Biomedical Application of Microwave in Cardiac Tissue Ablation: from in Vitro Analyses to Clinical use

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Background. Recently, there has been renewed interest in simplifying a surgical cure for atrial fibrillation. Mi-crowave energy ablation provides an easier and faster surgical technique, in lieu of traditional "cut and sew," which can also be applied on the beating heart.

Methods. Specific absorption rate (SAR) and thermal profiles were determined after microwave energy abla-tion intended for clinical application. Lesion geometry measures obtained in vitro with tissue equivalent media were compared with values collected from animal myocardium.

Results. Thermal profile analysis demonstrated lesion penetration depths of 2.5, 3, and 5 mm after 8, 16, and 24 seconds, respectively, with microwave power application of 40 W. Dosimetric studies performed using animal myocardium corresponded to the thermal profile analysis and showed that lesion depth was controlled by the output power and the ablation time.

Conclusions. Lesion geometry in tissue using micro-wave energy is similar to that predicted from in vitro analysis. The ablation depths and thermal profile of microwave ablation is favorable for performing atrial ablation, and this is corroborated by favorable early clinical results.

In 1989, the Maze procedure was introduced by Dr James Cox to treat chronic atrial fibrillation (AF) [1].
With this technique, several surgical incisions are made in both atria in order to interrupt principal reentrant circuits. Scar tissue formation at incision sites limits the spread of the multiple wavelets potentially responsible for maintaining atrial fibrillation [2, 3]. The Maze procedure was later simplified [4]; nevertheless, it remains complex and lengthy, and is associated with high bleeding risk and postoperative impaired atrial contractility [5]. For these reasons, it has not been widely applied.

Alternative approaches, using energy ablation in lieu of incisions, have evolved to further simplify surgical treatment of AF and avoid the drawbacks associated with the Maze procedure [6–9]. Several groups have used radiofrequency intraoperatively for treating AF during mitral valve repair or replacement [10 –13] and in patients with lone AF [11], whereas others have used microwave energy [14, 15] or cryotherapy [16, 17]. Energy ablation methods, which are easier and faster to perform than the "cut and sew" Maze procedure, have demonstrated promising success rates, and may pose less risk of peri-and posttherapy complications.

Despite recent use of newer energy modalities in the clinical setting, there has been very little "basic science" performed to understand the behavior and characteristics of clinical energy ablation. Lack of this basic knowledge may alter success or increase the morbidity with these procedures.

Microwave energy may offer several advantages. In general, these include the ability to produce long narrow lesions without gaps, high reproducibility in ablation depth and length, capacity to produce a flexible ablating probe, and capability for creating transmural lesions, with no surface sticking or charring. The purpose of this study was to characterize dynamics of lesion formation with microwave energy ablation developed for clinical use.

I. MATERIAL AND METHODS

A. Microwave Ablation System

The microwave ablation system (AFx, Inc, Fremont, CA) used in this study consisted of a surgical ablation probe (FLEX 2) connected by a coaxial cable to a microwave generator. At present, three different probes, the FLEX 2, FLEX 4, and FLEX 10, are commercially available. The ablating element in the FLEX 2, the probe used in this

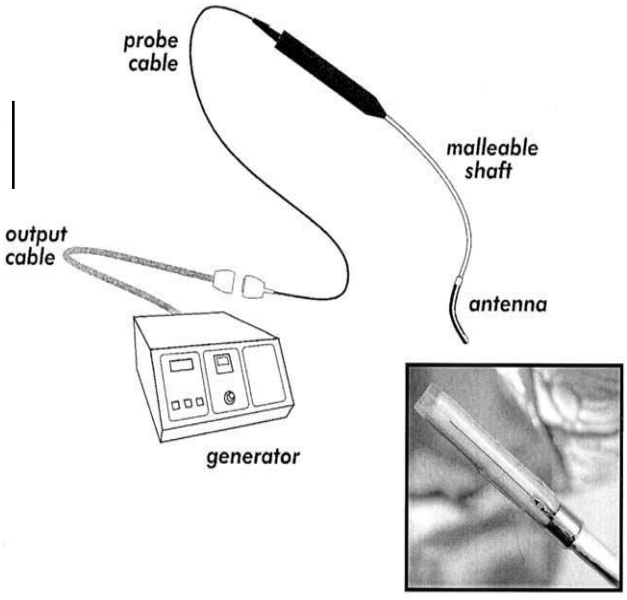

Fig 1. Microwave ablation system. Close-up of ablating probe [inset].

study, is a 25-mm-long antenna located at the distal end of the probe (Fig 1), and is designed with a reflector to direct the electromagnetic energy through a defined window into the tissue to be ablated. The microwave generator delivers a continuous wave of 2.45 GHz and allows for variable power output between 35 and 75 W, adjustable by 5-W increments. All output powers mentioned in this study refer to the output connector of the microwave generator.

Because of the losses in the coaxial cable, only 60% of the power ultimately reaches the antenna. For example, a power of 40 W from the generator corresponds to 24 W reaching the surgical ablation probe. For the FLEX 2, this is equal to a linear power density of 9.6 W/cm of tissue.

B. In Vitro Analyses

SPECIFIC ABSORPTION RATE (SAR) MEASUREMENTS –

To characterize the ablating probe and predict its microwave emission properties, SAR measurements were carried out using tissue-equivalent media. The SAR pattern, expressed in power per unit of volume (W/m^3), is presented in normalized SAR amplitudes and illustrates how and where the microwave energy is emitted and absorbed into the medium. The SAR is proportional to the electrical conductivity (σ) and the square of the electric field (E) emitted in the medium ($SAR = \sigma * E^2/2$). It is also proportional to the initial slope of the temperature (T) increase ($SAR \propto \partial T/\partial t$).

The tissue-equivalent medium (liquid phantom) was made up of deionized water (67%) and glycerol (33%) [18]. For this type of analysis, the dielectric properties of this mixture have been shown to be similar to the myocardium at 2.45 GHz (ε^*=57-31.j) [18, 19].

During measurement of SAR intensity, the ablating probe was completely immersed into the liquid phantom mixture. A miniature SAR measurement system, consisting of three orthogonal dipoles and an electronic amplifier (Model 8021B/C and Amplifier 8010 [Narda, Hauppauge, NY]) was used to determine SAR patterns. SAR was measured in 2,000 locations on a 4×1-cm plane facing the ablating tip, where data were electronically collected with a regular data acquisition system.

THERMAL PROFILE MEASUREMENTS

Thermal profiles show propagation of the thermal front through tissue introduced by the ablation probe. Thermal profiles were used to examine consistency and depth of the temperature increase over time along the length of the microwave energy antenna. Thermal profile measures were per-formed using a tissue-equivalent medium (solid phantom) that had dielectric and thermal properties approximating those of cardiac tissue [20]. It consisted of water (75.48%), NaCl (1.05%), polyethylene powder (15.01%), and TX-151 (8.46%), a solidifying agent. During application of microwave energy (40 W from the generator), the ablating tip was positioned in direct contact with the solid phantom surface.

A fiberoptic thermometry system (Luxtron Corporation, Mountain View, CA) with four 0.5-mm diameter fiberoptic probes was used to record internal temperature of the solid phantom. The solid phantom was placed in a plastic container drilled with an array of 5×2-mm access holes to ensure accurate positioning of the fiber-optic probes. Temperature measurements were simultaneously recorded at all four locations in a series of successive trials to collect data from the entire array. Time for each ablation was set at 2 minutes. The solid phantom was allowed to cool for 5 minutes between successive trials.

Temperature values used to create thermal profiles were corrected from measured values to reflect the base-line phantom tissue temperature of 30°C. This adjustment was made in order to simulate thermal conditions of open heart surgery, where myocardial temperature ranges between 8°C and 20°C during cold cardioplegic arrest. Use of this model assumes that thermal conductivity of the solid phantom is constant within the temperature range applied for this study. The 50°C isotherm defined lesion size, as indicated by Haines and colleagues [21], who reported that the temperature at the margin between viable and nonviable tissue is approximately 48°C. The software Matlab (MathWorks, Natick, MA) was used to plot the thermal profiles.

C. In Vivo Analyses

DOSIMETRIC STUDY: POWER DEPENDENCY

Results obtained from the solid phantom model were validated using freshly excised bovine hearts (n=11). Two lesions were made on the left ventricle of each heart specimen. Each lesion was produced with the generator set at 40 or 60 W of power, applied for 25 seconds. After completing the ablation procedure, tissue specimens were stained with the vital dye 2,3,5-triphenyltetrazolium chloride (TTC) to identify the viable and nonviable tissue. Depth and width of ablation were measured at the midpoint of each lesion.

DOSIMETRIC STUDY: TIME DEPENDENCY

Effect of ablation time on microwave energy penetration depth was also evaluated. Three ablations were performed on the left ventricle of each of four heart specimens. Output power from the generator was set at 40 W, with ablation time of either 10 or 40 seconds. Lesion geometry was measured as it was for the power dependency study.

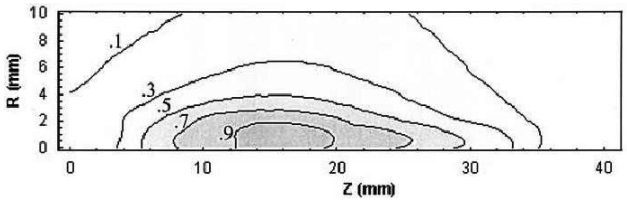

Fig2. Specific absorption rate (SAR) pattern showing microwave energy intensity produced by the ablating probe. The horizontal axis represents the distance along the ablating probe, whereas the vertical axis represents depth within the liquid phantom. The proximal end of the ablating probe was located at Z 4 mm, and the distal end at Z 29 mm. Normalized SAR values indicate maximal energy deposition, which was obtained at the interface between the ablating probe and phanto

Results obtained from the power dependency portion of the study for microwave power application of 40 W for 25 seconds completed the performance curve analysis for time dependency.

II. RESULTS

A. *In Vitro Analyses*

SPECIFIC ABSORPTION RATE (SAR) MEASUREMENTS.

The SAR measurement obtained using liquid phantom modeling is presented in Figure 2. The maximum SAR value (1.00) is located at the interface between the midsection of the ablating probe and the tissue (R 0; Z approximately 12 to 19 mm). The penetration depth of the electromagnetic (microwave) energy, defined as 37% of the maximal value, was approximately 4 mm. The emission of micro-wave energy was continuous all along the antenna.

THERMAL PROFILE MEASUREMENTS

Thermal profiles indicated that electromagnetic energy absorption produces a thermal gradient (Fig 3) in the phantom. With microwave power application of 40 W from the generator, achieved lesion penetration depth was approximately 2.5 mm after 8 seconds, 3 mm after 16 seconds, and between 4 and 5.5 mm after 24 seconds of ablation. The lesion was approximately 2.5 cm in length, which corresponded to the length of the microwave energy antenna.

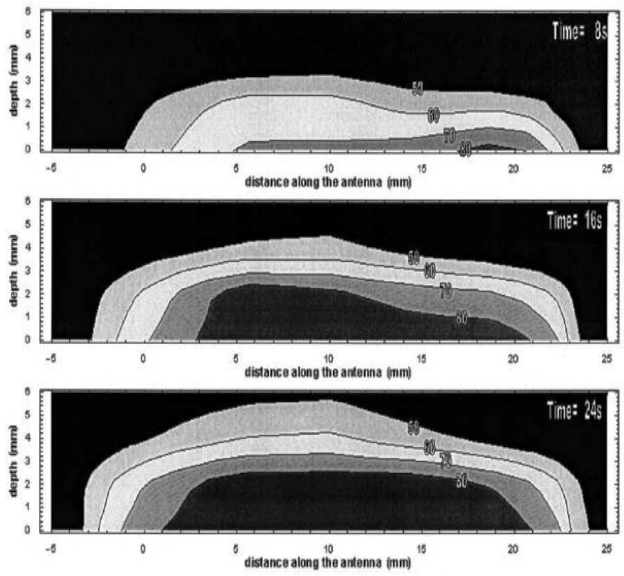

Fig.3. Thermal profiles obtained with microwave energy power application of 40 W for 8,16, and 24 seconds, respectively. Proximal end of the ablating probe was located at 0 mm, the distal end at 20 mm (x-axis). Lesion depth is given on the y-axis and isotherms are expressed in degrees Celsius. The zone of irreversible tissue damage begins at the 50°C isotherm line.

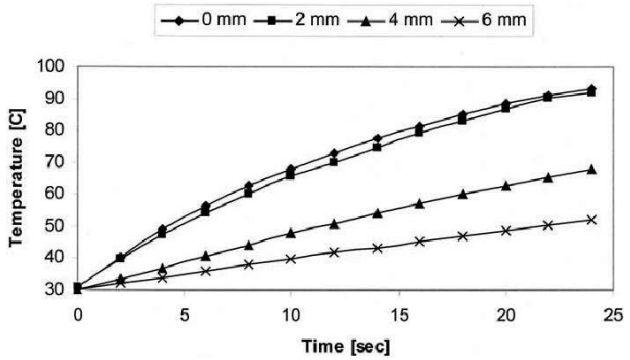

Fig 4. Temperature elevation (°C) demonstrated by solid phantom modeling with application of 40 W microwave power over 24 seconds at specified tissue depths (0, 2, 4, and 6 mm). Temperatures over time were similar at the solid phantom surface and 2 mm deep. Tissue temperature sufficient for a 4-mm-deep lesion (50°C) occurred with 12 to 13 seconds of ablation, and for a 6-mm-deep lesion with 24 seconds of ablation, while surface temperature remained below 100°C.

Tissue temperature elevation over time in the region with maximal SAR is presented in Figure 4 (Z 18; Fig 2). With microwave energy application of 40 W, solid phantom modeling demonstrated that a lesion 6 mm deep was produced in 24 seconds, while maintaining tissue temperature at the tissue surface/ablating probe interface below 100°C. The initial slope of temperature elevation curves was positive, indicating that microwave energy is directly deposited into the tissue and the initial tissue heating is not caused by thermal conduction.

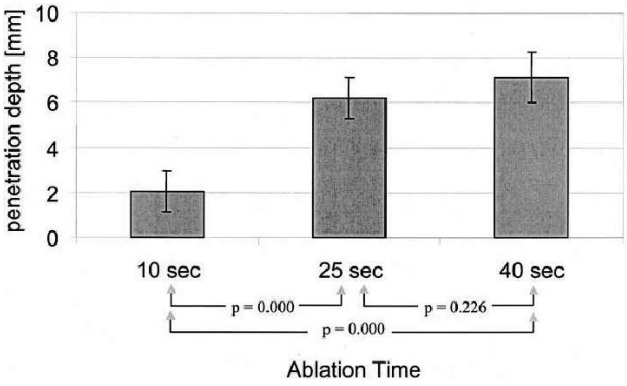

Fig 5. Average lesion penetration depths achieved with application of 40 W microwave energy for 10, 25, and 40 seconds. Penetration depth was successively and significantly deeper with increased ablation time.

Normalized SAR values obtained by direct measurement of the electromagnetic field (Fig 2) were compared with normalized SAR values calculated using thermal profile data (Fig 4). Direct SAR measures from the electromagnetic field were equivalent to those calculated from thermal profile analyses. For ablation depths of 0 (surface), 2, 4 and 6 mm, directly measured normalized SAR values were 1.00, 0.90, 0.45, and 0.28, respectively; normalized SAR values calculated using thermal profile data were 1.00, 0.91, 0.38, and 0.21.

B. In Vivo Analyses

DOSIMETRIC STUDY: POWER DEPENDENCY

With microwave application of 40 W over 25 seconds, average achieved penetration depth was 6.20 ± 0.92 mm and mean lesion width was 4.93 ± 0.98 mm. Mean penetration depth obtained with this energy application corresponded to results shown by thermal profile analysis (Fig 3), where after 25 seconds, temperature at 6 mm depth reached 50°C, which is sufficient for tissue ablation. Ablation width was significantly narrower than ablation depth ($p = 0.003$). With 60 W of power, average achieved penetration depth was 7.01 ± 0.83 mm and lesion width was 6.95 ± 1.49 mm. Depth and width did not differ statistically ($p = 0.866$). Penetration depth observed with application of 60 W power for 25 seconds was significantly deeper than depth achieved with 40 W for the same ablation time ($p < 0.000$). Lesion width also differed significantly between the two power settings ($p < 0.000$).

DOSIMETRIC STUDY: TIME DEPENDENCY

Association between ablation time for a given power and lesion geometry is shown in Figure 5. With power application of 40 W, average lesion depths were 2.05 ± 0.89 mm, 6.20 ± 0.92 mm, and 7.12 ± 1.12 mm for ablation times of 10, 25, and 40 seconds, respectively. Penetration depth differed significantly between ablation times (analysis of variance, $p < 0.000$); a post hoc test (Bonferroni) revealed that ablation depth differed significantly between ablation times of 10 and 25 seconds ($p < 0.000$) and 10 and 40 seconds ($p < 0.000$), but not between 25 and 40 seconds ($p = 0.226$). The association between ablation time and penetration depth was curvilinear, as indicated by thermal profile temperature elevation plots.

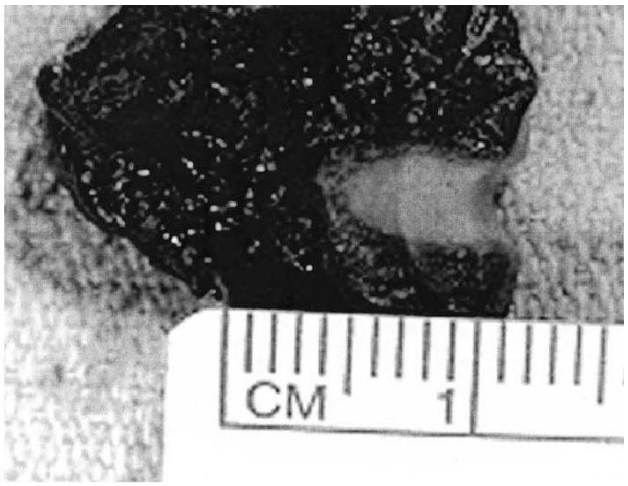

Fig 6. Cross section of a lesion produced using a power application of 40 W for 25 seconds. Although not apparent here, the length of the lesion was approximately 25 mm, corresponding to the length of the microwave energy antenna.

A cross section of a sample lesion obtained with a setting of 40 W for 25 seconds is shown in Figure 6. Lesion width was approximately 4 mm and depth was about 6 mm. Staining demonstrated a well-demarcated transition between the viable and nonviable zones.

III. COMMENT

Microwave (electromagnetic) energy heats by inducing dielectric losses in polar molecules such as water [22]. This electromagnetic field is capable of propagating through blood, desiccated tissue, and scars, which makes it desirable for atrial tissue ablation. Penetration depth achieved with microwave energy depends upon a number of factors, including the dielectric properties of the tissue, frequency of the microwave energy, and antenna design. The physics of this energy source may allow for deeper and more reliable ablation of atrial tissue than traditionally available technologies such as radiofrequency. The purpose of this study was to thoroughly characterize a microwave ablation probe designed for clinical use.

In vitro SAR analysis demonstrated good uniformity in distribution of the electromagnetic energy through the tissue and excellent penetration depth. Energy distribution was maximal near the center of the ablating element, indicating that depth of ablation was relatively deeper at the midpoint of a lesion. There was no indication of edge effect along the ablating tip, which could potentially produce overheating of the tissue surface and induce charring.

Findings from thermal profile analyses, using a solid phantom cardiac tissue model, corresponded with SAR results by showing continuous and even distribution of energy, with no areas of discontinuity over the length of the ablating probe. Temperature elevation plotted over time demonstrated smooth temperature increase in tissue cross sections, whereas temperature at the tissue surface remained below 100°C over the time required to produce a 6-mm-deep lesion. Because temperature remained below this critical value, charring and carbonization, as well as cavitation and wall disruption, should not occur. Indeed, neither of these problems occurred in any of the scenarios studied here. This is a critical finding because the ability to raise the tissue temperature to 50°C while maintaining one less than 100°C is paramount to both effective and safe hyperthermic ablation.

The results obtained on myocardial tissues demonstrated that ablation depth can be predictably controlled by modifying microwave energy power or ablation time. Ablation depth obtained after 25 seconds was significantly greater than depth achieved after 10 seconds; however, ablation depths achieved with 25 and 40 seconds did not differ significantly. This phenomenon can be explained by the fact that with progressively increased time of microwave energy application, a quasi-static state is reached where lesion growth essentially plateaus. The temperature elevation plot collected in vitro (Fig 4) corroborated observations in myocardial tissue. This was also an encouraging finding in that successful tissue ablation can be carried out in only 25 seconds, as op-posed to the 2 minutes required with cryoablation.

Agreement between in vitro and in vivo studies provides validity for predicting microwave lesion formation in clinical use. Depth of ablation, assessed by measuring the zone of

nonviable tissue in vivo, was the same as that shown by thermal profile analysis conducted in vitro for the same given microwave application. In vivo analyses demonstrated an average ablation depth of 2.05 ± 0.89 mm after 10 seconds and 6.20 ± 0.92 mm after 24 seconds, whereas in vitro analysis predicted an ablation depth of 2 to 3 mm after 8 seconds and 4 to 6 mm after 24 seconds of ablation. This reliable and consistent ablation depth plays an important role in clinical ablation, because as with other sources, there is no feedback mechanism to determine when a lesion has been successfully created. In the absence of a feedback mechanism, the reliable ablation depth demonstrated with microwave is important to assure safety and reproducibility in the clinical setting.

The microwave ablation probe used in this study was capable of producing narrow and deep lesions in the myocardium. The lesions were continuous with no gaps along the length of the antenna. Because of the metallic reflector built into the device, energy emission is unidirectional, which is important for ensuring that ablations can be performed safely. This study showed that penetration depth was predictably controlled by modifying microwave energy power and ablation time. At the suggested setting for this ablating probe (FLEX 2), which is 40 W of output power from the generator and 25 seconds of ablation time, geometry of an average lesion was approximately 6 mm deep and 5 mm wide. For the more commonly used FLEX 4, this power setting corresponds to 60 W for 45 seconds in the arrested heart. Because of good penetration of the microwave energy into the tissue, there was no evident tissue surface carbonization with ablation. Preliminary clinical experience has demonstrated that microwave energy using a system with this output design can be applied safely and successfully in cardiac tissue ablation [14].

Extrapolation between the models presented herein and clinical application requires addressing two potential limitations of this study. For the in vivo portion of the study, although our intention was to model atrial ablation, ventricular myocardial tissue was selected as the modus operandi in place of atrial tissue. Because the principal objective of the study was to characterize dosimetry of clinical application of microwave energy, it was essential to have adequate myocardial thickness in order to do so. Average atrial thickness in the normal human myocardium is 4 mm, significantly less than average achieved lesion depths reported here for selected power and time applications. It must be noted, however, that in patients with severe mitral valve disease (a large number of which could potentially receive cardiac ablation treatment), left atrial wall tissue can be fibrotic and significantly thicker (e.g., 7 to 8 mm) than in persons with no disease. Because of the importance of ensuring lesion transmurality for efficacy of treatment, it was vital to define dosimetry over a clinically relevant range of energy applications; use of ventricular myocardial tissue allowed this type of study.

Second, our in vivo experimental model assumes that energy diffusion and temperature gradients are similar to those existing in the fully perfused in vivo clinical model. The results of this study are effectively only valid under arrested heart conditions and cannot be extended to beating heart surgery. In beating heart surgery, the circulating blood pool within the atria acts as a heat-sink, where significant thermal energy can be lost through convective heat transfer. McRury and colleagues showed that energy losses to micro-circulation, however, are not significant, and that difference between perfused and nonperfused tissue in terms of intramyocardial thermal gradients are minimal [23]. Their observations also suggest that the freshly excised myocardial model provides a good representation of the clinical arrested heart environment.

The results of these laboratory studies demonstrate the efficiency of microwave energy for atrial ablation. While no laboratory work can reliably predict clinical outcome, this study would suggest that microwave energy is a safe and effective energy source that can quickly produce transmural atrial lesions. Microwave energy ablation, in addition to the characterization of ideal patient populations and lesion sets, should play a key role as we progress to a more minimally invasive cure of AF. Initial work is promising, and further characterization of micro-wave energy ablation from the epicardium of the beating heart will allow for optimization of this energy source.

IV. CONCLUSIONS

Lesion geometry in tissue using micro-wave energy is similar to that predicted from in vitro analysis. The ablation depths and thermal profile of microwave ablation is favorable for performing atrial ablation, and this is corroborated by favorable early clinical results.

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