Multiple Probe Radiofrequency Ablation: Pilot Study in an Animal Model

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PURPOSE: Radiofrequency ablation (RFA) is becoming increasingly popular for the minimally invasive treatment of benign and malignant tumors. Currently available systems are limited to the use of a single probe because of electrical interactions between probes. The purpose of this study was to test a new prototype multiple probe generator with a built-in switching mechanism to determine if multiple zones of necrosis could be formed simultaneously without a significant penalty in terms of lesion size and procedure time.

MATERIALS AND METHODS: A dual probe generator was created by modifying a commercially available system into an alternating monopolar system with an external electronic switch controlled by a temperature feedback loop. A total of 20 radiofrequency (RF) lesions (conventional single probe, n = 10; switched dual probe, n = 10) were created in the livers of six adult pigs (temperature, 100°C; 10-minute ablation). Lesions were excised and examined for volume, minimum diameter, and maximum diameter.

RESULTS: The time to target temperature was slightly greater for dual (3.5 minutes) versus single ablations (2.7 minutes). However, this resulted in only a 48 second (6.5%) longer total ablation time. There was no significant difference between conventional single and dual lesions for lesion volume (13.6 ± 9.3 cm^3 versus 13.7 ± 7.0 cm^3; P > .05), minimum diameter (1.63 ± 0.56 cm^3 versus 1.61 ± 0.53; P > .05) or maximum diameter (3.3 ± 0.84 versus 3.4 ± 0.55, P > .05).

CONCLUSION: A multiple probe RFA system that can simultaneously ablate multiple areas in the liver is feasible. If multiple probe units become clinically available, large or irregularly shaped lesions could be treated more effectively than with conventional single probe units, and multiple tumors could be ablated simultaneously, thus potentially decreasing procedure time and anesthetic complications.

J Vasc Interv Radiol 2003; 14:1437–1442

Abbreviations: RF = radiofrequency, RFA = radiofrequency ablation

RADIOFREQUENCY ablation (RFA) is a promising, minimally invasive heat-based method used to focally ablate cancer. It is currently used to ablate benign and malignant tumors of the liver, kidney, lung, and bone (1–4). A major advantage of RFA compared to conventional surgery is the ability to apply it percutaneously, laparoscopically, or through small incisions (5–8). This results in rapid recovery in most cases, and a low complication rate. Despite these advantages, radiofrequency (RF) devices have been limited to single probe ablations because of interference between multiple RF probes (Faraday Cage Effect) (9). This has created two main limitations that are clinically significant: (i) the ability to treat only a single lesion at one time, and (ii) the inability to create a precisely controlled, large zone of necrosis.

Unlike cryoablation and microwave ablation (two ablation modalities with the potential to use multiple probes), RF lesions cannot be "tailored" to the geometry of individual tumors by placing more probes in areas where higher heat is necessary, or fewer probes near heat-sensitive structures (10,11). This is particularly problematic when treating asymmetrically shaped tumors, tumors near blood vessels that may protect tumor tissue from heating by acting as "heat sinks," and tumors near vital structures that can not withstand heating (gallbladder, diaphragm, colon, stomach) (12–15). To overcome this limitation, several authors now advocate the use of sequential multiple overlapping ablations to assure adequate treatment of

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This study was funded in part by the National Institutes of Health 5 R01 Dk58839-02.

DOI: 10.1097/01.RVI.0000096771.74047.C8

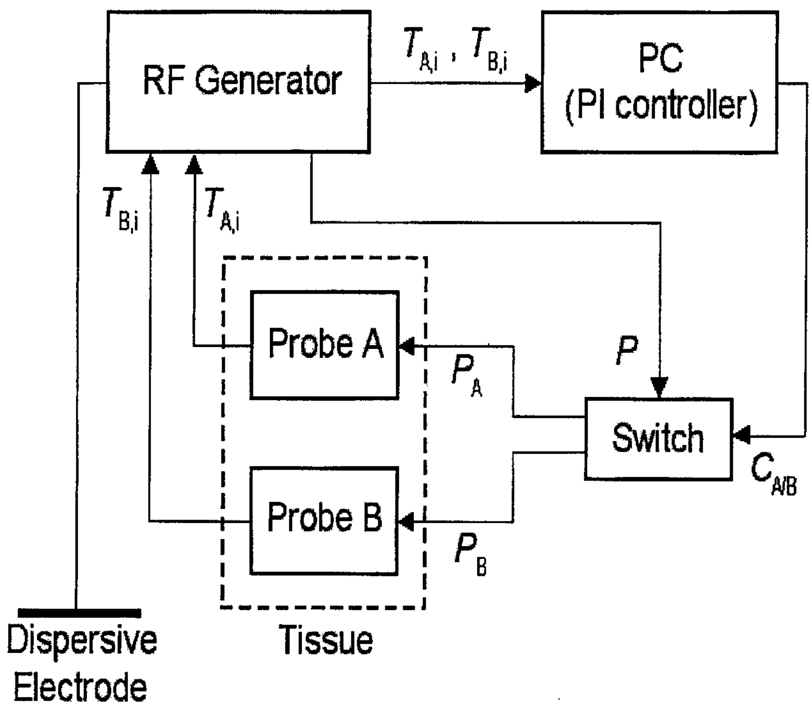

Figure 1. Block diagram of multiple probe RF ablation unit. (T = temperature, P = power, C = control signal from PC to switch). The PC continuously measures probe temperature and commands the switch to preferentially power the coolest probe. Thus, both probes are kept at the preselected target temperature.

tumors greater than 3.0 cm (16). This strategy greatly increases treatment time and may increase procedural and anesthetic risks. Even with multiple ablations, the recurrence rate for lesions greater than 3.0 cm remains much higher than those less than 3.0 cm (17).

Observations in clinical and laboratory experiences during this study have shown that during RFA, high power is needed in most cases only during the initial phase of rapidly increasing temperature. During the remainder of the ablation, the generator only uses a small fraction of available power to maintain temperature. Therefore, this use of power is inefficient in terms of the duty cycle of the RF generator. This study describes a prototype electrical switching circuit that increases generator efficiency by sequentially activating two electrically independent RF probes running off of a single generator. This unit was tested in in vivo porcine liver to determine if multiple lesions can be produced in the same time that a single conventional ablation can be performed. If clinically available, a multiple probe RF device could potentially simultaneously ablate multiple tumors, rapidly form large conglomerate zones of necrosis tailored to individual tumor shape, reduce treatment time, and potentially reduce anesthetic complications associated with RF ablation.

MATERIALS AND METHODS

Development of a Dual Probe RFA Unit

For all experiments described in this manuscript, a RITA model 1500 RF generator and RITA model-90 multiple prong probes extended to 3.0 cm (RITA Medical Systems, Mountain View, CA) were used. Each model-90 probe has five thermocouples placed at the prong tips, which report the tip temperatures to the RF generator. The RF generator allows for monitoring of nine temperatures. For dual probe ablations, we monitored all five tip temperatures of probe A ($T_{A,i}$), and four tip temperatures of probe B ($T_{B,i}$).

This system is based on use of an alternating monopolar (switched) method to heat tissue where power is applied in alternating fashion to two probes (18,19). The probe output from the RF generator is routed to an electromechanical switch capable of switching between probes approximately every 0.5 seconds. The tip temperatures of both probes ($T_{A,i}$, $T_{B,i}$) are reported to the RF generator, which relays the values to a PC. The PC runs a software implemented PI controller, which controls an electronic switch with a D/A-converter (Module DI-220; DataQ Instruments, Akron, OH) connected to the PC's parallel port. The power P is relayed to probes A and B by the electronic switch, so that the average tip temperature of the two probes is kept equal. The signal $C_{A/B}$ determines which probe is activated. At a certain time during ablation, current flows from either probe A or probe B toward the ground pad, but never simultaneously. A schematic diagram of this dual probe system is shown in **Figure 1**.

Animals, Anesthesia, and Surgery

Approval for this protocol was obtained from the institutional animal research committee and all experimentation met the National Institutes of Health Public Health Service Policy on Humane Care and Use of Laboratory Animals. Six female domestic swine were used in this study (mean weight, 23.4 kg; range, 19.7–33.2 kg). The pigs were anesthetized with Tiletamine and Zolazepam 7 mg/kg (Telazol, Fort Dodge Animal Health, Fort Dodge, IA) and Xylazine 0.45 mg/kg intramuscularly (Rompun, Phoenix Pharmaceutical, St. Joseph, MO). Anesthesia was maintained with inhaled Halothane gas (Halocarbon Laboratories, River Edge, NJ), 1% to effect. After application of a 10% povidone-iodine solution, the liver and kidney were exposed through a subcostal incision.

RF Procedure

A total of 20 RF lesions were created for this study. Lesions were created either as a single lesion in a conventional manner (single), or as paired lesions created simultaneously (dual). Lesions were formed by placing the RF probe in pig liver under direct vision. After placement in the liver parenchyma, the prongs of the probe were deployed to 3.0 cm so that all prongs were contained within liver parenchyma. Current was applied to RF probes with the following parameters: 100°C target temperature, 10 minute time at temperature. The time to target temperature was recorded for all ablations.

Pathology and Statistics

Just before euthanasia, animals were anticoagulated with 5,000 units of Heparin (Elkins-Sinn, Cherry Hill, NJ). Animals were then euthanized with intravenous Beuthanasia-D (390 mg Pentobarbital Sodium and 50 mg Phenytoin sodium/100 mL; King Pharmaceuticals, Bristol, TN). The liver was preserved with use of a previously described technique (20). The portal vein was dissected and cannulated, and the hepatic veins lacerated. Formalin (10% neutral buffered, 1.0 liter) was infused through the portal vein and allowed to drain from the hepatic veins. The liver was removed and immersed in formalin for a minimum of 24 hours. After fixation, each lesion was sliced at 3.0 mm intervals. Sections were placed on an optical scanner (Scan Jet 4c/T; Hewlett-Packard, Palo Alto, CA) and images recorded in an electronic data base. Images were measured with use of Image J software (http://rsb.info.nih.gov) and minimum diameter, maximum diameter, and area of the zone of necrosis were recorded for each slice. Volume was computed by integrating the area of each slice across the entire length of the lesion. Measurements were compared with use of unpaired Student t tests. Statistical significance was designated as $P < .05$.

RESULTS

All pigs survived to undergo thermal ablation. The dual probe switch successfully drove the cooler probe so that each probe achieved target temperature at the same time.

Time to Target Temperature

Dual lesions took slightly longer to reach the target temperature of 100°C (3.5 minutes) compared with single lesions (2.7 minutes). This difference was statistically significant ($P = .012$). Although the time to temperature for dual lesions increased 31% compared with single lesions, the length of the entire ablation procedure (time to temperature plus ablation time) was increased for dual lesions by only 48 seconds, or 6.5%.

Lesion Size

No differences could be detected between minimum diameter of the RF lesion (1.63 ± 0.56 cm single versus 1.61 ± 0.53 cm dual, $P = .94$) or maximum diameter (3.3 ± 0.84 cm single versus 3.4 ± 0.55 cm dual; $P = .79$). In addition, no detectable difference between lesion volumes was observed (13.6 ± 9.3 cm (3) single vs. 13.7 ± 7.0 cm^3 dual; $P = .97$).

Lesion Shape.—Lesion shapes were indistinguishable between groups. All lesions were near spherical with some distortion from adjacent large blood vessels (**Fig 2**).

DISCUSSION

Currently available RF generators are limited to the use of a single probe (or several probes which behave electrically like a single large probe) because of electrical field interactions between probes. If multiple electrodes are placed in tissue and activated at the same voltage, current preferentially travels away from the probes, rather than between them because of electric shielding of the probes, similar to the Faraday Cage Effect. Therefore, very little tissue heating takes place between probes activated at the same voltage (19). When multiple probes or prongs are placed in close proximity to each other (such as with the RITA or RadioTherapeutics [LeVeen Needle Electrode, RadioTherapeutics Corporation, Sunnyvale, CA] multiple prong electrodes or the Radionics [Cool-Tip Cluster; Radionics, Burlington, MA], cluster electrode), this is not a major problem because thermal conduction creates lethal temperatures between prongs/probes. However, if the probes are placed farther apart in an attempt to make a larger RF lesion or simultaneously ablate multiple lesions, electrical interactions create an unpredictable shaped lesion with central cool spots (21). If the probes are activated at different voltages (ie, in bipolar mode), current flows between the probes. This results in a high current density and temperatures between probes if they are closely spaced, but little or no heating in other areas. If the probes are remotely spaced, unpredictable lesion shapes result (19).

Our design takes advantage of the fact that the amount of energy required to heat a tumor is greater than that required to maintain tissue at a given temperature. Thus, a large amount of "dead time" between active heating is the norm for modern RF generators. This is an inefficient use of generator power. In theory, more than two probes can be driven by a single generator, up to a certain limit, when the time between probe activations becomes great enough that tissue cooling starts to take place. In this study, there was a small time penalty for driving two probes simultaneously, and this may increase as more probes are brought on line. However, this time penalty is small compared to the time required for accurate probe placement, and even smaller than that required for multiple sequential ablations. As generators become increasingly powerful, the time penalty for sequential RF ablation should decrease. The authors predict that generators with four probes should be feasible in the near future with the current generator design and switching concept described in this study.

The current prototype system described in this study uses a temperature control feedback algorithm (19). This has the advantage of keeping the probes at nearly identical predetermined temperatures, regardless of their thermal environment. However, the authors of this study have already built a prototype multiple probe system based on an impedance feedback algorithm (20). It is also theoretically possible to simply switch between multiple probes with use of a time or power control algorithm.

An issue that has not been extensively discussed in the medical literature is the concept of precise control of large zones of necrosis caused by thermal ablation. Because many of the early generation RF devices were underpowered and could not create even a moderate size zone of necrosis on a consistent basis, tailoring of the zone of ablation to a precise shape was a

a. b. c.

Figure 2. Lesions created in different parts of the liver with use of single or double probes simultaneously. **(a)** Single burn created in conventional mode. **(b,c)** Noncontiguous lesions created simultaneously in dual mode. Each lesion is virtually identical in size to the single burn in **(a)**. Images are shown at same scale.

lower priority than increasing the volume of ablated tissue. However, current RF devices have the capability to create relatively spherical areas of necrosis up to 7.0 cm in diameter with a single ablation. Because most liver tumors of large size are not spherically shaped, or are in close proximity to the gallbladder, major bile duct, large vessel, or liver surface adjacent to a bowel loop, over- or under-treatment may increase complications or local failure rates. This is coupled with the lack of an effective imaging modality to estimate the extent of necrosis during the ablation procedure. The authors believe that the combination of large RF lesions that are not precisely controlled, combined with the limited imaging guidance currently available, will increase the rate of serious complications in the future. Strategies to more precisely control the zone of ablation by precisely shaping the RF lesion to cover the tumor with minimal collateral damage are needed.

The strategy of increased control that the authors have chosen to pursue is that of multiple probes to create a conglomerate zone of necrosis. This is a lesson learned through the use of cryoablation and microwave ablation, two modalities that have the capacity to simultaneously employ multiple probes. Besides the use of multiple probe capacity to create a larger and more precisely shaped zone of necrosis than is possible with single probe ablations, there are thermodynamic advantages to this approach (11,19). More power is delivered to tissue with use of multiple probes because the generator can operate in a more continuous fashion. Multiple probe RF lesions are hotter in the regions between closely placed probes than single probe lesions because of both the increased power deposition, and the thermal shielding effect of probes from vascular mediated cooling (11,21,22). Single probe devices with a single central zone of heating are limited by a precipitous drop in current density away from the energy source ($1/r^4$) that makes the periphery of the RF lesion particularly prone to vascular cooling. With multiple probe capability, areas of the tumor that are in close proximity to major blood vessels could be treated with more tightly clustered probes, and those nearer to thermally sensitive structures (gallbladder, bowel, bile ducts) could be treated with less. Likewise, a tumor that is irregularly shaped could be treated as effectively as a round tumor by placing probes in areas where tumor is present, rather than simply making a large round lesion with a single centrally-placed probe.

In this study, there were no ground pad burns, but it is possible that patients could be at higher risk for burns with multiple probe systems. The same amount of current is delivered to the ground pads by multiple probe systems versus single probe systems at any time since only one probe is active at a time. However, the more continuous deposition of power into the subject (particularly with three or four probe systems) may increase ground pad temperature because of the lack of interval cooling. Therefore, increased number of ground pads or ground pad cooling may be needed, not to disperse electrical current, but to increase pad surface area and increase cooling capacity.

Currently, when ultrasound is used for imaging guidance, and a large tumor is treated with multiple sequential RF applications, a large amount of gas is created that degrades the ultrasound image. With an increasing number of applications it becomes highly complex to determine the spatial relationship between the multiple RF thermal lesions, RF probes, and residual tumor. In contrast, the use of multiple RF probes activated simultaneously drastically simplifies this problem because the probes are all placed before the creation of the thermal lesion. This simplified treatment planning and monitoring may further reduce treatment time, and may also lead to lower local recurrence rates.

An important limitation to this feasibility study is that it was performed in normal pig liver, and not in human tumors. It is possible that this system would create different results in tumor tissue. Unfortunately an implantable, reproducible, and reasonably inexpensive large animal tumor model is not currently available, and thus this system will ultimately need to be tested in a human clinical trial.

The ability to ablate several tumors simultaneously or a large tumor with a single application of multiple probes would substantially decrease treatment time in many cases. This should help decrease anesthetic related morbidity, and speed postprocedure recovery. At the authors' institution, RF ablation is performed with both CT and ultrasound guidance and general anesthesia because of the painful nature of the procedure. The impact of this extensive use of resources could be lessened with shorter procedure times.

Acknowledgments: The authors thank Carrie E. Poole for assistance in manuscript preparation.

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