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Multiple-Electrode RF Ablation Creates Confluent Areas of Necrosis: Results in *in vivo* Porcine Liver

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Abstract

PURPOSE—To prospectively evaluate an impedance-based multiple-electrode RF ablation system for creation of confluent areas of hepatic coagulation in an *in vivo* porcine model.

MATERIALS & METHODS—Pre-approval was obtained from our institutional research animal care and use committee. A prototype multiple-electrode RF system was created allowing switching between three electrically-independent electrodes at impedance spikes (30 Ω increase). Forty-two coagulation zones [single=18, cluster=12, multiple-electrode (three singles spaced 2 cm apart)=12] were created at laparotomy in fifteen ~90 kg female pigs. Half of the ablations were performed for 12 minutes and half for 16 minutes. Coagulation zones were excised and sliced (~3 mm) for measurements. ANOVA and two sample t-tests (Bonferroni's correction, $\alpha=.0033$) were used to test for differences between groups.

RESULTS—At 12 minutes, mean ($\pm$ SD) multiple-electrode coagulation was significantly larger than single (minimum diameter: 2.8 ± 0.6 vs. 1.6 ± 0.6 cm; maximum diameter: 4.2 ± 0.7 vs. 2.0 ± 0.5 cm; volume: 22.1 ± 10.7 vs. 6.7 ± 3.7 cm³; $P<.0033$, all comparisons). Multiple-electrode maximum diameter was significantly larger than cluster at 12 minutes (4.2 ± 0.7 vs. 2.9 ± 0.3 cm, $P=.02$). At 16 minutes, multiple-electrode coagulation zones (minimum diameter: 3.2 ± 0.6 cm; maximum diameter: 4.2 ± 0.6 cm; volume: 29.1 ± 8.3 cm³) were significantly greater than single (minimum diameter: 1.7 ± 0.5 cm; maximum diameter: 2.2 ± 0.6 cm; volume: 7.1 ± 3.5 cm³; $P<.0033$, all comparisons) and cluster controls (minimum diameter: 2.3 ± 0.3 cm, $P=.007$; maximum diameter: 3.2 ± 0.4 cm, $P=.005$; volume: 13.1 ± 3.0 cm³, $P<.0033$).

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Advances in knowledge:

1. *In vivo* preclinical experience with impedance-based multiple-electrode RF ablation
2. *In vivo* demonstration of thermal synergy and creation of large, conglomerate areas of hepatic coagulation with multiple-electrode RF ablation
3. Effect of inter-electrode spacing and ablation time on resulting zone of coagulation

CONCLUSION—An impedance-based multiple-electrode RF ablation system was able to create significantly larger zones of coagulation in a porcine liver model compared with single and cluster controls.

INTRODUCTION

Radiofrequency (RF) ablation has been used successfully in the treatment of tumors of the liver, lung, bone, breast, and kidney (1-4). Successful tumor ablation is predicated upon complete eradication of the target tumor as well as an ablative margin, similar in concept to operative removal of a tumor plus a surgical margin of approximately 1 cm (5, 6). To date, RF ablation has been shown to be highly effective in achieving complete coagulation in tumors less than 3.0 cm in diameter (7). However, treatment of larger tumors has been more problematic, with malignancies greater than 4.0 cm in diameter associated with high rates of local tumor progression (8-10).

Several factors have contributed to the inability to consistently achieve complete destruction of large tumors plus an adequate ablative margin. Most important is the fact that current monopolar RF ablation systems do not support the simultaneous use of multiple electrodes due to electrical interactions when electrodes are closely-spaced (11-13). Therefore, sequential, overlapping ablations are needed to treat all but the smallest tumors (14). Producing a conglomerate zone of coagulation by overlapping multiple sequential ablations is a complex and time-consuming procedure. Microbubbles created by boiling tissue, bleeding, and edema all contribute to difficult visualization of both the tumor and the zone of ablation with either CT or ultrasound guidance (15, 16). Furthermore, prolonged treatment times may increase the overall cost as well as anesthesia complications associated with the procedure (17, 18).

Haemmerich et al. previously showed *ex vivo* that rapidly switching between multiple closely spaced electrodes can create large zones of coagulation (13). The system was designed to take advantage of the thermal synergy inherent in placing multiple independent electrodes in close proximity to one another (19). While encouraging, these experiments were limited in two ways: 1) the use of an *ex vivo* model and 2) switching on a fixed time interval. An *ex vivo* model lacks perfusion, a clinically important factor in electrode performance, while switching on a fixed time interval does not account for biological changes occurring during the ablation and is not time-efficient. Thus, the purpose of our study was to prospectively evaluate an impedance-based multiple-electrode RF ablation system for creation of confluent areas of hepatic coagulation in an *in vivo* porcine model.

MATERIALS AND METHODS

Financial support and the prototype multiple-electrode RF ablation system used for this project were provided by Valleylab (Boulder, CO). Authors who are not consultants for Valleylab had control of inclusion of data and information that might present a conflict of interest for authors who are consultants.

Animals, anesthesia and procedures

Fifteen large female domestic swine (mean weight ~ 90 kg) were used for our study. Pre-approval was obtained from the research animal care and use committee of our institution, and all husbandry and experimental studies were compliant with the NIH Guide for Care and Use of Laboratory Animals (<http://oacu.od.nih.gov/regs/guide/guidex.htm>). Anesthetic induction was achieved with intramuscular tiletamine hydrochloride and zolazepam hydrochloride (Telazol; Fort Dodge, IA), atropine (Phoenix Pharmaceutical, St. Joseph, MO), and xylazine hydrochloride (Xyla-Ject; Phoenix Pharmaceutical, St. Joseph, MO). Animals were intubated and anesthesia was maintained with inhaled isoflurane (Halocarbon Laboratories, River Edge, NJ) to effect. The liver was surgically exposed using a chevron incision. RF ablations were performed using various electrode types as described in *Experimental groups*.

Pigs have four relatively flat liver lobes (left lateral, left medial, right medial, and right lateral), and a maximum of one ablation was performed per lobe varying the ablation order in each liver. In an effort to avoid bigger ablations being limited by lobe size, multiple-electrode and cluster ablations were performed in the larger, more vascular medial lobes of the liver (alternating these groups between the two lobes). Single ablations were performed in one of the smaller lateral lobes of the liver. Several of the livers were large enough to place single-electrode ablations in both of the lateral lobes, thereby allowing higher sample numbers for this group.

After all ablations were performed, animals were euthanized with an intravenous overdose of pentobarbital sodium and phenytoin sodium (Beuthanasia-D, Schering-Plough, Kenilworth, NJ), and the livers were removed *en bloc*. All animals survived until sacrifice. No apparent complications from any of the RF procedures in any group were encountered. The multiple-electrode device functioned without unexpected events or complications.

Experimental groups

Forty two zones of coagulation were created during our study. Groups 1 and 2 consisted of ablations performed with a commercially available single-applicator RF ablation system (Cool Tip™ RF System; Valleylab, Boulder, CO) that employs either one single RF electrode or one multiple-prong cluster RF electrode. Ablations in group 1 (n=18) were performed with the single electrode, while group 2 (n=12) consisted of ablations performed with the cluster electrode. Group 3 (n=12) consisted of ablations performed with a prototype multiple-electrode RF device. A clinical device based on this prototype has just become commercially available (Cool-tip™ Switching Controller; Valleylab, Boulder, CO).

Radiofrequency ablation - controls (Groups 1, 2)

All control RF procedures described in our study were performed by one author (PFL, 2 years experience pre-clinical RF ablation) with the single-applicator Cool-tip™ RF system (Valleylab, Boulder, CO). The RF generator is a 480-kHz monopolar radiofrequency generator that operates at a maximum of 200 W (2.0 A at 50 Ω). The generator employs an impedance feedback loop to maximize energy delivery by minimizing charring. A peristaltic pump (Model PE-PM; Valleylab, Boulder, CO) circulates chilled sterile water

(approximately 18-20 °C at the electrode tips) through the electrodes. Single RF electrodes are 17-gauge (1.5 mm) in diameter, and the shaft is insulated with the exception of a 3.0 cm exposed tip. Cluster electrodes consist of three single electrodes in a triangular configuration fixed at 5.0 mm of separation. Each of the electrodes in the cluster configuration is identical to a single electrode with the exception of a 2.5 cm exposed tip.

Group 1 (single electrode controls) and Group 2 (cluster electrode controls) zones of coagulation were created at both 12 and 16 minutes. Twelve minutes is the accepted clinical standard for single-electrode liver ablation using the Cool-tip™ system, and longer ablation times are not associated with larger volumes of coagulation (20). A second longer time point (16 min) was chosen because of the uncertainty as to whether longer multiple-electrode ablations could create larger zones of coagulation.

Radiofrequency ablation - multiple-electrode (Group 3)

All multiple-electrode RF ablations described in our study were performed by one author (PFL, 2 years experience pre-clinical RF ablation) using a prototype system based on switching between three electrodes (21). In this system, the RF generator output was delivered to the electrodes through a PC-controlled electronic switch (Figure 1). Three single RF electrodes (3 cm active tip, each electrode identical to the single control group) were placed in an equilateral triangle 2.0 cm apart using a template to ensure parallel placement. The inter-electrode spacing of 2.0 cm was optimized in preliminary pilot experiments, in which spacings of 2.5 cm and greater resulted in clefted, non-conglomerate zones of coagulation. The impedance at each electrode was relayed to a PC which controlled the electronic switch. Power was switched from one electrode to the next when the impedance reached 30 Ω above baseline (Figure 2). If the amount of time an electrode was off fell below 5 seconds (due to high impedance levels at all three electrodes), power was diverted to a 150 Ω resistive load for the remainder of the 5 seconds to allow the impedance of the tissue to decrease. As was the case for the control groups, half of the multiple-electrode ablations were performed by applying power for 12 minutes, and half were performed by applying power for 16 minutes.

Zone of coagulation volume and diameter determination

One author (PFL) performed the measurements and analysis on the zones of coagulation. Lengths were measured using calipers and were then sliced axially at 3-4 mm intervals. Liver slices were placed directly onto an optical scanner (Perfection 2450 Photo Model G860A; Epson, Long Beach, CA), and saved as electronic images. Coagulation size was analyzed using the freeware ImageJ (National Institute of Mental Health, Bethesda, MD). Measurements were taken on the central, white zone of complete coagulation, not the surrounding red zone shown to contain viable cells (22-25). Volumes of coagulation were calculated using the formula for the volume of an ellipsoid: $\frac{4}{3}\pi abc$, where a , b , and c are the length axis radius, width axis radius, and height axis radius. Length, minimum diameter, and maximum diameter were used for these values in our study.

Shape of zone of coagulation

The shape of the zone of coagulation was estimated by one author (PFL) by calculating the mean isoperimetric ratio (IR) for each group using a representative slice (the same slice used to measure minimum and maximum diameter). This ratio provides an estimation of “roundness” in two dimensions (24, 26). The closer the value is to 1.0, the more round the zone of coagulation. This value was computed using the equation

$$IR = \frac{4\pi \times Area}{Perimeter^2} \quad (1)$$

with the area and perimeter being measured on the same slice that the minimum and maximum diameters were measured.

Statistical analysis

Single RF, cluster RF, and multiple-electrode RF were compared with respect to zone of coagulation size and shape. ANOVA was used to test for overall differences in isoperimetric ratio and mean minimum diameter, maximum diameter, length, and volume of coagulation across the different ablation techniques. Two sample t-tests were performed to do pairwise comparisons between groups for each dimension, and to check for differences within groups between 12 and 16 minutes. Bonferroni's correction was used because of the large number of tests being performed ($5 \times 3 = 15$). Therefore, statistical significance (using a standard cutoff of $P < .05$) was based on $\alpha = 0.05/15 = 0.0033$. P -values between .05 and .0033 were considered to be suggestive of statistical significance.

RESULTS

Comparison of extent of coagulation (Tables 1 and 2, Figures 3-6)

Multiple-electrode RF created zones of coagulation with significantly larger mean diameters and volumes than single RF at both 12 and 16 min (ANOVA, pairwise t-tests, $P < .0033$). Multiple-electrode RF mean minimum diameter, maximum diameter, and volume were significantly larger than cluster at 16 min, but only maximum diameter was significantly larger at 12 min (ANOVA and pairwise t-tests; $P = .02$ for maximum diameter at 12 min, $P = .007$ for minimum diameter at 16 min, $P = .005$ for maximum diameter at 16 min, $P < .0033$ for volume at 16 min). No significant differences in size of induced coagulation were seen within groups between 12 and 16 minutes except for an increase in length in the multiple-electrode group (3.4 ± 0.5 cm vs. 4.1 ± 0.2 cm, $P = .015$).

Shape of zone of necrosis (Tables 1 and 2, Figures 7 and 8)

The IR of the multiple-electrode group was lower than the control groups partly because the three electrodes were placed in a triangular configuration. These differences were not significant at 12 minutes. However, multiple-electrode IR was significantly smaller at 16 minutes compared to both cluster and single ($P < .0033$, both comparisons). This is due in part to an increase in IR for both single and cluster going from 12 to 16 minutes ($P = .017$ and .039, respectively).

DISCUSSION

To date, RF ablation has been limited by an inability to induce coagulation large enough to consistently envelope the targeted tumor plus a 1.0 cm ablative margin. To treat a spherical tumor greater than 1.0 cm in size, a zone of coagulation with a minimum diameter of greater than 3.0 cm is necessary. Reports of induced coagulation much larger than 3.0 cm have been published, primarily using multiple-prong electrodes combined with saline infusion (27). However, many reports of large zones of coagulation do not indicate the minimum diameter or shape, both of which are limiting factors when determining the effectiveness of a particular ablation. Furthermore, high local recurrence rates for large tumors (particularly when treating hepatic colorectal metastases) suggest that the current time-consuming strategy of consecutive overlapping ablations with single electrodes is not optimal. Therefore, more effective means of achieving large volumes of coagulation are needed. In our study, the multiple-electrode system created volumes of coagulation 74 (22.1 cm³ / 12.7 cm³) and 122 (29.1 cm³ / 13.1 cm³) percent greater than a cluster electrode at 12 and 16 minutes, respectively. Multiple-electrode ablation volumes (3.3× and 4.1× that of a single electrode at 12 and 16 minutes, respectively) also surpassed the predicted volume increase (3×) when using three single electrodes simultaneously, *in one-third of the time*. These disproportionate volume increases infer that thermal synergy was achieved. To our knowledge, our study is the first to demonstrate the ability of a multiple-electrode RF system to achieve thermal synergy in an *in vivo* environment.

Thermal synergy is a phenomenon unique to multiple-applicator ablation systems. This effect has been demonstrated for both microwave ablation and cryoablation, where three simultaneously activated applicators create a conglomerate zone of coagulation with a volume greater than three times the volume of a single-applicator ablation (19, 28). We believe that thermal synergy in multiple-electrode RF ablation has several mechanisms. First, the application of RF energy results in progressive vascular thrombosis and devascularization of hepatic parenchyma. Therefore, activation of the first electrode helps decrease the perfusion-mediated cooling at the remaining two electrodes. Activation of the second electrode decreases perfusion-mediated cooling at the other two electrodes and so forth. This results in the rapid development of a large conglomerate zone of coagulation (24, 29). Second, higher temperatures between simultaneously heated electrodes are achieved and maintained compared to sequential ablation because tissue heating occurs much faster than tissue cooling (13). Finally, the thermal boundary conditions are altered such that less energy is required to heat the periphery of each ablation zone because it is heated above 37 °C as the adjacent zone of ablation is created.

Development of multiple-electrode RF systems has been hindered by electrical interactions that occur between simultaneously activated, closely-spaced electrodes (11, 13). Electric current flows between areas of high voltage (i.e. the electrode) and areas of low voltage (i.e. ground pad). When multiple electrodes from the same power source are placed in close proximity, little current flows between the electrodes because they are at the same voltage (12). This fundamentally limits the distance at which the electrodes can be separated due to cool spots in the center of the ablation, an observation made by Goldberg et al during development of the cluster electrode (30). Commercially available multiple-prong devices

are limited by low current flow between prongs. Attempting to increase ablation zone size by deploying the prongs further apart would increase the irregularity of shape of induced coagulation, already a problem for these electrodes (31). The multiple-electrode device presented in our study allows for the use of three electrically independent electrodes and obviates electrical interactions between them by only powering one electrode at a time. Therefore, the electrodes generate heat in all directions and can be placed further apart than with commercially available RF systems (13). In effect, the system simultaneously creates multiple overlapping ablations without the need for consecutive repositioning of a single electrode, which can be complicated by microbubbles, edema, and hemorrhage from earlier ablations.

The system is based on switching at each impedance spike ($>30\ \Omega$ above baseline) because sharp rises in impedance are associated with tissue coagulation and vascular thrombosis, both desirable endpoints for creating a conglomerate zone of coagulation (32, 33). Instead of temporarily switching the system off when an impedance spike is encountered, the generator powers a second electrode to an impedance spike, and then a third, etc. Switching at a fixed time interval is less efficient than an impedance-controlled algorithm. For example, switching at times less than that required for creation of impedance spikes may lead to inadequate vascular thrombosis, allowing intact perfusion to cool tissue close to this electrode while other electrodes are activated. This tissue would have to be reheated during the next cycle of power application. Longer time intervals may be more effective in creating vascular thrombosis. However, only minimal power can be deposited after the impedance has spiked, thus increasing the time during which no electrodes are delivering power.

An electrode spacing of 2.0 cm was chosen to maximize the extent of induced coagulation without compromising its shape. Pilot experience demonstrated that spacings of 2.5 cm and greater resulted in clefting at the periphery of the zone of coagulation. These greater spacings may increase the overall volume of coagulation, but the risk of creating irregular zones of coagulation is increased. To increase electrode spacing and still create a conglomerate zone of coagulation, power deposition would need to be increased either by using a high-power RF generator or lowering impedance. These modifications are being actively pursued by our team and others, but are beyond the scope of our study. Finally, our intention in this non-tumor model was to create spherical zones of coagulation. Ultimately, the best shape may not be exactly spherical and will likely need to be tailored on a case-by-case basis. For instance, electrode placement may be skewed to one side to minimize the heat sink effect of a vessel. Clinically, it is anticipated that electrodes could be placed to conform to the shape of the tumor.

Our study has limitations. The first is that all of the RF ablations were performed in highly vascular normal porcine liver. A large animal tumor model would serve as a better model, but we are unaware of any such models with large enough tumors/organs for the volume of tissue ablated in our study. Also, the right and left medial lobes of pig livers are the largest of the four lobes and the associated hepatic and portal veins are very large. For the purposes of our study, multiple-electrode ablations were performed in these medial lobes due to the large size of the resulting coagulation that would overwhelm the lateral lobes. Consequently, the multiple-electrode zones of coagulation were potentially smaller than if we had been

able to distribute them more evenly throughout the liver. Therefore, our study is potentially conservative in its claims, as larger zones of coagulation would be expected in less vascular human tumors.

The open surgical model used for our study was designed to maximize the number of ablations per animal and ultimately decrease the number of animals sacrificed. However, further investigation using the multiple-electrode system in a percutaneous environment is needed. In particular, it may be more difficult to place the electrodes in a percutaneous setting, especially when using an intercostal approach. While our results indicate that optimal performance is achieved when the electrodes are spaced 2 cm, they do not have to be placed exactly parallel and more than one intercostal space may be used.

Practical Application

Our study demonstrates the ability of a switched multiple-electrode RF device to achieve thermal synergy and create large areas of coagulation in *in vivo* porcine liver. Further studies using techniques to increase power deposition into tissue may produce even larger zones of coagulation. Large-volume ablation with multiple-electrode systems may increase the effectiveness of RF ablation in treating larger tumors by allowing for more consistent destruction of the entire tumor and a surrounding margin.

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Figure 1.

Schematic diagram of multiple-electrode RF system. The impedances of electrodes 1-3 (Z_1 - Z_3) are reported to the RF generator, which relays the values to a PC. The power P is relayed to electrodes 1-3 and the load (a $150\ \Omega$ resistive load) via the electronic switch. The signal C_{1-4} determines which electrode (or the load) the power is relayed to. If the system cycles too rapidly or the impedance values on electrodes 1-3 are too high, the power is diverted to the load for a predetermined amount of time.

Figure 2.

Block diagram of the impedance switching algorithm. The algorithm consisted of activating each electrode sequentially until its impedance level reached $30\ \Omega$ above its baseline level or a maximum time ($t_{\max}$) interval was reached. A minimum time interval of 5 s was set for the amount of time that each electrode must be off. If the system cycled too rapidly, the power was diverted to the load, a $150\ \Omega$ resistor, for the remainder of the 5 s interval. Note: Z_i = the rise in impedance above that electrode's baseline level, t_i = amount of time an electrode has been off.

Figure 3.

Graph depicts mean ($\pm$ SD) minimum diameters for the three groups. Differences between single/multiple-electrode were significant at the usual uncorrected (.05) and corrected (.0033) cutoff at both time points. Single/cluster and cluster/multiple-electrode differences were significant at the uncorrected cutoff at 16 minutes.

Figure 4.

Graph depicts mean maximum diameter ($\pm$ SD) for each of the three groups. Differences were significant at the uncorrected (.05) and corrected cutoff (.0033) for single/multiple-electrode at 12 and 16 minutes and single/cluster at 12 minutes. Using the conservative, uncorrected cutoff (.05) differences in maximum diameter were significant between all three groups at both time points. No significant differences were seen between 12 and 16 minutes within groups.

Figure 5.

Length of induced coagulation - the difference in mean length was significant between cluster and multiple-electrode at 16 minutes ($P = .006$). Furthermore, the multiple-electrode zones of coagulation were significantly longer at 16 minutes versus 12 minutes ($P = .015$). Note that some variation in length is expected given that the active electrodes in the single- and multiple-electrode groups were 3 cm long while the cluster electrodes were 2.5 cm. Error bars correspond to standard deviations.

Figure 6.

Differences in volume were significant at both cutoffs (.05 and .0033) between multiple-electrode and single at both time points and between multiple-electrode and cluster at 16 min. The difference in mean volume of coagulation between cluster and single was only significant at 16 minutes using the conservative uncorrected cutoff. Differences across time points within groups were not significant. Error bars correspond to standard deviations.

Figure 7.

Mean zone of coagulation isoperimetric ratio for the multiple-electrode group was significantly smaller at 16 min compared to both cluster ($P = .0003$) and single ($P < .0001$). This is due in part to a significant increase in isoperimetric ratio for both single and cluster when ablation time increases from 12 to 16 min ($P = .017$ and $.039$, respectively).

Figure 8.

Figure 8a: Characteristic zone of coagulation created with a single RF electrode that measured 2.0 cm in minimum diameter and 2.1 cm in maximum diameter.

Figure 8b: Example of coagulation induced using a cluster RF electrode that measured 2.8 cm in minimum diameter and 3.6 cm in maximum diameter.

Figure 8c: Representative multiple-electrode RF zone of coagulation that measured 4.0 cm in minimum diameter and 4.7 cm in maximum diameter. The three electrodes were placed in an equilateral triangle configuration spaced 2.0 cm apart using a template to ensure proper inter-electrode spacing at the tips of the electrodes.

Table 1

RF-induced coagulation dimensions and volume at 12 min

<i>Group</i>	<i>n</i>	<i>Minimum Diameter (cm)</i>	<i>Maximum Diameter (cm)</i>	<i>Length (cm)</i>	<i>Volume (cm³)</i>	<i>Isoperimetric Ratio</i>
Single	9	1.6 ± 0.6 ^a	2.0 ± 0.5 ^{b,c}	3.6 ± 0.3	6.7 ± 3.7 ^{e,f}	0.78 ± 0.15
Cluster	6	2.1 ± 0.5	2.9 ± 0.3 ^d	3.8 ± 0.2	12.7 ± 5.2	0.77 ± 0.11
Multiple-electrode	6	2.8 ± 0.6	4.2 ± 0.7	3.4 ± 0.5	22.1 ± 10.7	0.71 ± 0.22
ANOVA <i>P</i> -value	-	.006	< .0001	.20	.002	.75

Values are given as mean ± SD

^a *P* = .003 vs. multiple-electrode

^b *P* = .001 vs. cluster

^c *P* < .0001 vs. multiple-electrode

^d *P* = .02 vs. multiple-electrode

^e *P* = .021 vs. cluster

^f *P* = .001 vs. multiple-electrode

Table 2

RF-induced coagulation dimensions and volume at 16 min

Group	n	Minimum Diameter (cm)	Maximum Diameter (cm)	Length (cm)	Volume (cm ³)	Isoperimetric Ratio
Single	9	1.7 ± 0.5 ^{a,b}	2.2 ± 0.6 ^d	3.6 ± 0.8	7.1 ± 3.5 ^{e,h}	0.92 ± 0.05 ^e
Cluster	6	2.3 ± 0.3 ^c	3.2 ± 0.4 ^f	3.4 ± 0.4 ^g	13.1 ± 3.0 ⁱ	0.88 ± 0.04 ^j
Multiple probe	6	3.2 ± 0.6	4.2 ± 0.6	4.1 ± 0.2	29.1 ± 8.3	0.66 ± 0.09
ANOVA P-value	-	< .0001	< .0001	.16	< .0001	< .0001

Values are given as mean ± SD

^a *P* = .036 vs. cluster^b *P* = .0001 vs. multiple-electrode^c *P* = .007 vs. multiple-electrode^d *P* = .004 vs. cluster^e *P* < .0001 vs. multiple-electrode^f *P* = .005 vs. multiple-electrode^g *P* = .006 vs. multiple-electrode^h *P* = .004 vs. clusterⁱ *P* = .001 vs. multiple-electrode^j *P* = .0003 vs. multiple-electrode