Microwave Catheter Ablation of Myocardium In Vitro
Assessment of the Characteristics of Tissue Heating and Injury

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Background  Radiofrequency (RF) catheter ablation lesion size has been limited by the small volume of tissue directly heated by the RF electrode. Microwave (MW) energy has been proposed as an alternative energy source to generate larger lesions because of its increased volume of direct tissue heating. To further characterize MW ablation of myocardium, we studied the temperature-versus-distance profiles during MW ablation in an in vitro model of perfused and superfused porcine right ventricular free wall.

Methods and Results  Radial tissue temperatures in 19 isolated porcine right ventricles were measured and recorded with four fluoroptic thermometry probes placed within the myocardium at 2.5-mm radial increments from the catheter. The MW antenna catheters used were monopolar and helical-coil antennas resonating at 915 and 2450 MHz. Durations of energy delivery for a 915-MHz MW monopolar antenna (60 to 600 seconds) and a 4-mm-tip RF electrode (60 and 300 seconds) were varied to compare time courses of lesion formation. For each lesion, the temperature at the lesion border zone (the isotherm of irreversible tissue injury) was determined. Similar lesion size and temperature profiles were observed for 915- versus 2450-MHz MW antennas and monopolar versus helical-coil MW antennas. Lesion depth for the 915-MHz monopolar antenna increased monoexponentially with a half-time of 170 seconds. The isotherms for all MW antenna designs were not significantly different. The mean isotherm of irreversible tissue injury for MW lesions was not significantly different from the mean isotherm for RF lesions (54.4°C versus 53.6°C, respectively).

Conclusions  Microwave ablation has the potential to directly heat a greater volume of tissue than RF ablation but only with efficient MW antennas. The primary mechanism of tissue injury for both MW and RF ablation appears to be thermal. (Circulation. 1994;89:2390-2395.)

Key Words  • radiofrequency • microwave • myocardium

The primary mechanism of tissue injury by radiofrequency ablation is presumed to be thermal. A major limitation of radiofrequency ablation is the relatively small depth of tissue injury produced by this technique. This may be attributed to the precipitous falloff of direct tissue heating (volume heating) by the radiofrequency energy as the distance from the electrode/tissue interface increases.1,2 Deeper tissue layers may be ablated by heat conduction from the volume-heated source, but the maximum lesion depth is limited. Radiofrequency ablation has been demonstrated to be highly successful for easily accessible and localized substrates such as accessory pathways or the atrioventricular node, but sites of arrhythmia origin that may lie deep within the myocardium, such as those resulting in reentrant ventricular tachycardias, may require an alternative mode of heating that heats a greater volume of myocardium.

Microwave energy has been proposed as an alternative mode of energy delivery for catheter ablation in the heart.3-5 In contrast to heating by electrical resistance as observed during radiofrequency ablation, the mechanism of heating from a high-frequency microwave energy source is dielectric.6 Dielectric heating occurs when electromagnetic radiation stimulates oscillation of dipoles (such as water molecules) in the surrounding medium and the electromagnetic energy is converted into kinetic energy (or heat). This mode of heating lends microwave ablation the potential for a greater depth of volume heating than radiofrequency ablation and should result in a larger lesion size. However, few data are available regarding the characteristics of microwave ablation in myocardium and the response of myocardium to microwave hyperthermic exposure. The effectiveness of microwave ablation depends on the radiating ability of the microwave antenna that directs the electric field and determines the amount transmitted into the myocardium, which is critical for heating.7 Monopolar antennas have previously been shown in hyperthermia oncology literature to radiate a significant electric field into tumors and generate heat.8 The energy deposition, while maximal at the terminal gap between the inner and outer conductor, tends to be distributed widely along the transmission line. To concentrate more of the energy distribution near the electrode tip, circularly polarized coil antennas have been developed.9 Unfortunately, the application of either one of these standard microwave antenna designs to invasive cardiac ablation has not been carefully investigated.

To define the characteristics of microwave heating in myocardial tissue, in vitro experiments were performed in isolated perfused and superfused porcine right ventricular free wall. The purposes of this study were (1) to determine the effect of various microwave antenna designs and frequencies on radial tissue temperature

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gradients and lesion size, (2) to demonstrate the time course of tissue temperature rise and lesion growth during microwave ablation, and (3) to compare the tissue temperatures at the border zone of irreversible tissue injury with different microwave antennas and various durations of microwave and radiofrequency energy delivery.

**Methods**

**Experimental Preparation**

All experimental protocols observed the “Position of the American Heart Association on Research Animal Use” and were accepted by an internal Animal Research Review Committee.

Nineteen pigs weighing 30 to 70 kg were anesthetized with intravenous ketamine/xylazine (20/2 mg/kg), and anesthesia was maintained with intravenous sodium pentobarbital (25 mg/kg). A right thoracotomy exposed the heart. After the pericardium was opened, the beating heart was grasped and quickly excised, with care taken to preserve the integrity of the aortic root. The heart was immersed and rinsed in serial baths of iced 0.9% saline at 4°C. The right coronary artery ostium was cannulated. The right atrium and ventricle were dissected free from the rest of the heart, with the portion of the aortic root preserved that contains the right coronary ostium. The cannula was sutured into place with two 2-0 silk sutures. The isolated right ventricular free wall was transferred to a Plexiglas tissue chamber warmed by a surrounding water jacket. The preparation was perfused and superfused with Krebs-Henseleit buffer containing (in mmol/L) NaCl 121.5, KCl 4.7, CaCl₂ 2.5, MgSO₄ 1.17, KH₂PO₄ 1.17, glucose 11.1, NaHCO₃ 0.25, NaEDTA 0.57, and ascorbic acid 0.00126. The superfusate was warmed to 36.5±0.5°C, and flow was maintained at a constant rate of 10 mL/min with a Gilson Minipuls 2 electrical roller pump. Appropriate coronary perfusion was confirmed by bolus injection of fluorescein dye under ultraviolet light. Transsected arteries were ligated, and unperfused regions were resected. During the course of the experiment, tissue temperature was continuously monitored, and the viability of the preparation was intermittently tested by observation of its response to external pacing.¹

**Lesion Generation**

Microwave lesions were created with either a 915-MHz microwave generator (Tex-L) or a 2450-MHz generator (EP Technologies). Because heating with current microwave ablation catheters was slow, titration of power to achieve a constant antenna/tissue interface temperature of 85°C was not possible. Therefore, microwave-transmitted power was fixed at 50 W. Use of higher power levels with the current prototype catheter designs was not possible because of breakdown of the dielectric material. The forward and reflected powers were recorded. Because the direction of microwave electric field propagation is radial, each catheter was positioned with the antenna axis parallel to the endocardium. A fulcrum balanced the weight of the antenna and ensured constant antenna/tissue contact pressure.

All radiofrequency lesions were produced with a radiofrequency lesion generator (model RFG-3AV, Radionics) transmitting 500-kHz energy to a 1.6-mm-diameter catheter electrode with a thermistor integrated into the tip (Radionics). The radiofrequency output was grounded to a metallic strip in the floor of the tissue bath. The radiofrequency catheter electrode was positioned perpendicular to the endocardium. The tip of the electrode housing the thermistor was in direct contact with the endocardial surface so as to measure electrode/tissue interface temperature. Electrode/tissue interface temperature was kept constant at 85°C by power adjustment.

**Fig 1.** Illustration of the designs for impedance-matched monopolar and helical-coil microwave antennas. The quarter wavelengths for the 915- and 2450-MHz antennas that defined the lengths of protrusion of the inner conductor beyond the outer conductor termi- 

A balanced fulcrum maintained constant catheter/tissue contact pressure.

**Antenna Designs**

Two antenna designs were used in the in vitro myocardial preparation. The monopolar antenna consisted of an inner conductor of a coaxial cable that protruded one-quarter wavelength beyond the outer conductor. The helical-coil antennas were constructed with the inner conductor of the coaxial cable protruding one-quarter wavelength beyond the outer conductor, then coiling back toward the outer conductor (Fig 1). The pitch angle of the coil was 12°. The transmission line of each catheter was a coaxial cable with a characteristic impedance of 50 Ω.

**Temperature Recording**

All in vitro tissue temperature measurements were performed with a modified Luxtron 3000-4 fluoroptic thermometer system. The temperature probes were placed in the tissue 2 mm below the endocardial surface in a line emanating from the energy source. For microwave lesions, the probes were placed perpendicular to the gap between the protrusion of the inner conductor beyond the outer conductor, which was determined with a phantom tissue model and thermographs to be the point of maximal heating. For radiofrequency lesions, the probes were placed radially from the proximal point of the electrode/tissue contact point. For data analysis purposes, temperatures were measured at five radial distances in 2.5-mm increments.

**Protocols**

To determine the effect of catheter design and frequency on radial temperature profiles, lesions were generated with the 915- and 2450-MHz helical-coil antennas and the 915- and 2450-MHz monopolar antennas. Radial temperature measurements were made in vitro continuously during lesion generation. Microwave energy was delivered at 50 W for 5 minutes for each lesion.

To assess the time course of microwave lesion formation, lesions were created with a 915-MHz monopolar antenna at energy delivery durations of 60, 180, 300, and 600 seconds. For comparison, radiofrequency lesions were generated with energy delivery durations of 60 and 300 seconds.

**Lesion Size Determination**

The histochemical stain nitro blue tetrazolium was used to determine tissue viability after lesion generation.¹¹ After le-
Fig 2. Graphical demonstration of the methodology for calculation of the isotherm of irreversible tissue injury for each lesion. A best-fit inverse exponential function is determined for the measured temperatures at remote tissue distances from the antenna. The lesion half-width is substituted into this best-fit function as the distance, and the resulting temperature is the temperature at the lesion edge or the isotherm.

Fig 3. Plot of the peak tissue temperature measured at a 2-mm depth versus radial distance from the antenna. ○ indicates mean measured temperatures at each distance ±1 SD for the 2450-MHz applicators; ●, measured temperatures ±1 SD for the 915-MHz applicators. The dashed line is the best-fit inverse proportional function to the 2450-MHz measured temperatures, and the solid line corresponds to that of the 915-MHz values.

Lesions were identified, transmural blocks containing the lesions of the isolated right ventricular free wall were removed, and then the lesions were bisected. These blocks were incubated in a solution of 0.5 mg nitro blue tetrazolium per 1.0 mL of 0.2 mol/L Sorenson’s buffer. The viable regions of tissue stained purple and were sharply demarcated from the pale yellow nonviable regions. For each lesion, the maximum depth and width were measured. Lesion depth was measured as the distance from the endocardial surface to the farthest point in the myocardium of nonviable tissue. Lesion width was measured at the point of maximum lesion width in a plane parallel to the endocardial surface.

Isotherm of Irreversible Tissue Injury

Fig 2 demonstrates the method for calculation of the temperature at the border of each ablation lesion (the isotherm of irreversible tissue injury). An inverse proportional function characterizing the tissue temperature versus distance from the center of the microwave source was fit to the peak temperatures recorded at the five radial measurement sites for each lesion. The lesion radius, defined as one half of the maximum lesion width, was substituted into each best-fit function, and the isotherm at the lesion border was calculated. Mean isotherms, lesion widths, and lesion depths were compared among conditions.

Statistics

All raw data were immediately measured and entered into a computerized data bank. Subsequent data analysis, curve fitting, and statistics were executed through the RS/1 statistical package (BBN Software). Normally distributed data were expressed as mean ± SD. Comparisons among means were determined with unpaired t statistics. Comparisons among groups of nonnormal data were made using median values and the Mann-Whitney test. To compare the possible interaction of microwave frequency and antenna design on lesion size, the data were compared by a two-way ANOVA. For the purposes of this analysis, a logarithmic transformation of the data was performed to achieve a normal distribution. Values of P < .05 were defined as significant.

Results

Effect of Frequency and Antenna Design on Microwave Ablation In Vitro

Microwave lesions were created in vitro with the 915-MHz monopolar (n=11), 915-MHz helical-coil (n=11), 2450-MHz monopolar (n=14), and 2450-MHz helical-coil (n=11) antennas. The radial temperature profiles for the 915- and 2450-MHz antennas are presented in Fig 3. At 50 W, peak temperatures achieved at the antenna/tissue interface were similar for all conditions. The resultant radial temperature profiles for the mean data were similar for the 915- and 2450-MHz applied frequencies. Mean lesion widths for the 915- and 2450-MHz antennas were 8.1±2.0 and 7.2±1.5 mm, and mean lesion depths were 4.9±1.3 and 4.5±1.0 mm, respectively (P=NS). No lesions were transmural. When the two antenna designs were compared, the radial temperature profiles achieved were similar, as were the lesion widths (7.7±1.8 mm for the helical-coil versus 7.5±2.1 mm for the monopolar antenna). However, the lesion depth achieved with the helical coil was slightly greater than that with the monopole (5.1±1.3 versus 4.3±0.9 mm, respectively; P<.01). When lesion dimensions were compared among all four conditions, there was no evidence of interaction between the two factors of frequency of microwave energy delivery and antenna design.

Time Course of Lesion Formation With Microwave Ablation

Fifty-one microwave lesions were created with energy delivery durations of 60, 180, 300, and 600 seconds. For comparative purposes, 16 radiofrequency lesions were made with energy delivery durations of 60 and 300 seconds. The time courses of lesion growth for all radiofrequency and microwave lesions are presented in Fig 4. Mean lesion depth for the 915-MHz monopolar antenna increased in a monoeponential fashion with increasing duration of energy delivery (P<.001, r=.76). The half-time of tissue temperature rise for microwave ablation was 170 seconds. Mean lesion depth and width were 2.6±0.8 and 4.9±1.1 mm at 60 seconds compared with 4.4±1.1 and 7.8±2.1 mm at 300 seconds (P<.001 for both comparisons). In comparison, mean lesion depths for radiofrequency lesions were 3.9±0.4 mm at 60 seconds of energy delivery versus 4.2±0.6 mm at 300 seconds (P=NS), and mean lesion widths were 6.6±0.5 versus 7.2±0.8 mm, respectively (P=NS). Therefore, radiofrequency lesion size achieved steady state within 60 seconds of energy delivery, whereas microwave lesions continued to significantly increase in size over at least 5 minutes. The temperature at
Fig 4. Graph of mean lesion depths ± 1 SD for radiofrequency (RF, △) and microwave (MW, ■) lesions at various energy delivery durations. A monoexponential function (solid line) is fit to the microwave data; to aid visual comparison, the radiofrequency data points are connected with straight dashed lines. The microwave lesion continues to increase in size over the 600-minute range of energy delivery, whereas the radiofrequency lesion has reached steady state by 60 seconds.

The antenna/tissue interface achieved steady state by 60 seconds. Despite similar lesion dimensions, the steady-state temperature at the antenna/tissue interface at 300 seconds was 70.4±13.5°C for microwave lesions and 83.6±7.9°C for radiofrequency lesions (P=.004).

Determination of Isotherms From Temperature Profiles

Representative isotherm calculations of irreversible tissue damage for three ablations are shown in Fig 5; summary data for these calculated values with various microwave frequencies and antenna designs are presented in Fig 6. No significant difference was seen among conditions for this value. The isotherms for radiofrequency ablation after energy delivery durations of 60 and 300 seconds and for a 915-MHz monopolar antenna at 60, 180, 300, and 600 seconds are presented in Fig 7. All mean values were similar despite differing modes of heating and varying durations of hyperthermic exposure. The isotherm of irreversible tissue injury for all microwave lesions was 54.4±4.2°C, which was similar to that observed for the radiofrequency lesions (53.6±3.2°C, P=NS).

Fig 5. Graph illustrating measured radial tissue temperature gradients and the associated best-fit inverse proportional functions for three typical microwave and radiofrequency lesions. ■, ●, and △ mark specific temperatures at each distance for an individual lesion. ○ corresponds to the point at which the lesion half-width, shown by vertical dotted lines, intersects these best-fit functions. Horizontal dotted lines mark the calculated isotherm of irreversible tissue injury for each example.

Fig 6. Bar graph. Each bar corresponds to mean calculated isotherms of irreversible tissue injury ± 1 SD for subgroups of microwave ablation. Bars for helical-coil (HC) antennas resonating at 915 MHz (915 HC) and 2450 MHz (2450 HC) as well as monopolar (or whip [WH]) antennas tuned to 915 MHz (915 WH) and 2450 MHz (2450 WH) are shown (P=NS for all comparisons).

Discussion

The present study compared the radial temperature profiles, lesion sizes, and isotherms of irreversible tissue injury produced by microwave and radiofrequency ablation. The major findings of the study were that 915- and 2450-MHz microwave antennas had similar tissue temperature profiles and produced lesion sizes that were not significantly different. Ablation with the monopolar antenna resulted in temperature profiles and lesion sizes similar to those created with the helical-coil antenna, although lesion depth was slightly greater with the latter. The time course of lesion formation with microwave ablation was significantly longer than that seen with radiofrequency ablation, and the mean isotherm of irreversible tissue injury was similar between both ablation modalities and among a variety of experimental conditions.

Comparisons of Modes of Microwave Delivery

Tissue temperature profiles produced by the 915- and 2450-MHz microwave antennas were similar in the present study, which implies that they had comparable amounts of volume heating. This was supported by the similarity between lesion width and depth between 915- and 2450-MHz antennas in the setting of similar temperatures achieved at the antenna/tissue interface. Since the depth of penetration for a frequency of 915 MHz in tissue (3.04 cm) is larger than that of 2450 MHz (1.70 cm),12 the 915-MHz antennas should theoretically
heat a larger volume of tissue than the 2450-MHz antennas. However, because antennas resonating at the two frequencies had similar radial tissue temperature profiles and yielded lesions of similar sizes, this suggests that the 2450-MHz antennas were more efficient than the 915-MHz antennas used in this study. The ablative lesions created with the helical-coil antenna were marginally larger than those with the monopolar antenna. This probably represents a minor difference in efficiency among the prototype catheters. The differences in three-dimensional lesion geometry that might be anticipated with different antenna designs were not examined in the present protocols.

The rate of temperature increase during microwave heating is determined by the specific absorption rate, which is proportional to the square of the magnitude of the electric field. Since microwave ablation has a lower energy field density but a larger volume of energy distribution than radiofrequency ablation, the rate of tissue heating should be slower with microwave ablation than with radiofrequency ablation. This was observed experimentally, since the half-times of lesion formation and the rate of tissue temperature rise at remote distances from the energy source were significantly longer during ablations with a 915-MHz microwave source than during ablations with radiofrequency energy. Lesion sizes created with the 915-MHz monopolar antenna for a 300-second duration were comparable to those created with radiofrequency for 300 seconds despite significantly lower steady-state temperatures achieved at the antenna/tissue interface. Since microwave ablation resulted in deep tissue temperatures similar to those with radiofrequency ablation (ie, similar depths of thermal injury) but had lower measured temperatures at the catheter/tissue contact point, it appears that a larger volume of tissue remote from the antenna was directly heated by the microwave energy. If higher microwave powers could have been used, therefore, significantly larger lesion sizes would have been anticipated in comparison with radiofrequency ablation for comparable source temperatures.

Mechanisms of Myocardial Tissue Injury

The isotherms of irreversible tissue injury were calculated for all antenna types and energy delivery durations. No significant difference in isotherms were observed for 500-kHz and 915- and 2450-MHz frequencies. Isotherms for microwave ablation were similar despite varying durations of energy delivery. This demonstrates that hyperthermic exposure durations of up to 10 minutes do not result in a significant increase in myocyte killing compared with shorter durations, suggesting similar mechanisms of cellular injury within the 1- to 10-minute time range. The ablative lesion isotherms were similar between the radiofrequency and microwave lesions. Since the common link between these two techniques is that they both induce tissue heating, these data imply that the dominant mechanism of tissue injury for all electromagnetic frequencies is thermal.

It has been observed that irreversible cellular electrophysiological changes including membrane depolarization and contracture develop in isolated guinea pig papillary muscles at hyperthermic temperatures above 50°C. However, the sensitivity of tissue to hyperthermia is tissue specific and may show interspecies variability. Human erythrocytes were shown to fragment with exposure to temperatures of 50°C for 1 second. Cancer cells are more thermally sensitive but also show minimal injury with brief (<30-minute) hyperthermic exposure until temperatures reach 46°C. The mean isotherms at the lesion border zones in the present protocol were 54.4°C for microwave lesions and 53.6°C for radiofrequency lesions. The data from the present study were defined by histochemical staining with nitro blue tetrazolium, which is an indicator of active cellular dehydrogenase and has been validated as a marker for myocyte viability in the setting of ischemic necrosis. However, the true isotherm of irreversible myocyte injury may vary depending on which histological markers of acute cell death are used.

Limitations of the Study

Despite evidence of volume heating, the lesions were not as large as expected. The inefficiency of current microwave antenna designs may account for the smaller lesion sizes observed in the present study, since the degree of volume heating with microwave ablation depends on the transmission of energy into the myocardium. Microwave energy delivery resulted in considerable heating of the microwave antennas, producing dielectric breakdown of the antenna in certain cases. The maximum power that could be reliably delivered was 50 W. Higher power or more efficient antenna catheters should produce more heating and larger lesions. The antennas used in this study were impedance matched with the consideration that they will traverse the blood vessels indicative of an in vivo case; but in vitro, the majority of the catheter body was exposed to air. This could have produced an impedance mismatch, although no evidence was seen by the reflected power meter of the microwave generator. Finally, the findings made in this in vitro model of microwave ablation may not correlate to what may be observed in vivo.

Clinical Implications

The lower clinical success rate of radiofrequency ablation in the treatment of ventricular tachycardia associated with coronary artery disease has been attributed to the small lesion size produced with currently available radiofrequency ablation catheters. Microwave has been proposed as an alternative energy source in catheter ablation because the potential volume heating capabilities of this technique could result in larger lesions. In addition, microwave ablation may decrease the time required for the extensive and detailed intracardiac mapping currently required with radiofrequency ablation, thus decreasing fluoroscopy and overall procedure time. This, however, would also increase the potential risk of complications from microwave ablation, because larger lesions would have a greater propensity for damage to nontargeted structures and might also generate potentially arrhythmogenic substrates. Incorporation of tissue temperature monitoring should ultimately allow for microwave energy to be delivered in a controlled fashion, with lesion size titrated to the desired effect. To successfully achieve larger lesion size with microwave catheter ablation, the efficiency of energy delivery with this technique must be improved. Future microwave antenna catheters will use alternative
designs to concentrate power radiation at the catheter tip with more radiation in the axial plane and new strategies such as antenna tip cooling with saline infusion to prevent direct heating of the antenna tip, which results in alteration of the dielectric properties and decreased efficiency. The choice of dielectric materials and impedance matching of the antenna to the targeted tissue at the antenna tip will be optimized to maximize energy coupling of the generator to the tissue and minimize power reflection and transmission line power loss. With improved efficiency of microwave energy delivery, large thermal lesions should be possible with power levels below 50 W and without the potential complication of microwave heating of the catheter body.

**Conclusions**

Currently available microwave antennas showed similar degrees of remote tissue heating and lesion size at frequencies of 915 and 2450 MHz. The half-time of microwave lesion formation is much longer than that of radiofrequency, and microwave ablation produces more volume heating than radiofrequency ablation. The dominant mechanism of tissue injury during microwave and radiofrequency ablation appears to be thermally mediated, with a critical temperature of irreversible tissue injury at 54.5±4.2°C. The principles of microwave energy make it a suitable alternative energy source for ablation, but an ideal microwave antenna catheter must be designed to efficiently radiate the energy into the desired region of myocardium to maximize the volume heating capabilities and thus lesion size.

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**References**


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