.
The initial E_{450} was 0.50-0.53.

where values represent the mean of three experiments $\pm$S.D. The student t-test analysis was used and the values were found to be significantly different for irradiated liposomes compared to those maintained at room temperature. No significant difference was observed for liposomes heated by the water bath compared to those maintained at room temperature ($p \leqslant 0.01$).

IV. CONCLUSIONS

The results presented in this work are for an exposure of liposomes containing K^+ and 9.2 GHz continuous irradiation for 1.5 h with an energy absorption of 20 mW/g. We found that irradiation modifies the gramicidin D-induced permeability to the cations K^+, Na^+, and Rb^+, through the liposomes and seems to facilitate the movement of Na^+ and Rb^+ across the membrane. Liposomes heated to the same temperature by a water bath did not react any differently to the action of gramicidin D than did those maintained at room temperature.

Our results provide evidence that microwave radiation induces changes to the structure of liposomes and, as a consequence, the conducting state of gramicidin D channels is modified.

REFERENCES

[1] J. H. Merritt, A. F. Chamness, and S. J. Allen, "Studies on blood-brain barrier permeability after microwave-radiation," *Radiat. Environ. Biophys.*, vol. 15, pp. 367–377, 1978.
[2] D. J. Peterson, L. M. Partlow, and O. P. Gandhi, "An investigation of thermal and athermal effects of microwave irradiation on erythrocytes," *IEEE Trans. Biomed. Eng.*, vol. BME-26, pp. 428–436, July 1979.
[3] R. B. Olcerst, S. Belman, M. Eisenbud, W. W. Mumford, and J. R. Rabinowitz, "The increased passive efflux of sodium and rubidium from rabbit erythrocytes by microwave radiation," *Radiat. Res.*, vol. 82, pp. 244–256, 1980.
[4] M. L. Piana, S. D. Hellums, and W. L. Wilson, "Effects of microwave irradiation on human blood platelets," *IEEE Trans. Biomed. Eng.*, vol. BME-28, pp. 661–664, Sept. 1981.
[5] A. W. Friend, S. L. Gartner, K. R. Foster, and H. Howe, "The effects of high power microwave pulses on red blood cells and the relationship to transmembrane thermal gradients," *IEEE Trans. Microwave Theory.*, vol. MTT-29, pp. 1271–1277, Dec. 1981.
[6] A. Nicolussi, S. Massari, and R. Colonna, "Effect of lipid mixing on the permeability and fusion of saturated lecithin membranes," *Biochemistry*, vol. 21, pp. 2134–2138, 1982.
[7] G. K. Livingston, C. C. Johnson, and L. A. Dethlefsen, "Comparative effects of water-bath and microwave-induced hyperthermia on survival of Chinese hamster ovary cells," *Radio Sci.*, vol. 14, pp. 117–123, 1979.
[8] J. W. Allis, C. F. Blackman, M. L. Fromme, and S. G. Benane, "Measurement of microwave radiation absorbed by biological systems. Analysis of heating and cooling data," *Radio Sci.*, vol. 12, pp. 1–8, 1977.
[9] A. D. Bangham, S. De Gier, and G. D. Greville, "Osmotic properties and water permeability of phospholipid liquid crystals," *Chem. Phys. Lipids*, vol. 1, pp. 225–246, 1967.

A Multifrequency Water-Filled Waveguide Applicator: Thermal Dosimetry *In Vivo*

GIORGIO A. LOVISOLO, MICHELE ADAMI, GIORGIO ARCANGELI, ANTONELLO BORRANI, GUIDO CALAMAI, ANNA CIVIDALLI, AND FRANCESCO MAURO

***Abstract* —A new horn-shaped waveguide hyperthermia applicator, operating in the range 300–1000 MHz, has been designed. The applicator is filled with deionized water acting as both a dielectric and a cooling fluid. Preliminary tests indicate that proper heating can be achieved at frequencies of about 340, 440, 560, and 690 MHz. A very low level of environmental pollution was observed. Thermodosimetry has been carried out on two young female sheep. Measurements *in vivo* have been carried out using up to 5 temperature sensors in different positions. The results indicate the occurrence of different temperature trends if the water is maintained at 15, 23, 30, and 35°C.**

I. INTRODUCTION

Reliable measurements in the field of radio frequency hyperthermia can be performed only on the condition that one is able to heat to a desired constant temperature level a satisfactorily thick stratum of living tissue.

Roughly, if we temporarily neglect tissue inhomogeneity, power deposition—and therefore temperature elevation—owing to medium attenuation, decreases exponentially from skin-applicator contact surface to inner layers. Therefore, it is necessary, as a first step, to reduce the temperature peak that will develop in the skin, by efficient cooling means characterized by an exponential decrease steeper than radiofrequency heating decrease. So it is possible to get a much smoother maximum—hence, a wider working range—at a depth depending on the external parameters: frequency, RF power, and temperature imposed on skin surface by cooling system (Fig. 1).

II. THE APPLICATOR

Efficient microwave applicators have to provide the following:

- deep heating and variable surface cooling,
- matching when in contact with the body and low environmental RF pollution,
- best fitting to irregular skin surfaces,
- large bandwidth for frequency diversity applications.

As an outcome of these requirements, the implementation of a ridged horn (Fig. 2) filled with high-permittivity liquid dielectric and working in the bandwidth from 300 to 1000 MHz has been chosen.

The reason leading to this choice is straightforward. To heat deeply and yet to get a reasonably sized applicator, it is necessary to use relatively low frequencies and a high-permittivity dielectric. This latter characteristic is very useful also to make easier the matching to living tissues (and/or relevant phantoms), while radiation in air is hindered by the heavy discontinuity between water and air permittivity and by the very small dimensions of the applicator with respect to air wavelength. Consequently, very

Manuscript received October 12, 1983; revised March 10, 1984.
G.A. Lovisolo, M. Adami, A. Cividalli, and F. Mauro are with Laboratorio di Dosimetria e Biofisica, ENEA Casaccia, 0060 Rome, Italy.
G. Arcangelli is with Istituto Medico e di Ricerca Scientifica, Via S. Stefano Rotondo, 6, 00184 Rome, Italy.
A. Borrani and G. Calamai are with S.M.A., Via del Ferrone, 50124, Florence, Italy.

0018-9480/84/0800-0893$01.00 ©1984 IEEE

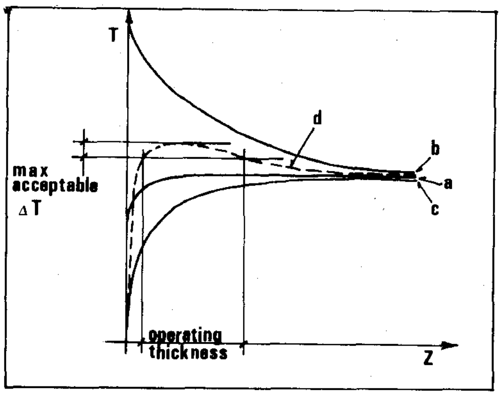

Fig. 1. Temperature versus depth qualitative diagrams for various considered cases. (a) Unperturbed, (b) only RF applied, (c) only surface cooling applied, (d) RF and surface cooling. Autothermostatization of living tissues is always considered present.

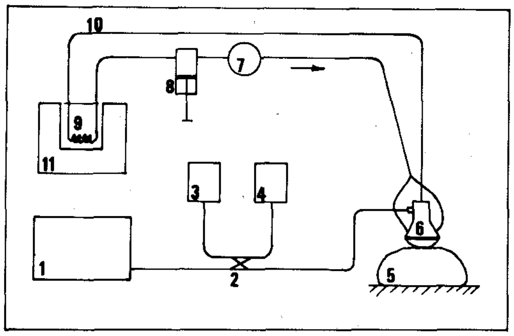

Fig. 3. A possible setup for RF dosimetry. 1—RF power generator, 2—double directional coupler, 3—reflected power monitor, 4—incident power monitor, 5—phantom, 6—applicator, 7—pump, 8—volume changer, 9—heat exchanger, 10—air-tight liquid circuit, 11—water warmer and cooler.

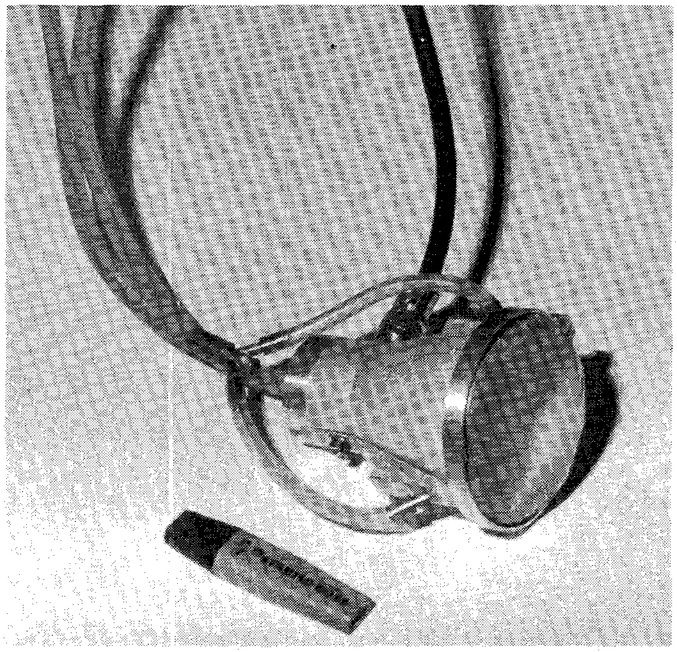

Fig. 2. Water-filled applicator.

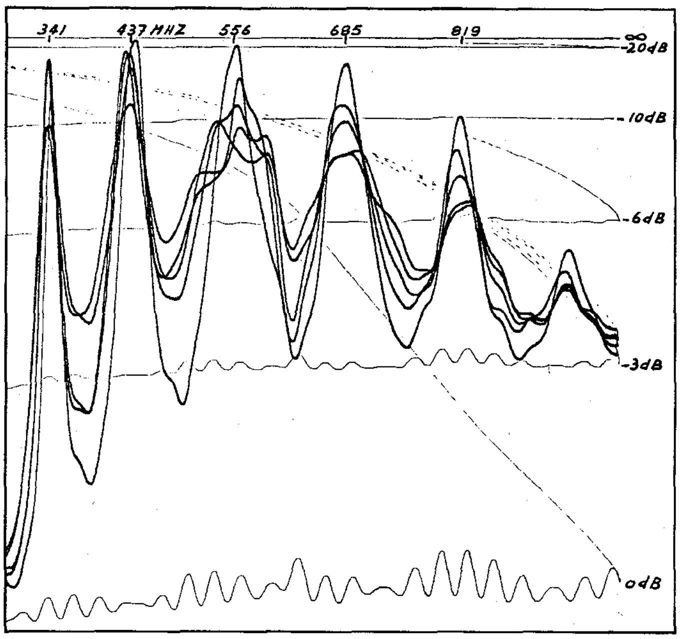

Fig. 4. Applicator return losses versus frequency for different contact.

low environmental pollution results (during dosimetry experiences, power density less than 20 $\mu W/cm^2$ at a 0.5-m distance has been measured by a Narda monitor). Furthermore, to get an efficient thermal exchange at the contact surface and a good fitting to irregular shapes, a circulating liquid is ideal. Therefore, a high-permittivity, not too lossy, liquid dielectric is required.

In this first approach, deionized water has been used as a good compromise between thermic and electric characteristics; other liquids or a liquid and gas emulsion would present better features, but technical problems of mixing and toxic hazard protection have to be considered.

The open end of the applicator is covered with a thin nylon bag that, when filled with liquid, is wide enough to conform to a variety of surface shapes. To conform to these shapes, the water circuit has a volume changer that allows the nylon bag to remain soft independent of the column of liquid and the position of the applicator (Fig. 3).

The ridged-horn-type shape, characterized by a constant λ_c along all the structure, is somewhat more complex than others available, but was selected because of its good stability of propagation mode, in spite of a wide frequency band and contact surface variability.

At present, the applicator can be utilized at four working frequencies arranged in about one octave bandwidth, and the average return losses are close to -6 dB (Fig. 4).

In future efforts, we expect to adjust to -10 dB, the average return losses in all the frequency band. We think it is ill-advised to try a further improvement of this parameter because, in operation, 10-percent variations of the incident wave power frequently occur due to different contact conditions, and water permittivity is not the same as tissue permittivity.

Also, insertion losses will be measured versus frequency and contact surface, for a careful evaluation of dosimetry.

III. Temperature Measurement and Control

As already mentioned, surface temperature was maintained at the desired level by using an over-sized Haake water bath. For core temperatures, noninvasive measurement techniques are not currently available; therefore, temperature was measured with a Baily TM 10A clinical monitoring thermometer for hyperthermic therapy, (five probe inputs radio frequency shielded in the range 1 MHz–10 GHz, using copper constantan thermocouple micro-

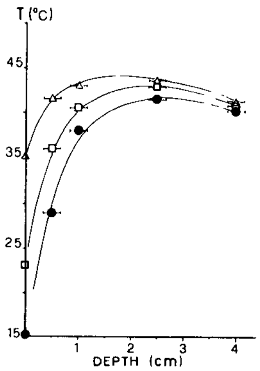

Fig. 5. Heating profiles (temperature versus depth) for various cooling water temperatures (marked on $z = 0$ axis). Operating frequency is about 440 MHz, RF power about 20 W. *In vivo* experiments on 25-kg sheep.

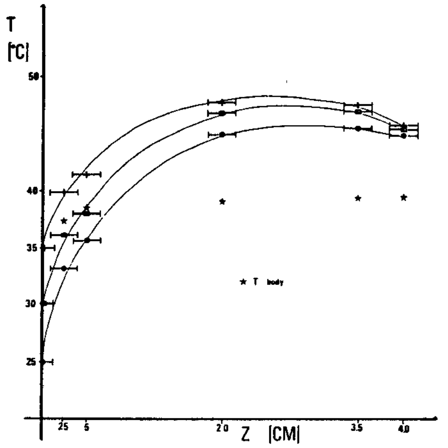

Fig. 6. As in Fig. 5, but with the 35-kg sheep. The unperturbed temperatures (T_{BODY}) were measured before starting heating.

probes IT 18 (time constant 0.1 s) and multisensor microprobes IT 17 with 3 thermocouple sensors along the length of the probe: at the tip, at 1.5 cm and at 3 cm). These allowed fewer needle insertions and therefore decreased tissue damage.

Measurements have been performed by deeply inserting (tip = 4 to 5 cm) a three-sensor microprobe orthogonally to the surface, about coincident with the applicator propagation axis. Other control probes were set as follows: a) two hypodermic, one in the center and the other on the edge of applicator-sheep contact pattern; b) one hypodermic centrally as before, and the other deeply on the edge, according to two different operation procedures.

Sometimes, two multisensor microprobes were inserted parallel to each other and orthogonal to the surface, to have more test points in the target. During tests, readings were made periodically by switching off the RF radiation for a short time.

IV. Experiments and Dosimetry

The above-described temperature test set and an Ailtech RF generator able to supply 60-W CW maximum power in a frequency band including 440 MHz were utilized.

Thermal maps were taken in a phantom material (10-kg compact beef thigh) to obtain a qualitative applicator radiation pattern. Each test was performed keeping deionized water at a constant temperature in the range 15–35°C. It is believed that colder temperatures are difficult to utilize in either clinical events or *in vivo* experiments because of the possibility of vexing or

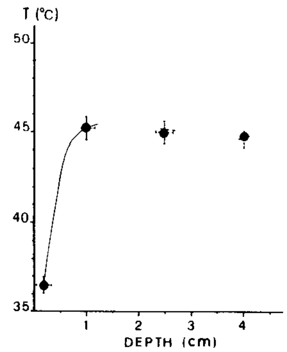

Fig. 7. Proper dynamic adjustment of water temperature (20–25° C) and RF radiation power (30–50 W) can ensure a quasi-constant hyperthermic level on a 3-cm-thick stratum of living tissue.

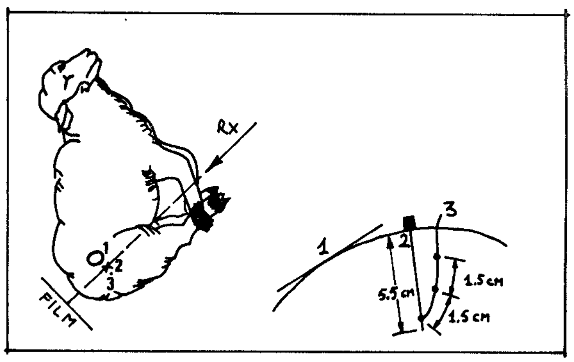

Fig. 8. Sketch of sensors position control radiograph. 1—annular reference, 2—needle reference, 3—multisensor probe, tip > 4 cm deep.

really damaging the skin. Higher temperatures are easy to obtain but probably are limited to use in superficial treatments, whereas our present work is intended to enhance the possibility of satisfactorily heating deep and thick strata.

In vivo experiments were performed on two sheep (25 kg and 35 kg, respectively) suitably shaved in the treatment area (thigh and gluteus), and anaesthetized by Valium and Ketalar for 1 to 1.5 h. This length of time was necessary to compare, at the achieved thermal balance for three different cooling temperatures, the temperatures read by sensors which assured the right test at the same point under changed conditions.

Radiographs were taken to determine with certainty the position of sensors in the sheep body and with regard to surface.

Sometimes a thin plastic bag filled with deionized water was interposed between the applicator and skin. This seemed to improve the possibility of obtaining better matching and cooling probably for the wider contact surface. In Figs. 5 and 6, the good agreement with qualitative behavior reported in Fig. 1 is pointed out. This is due mostly to the especially homogenous sample chosen. It is also seen, as expected, that the highest temperature is reached at a deeper point for a lower water temperature, but this effect applies in the first centimeters only, whereas, more deeply (4 to 5 cm), the effect of RF and tissue autothermostatization prevails. All curves are drawn at constant power (about 20 W), and this trend suggests that, by simultaneously reducing RF power and increasing water temperature, it is possible to shift toward the surface the maximum of temperature without changing its value. This is confirmed by Fig. 7, which was obtained by changing power and water cooling in a coordinated sequence such that homogeneous and deep heating was achieved. In this case, the position of thermal sensors was radiographed for control (Fig. 8).

V. Conclusions

In this first set of experiments at a frequency near 400 MHz with a liquid cooler applicator, we were able to verify the following.

a) At a depth of 4 cm or more, an efficient hyperthermic level was reached.

b) The maximum temperature can be shifted ad hoc from the surface to a depth of approximately 3 cm.

c) A quasi-constant hyperthermic level about 4 cm thick (starting from surface) can be obtained by controlling the cooling water temperature and RF power. Alternatively, one can perhaps keep constant (colder) water temperature and simultaneously operate on less deep strata by a second RF generator working at higher frequency which is less penetrating (the applicator is able to perform this test).

d) a), b), and c) results seem interesting also for clinical cases, but it must be recalled that all tests were made on carefully selected homogenous living tissue (also on two animals of different weights). So, much more caution is necessary, and it is important to get the best possible map of inner temperature distribution.

References

[1] T.C. Cetas, W.G. Conner, and M.L.M. Boone, "Thermal dosimetry: Some biophysical considerations," *Cancer Therapy by Hyperthermia and Radiation*, p. 3, 1978.

[2] D.A. Christensen and C.H. Durney, "Hyperthermia production for cancer therapy: A review of fundamentals and methods," *Microwave Power*, vol. 16, p. 2, 1981.

[3] G.M. Hahn, P. Kernahan, A. Martinez, D. Pounds, and S. Prionas, "Some heat transfer problems associated with heating by ultrasound, microwaves, or radiofrequency" *Ann NY Acad. Sci*, vol. 335, pp. 327–346, 1980.

[4] J. Mendecki, E. Friedenthal, C. Botstein, F Sterzer, R Paglione, M. Nowogrodzki, and E. Beck, "Microwave induced hyperthermia in cancer treatment. Apparatus and preliminary results," *Int. J. Radiat. Oncol. Biol. Phys.*, vol. 4, pp. 1095–1103, 1978.

[5] T.S. Sandhu, H.S. Kowal, and R.J.R. Johnson, "The development of microwave hyperthermia applicators," *Int. J. Radiat. Oncol Biol Phys.*, vol. 4, pp. 515–519, 1978.

Multi-Octave Performance of Single-Ended Microwave Solid-State Amplifiers

KARL B. NICLAS, SENIOR MEMBER, IEEE

(Invited Paper)

***Abstract*—The computed performances of multi-stage single-ended GaAs MESFET amplifiers are compared when employing one and the same transistor type. The circuit principles studied are of the reflective match, the lossy match, the feedback, the distributed, and the active-match amplifier variety. It was found that the gain characteristics of the single-stage modules using either passive or active matching do not conclusively identify the optimum circuit type in the band of interest (2–18 GHz). For the case of multistage devices, however, the gain and the VSWR performance clearly favor the distributed amplifier principle.**

In addition to the data reported in the literature, the paper discusses recent experimental results obtained from a 3–17.5-GHz reflective match module, a two-stage 2–18-GHz and a four-stage 0.5–18.5-GHz feedback amplifier, as well as a two-stage 2–20-GHz and a four-stage 2–18-GHz distributed amplifier.

I. Introduction

THE CONCEPT of the balanced reflective match amplifier has dominated the design of microwave solid-state amplifiers for nearly two decades [1]. Up to this day, quadrature hybrids of the type invented by J. Lange [2] are almost exclusively occupying the position of the signal combiner and divider yielding excellent performance, regardless of the mismatch presented by the two identical single-ended modules. However, the bandwidth of the balanced reflective match amplifier is limited to two octaves, at best. Extending the frequency band beyond this 4:1 ratio requires a minimum of three 90° couplers in tandem configuration [3]–[5]. Unfortunately, these tandem couplers are not only complicated, but space-consuming and costly to manufacture. Due to these reasons and their cost effectiveness, multi-octave single-ended amplifiers are gaining more and more in importance. Four circuit design principles exhibiting excellent ultra-wideband characteristics are now challenging the concept of the balanced reflective match amplifier [6]–[30]. Hence, the five competitors are:

1) the reflective match amplifier,

Manuscript received December 16, 1983; revised March 5, 1984.

The author is with the Watkins–Johnson Company, Stanford Industrial Park, Palo Alto, CA 94304.