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Abstract

The present study was performed to clarify the effect of hypertonic saline infusion into the lung parenchyma on radiofrequency ablation (RFA) of the lungs. A total of 20 ablation zones were created in 3 pigs. The ablation zones were divided into 3 groups. Group 1 (n6) consisted of ablation zones created by applying smaller radiofrequency (RF) power without saline infusion;group 2 (n5) zones were created by applying greater RF power without saline infusion;and group 3 (n9) zones were created by applying greater RF power with saline infusion. The techniques of saline infusion included administration of hypertonic saline 1ml before RFA, followed by continuous administration at a rate of 1ml/min during the first 2min after the initiation of RFA. The ablation parameters and coagulation necrosis volumes were compared among the groups. Group 3 had a tendency toward smaller mean impedance than group 1 (p0.059) and group 2 (p0.053). Group 3 showed significantly longer RF application time than group 2 (p0.004) and significantly greater maximum RF power than group 1 (p0.001) and group 2 (p0.004). Group 3 showed significantly larger coagulation necrosis volume (mean, 1,421mm3) than group 2 (mean, 858mm3, p0.039) and had a tendency toward larger necrosis volume than group 1 (mean, 878mm3, p0.077). Although this small study had limited statistical power, hypertonic saline infusion during RFA appeared to enlarge coagulation necrosis of the lung parenchyma.

KEYWORDS: radiofrequency ablation, lung, experimental study

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Original Article

Infusion of Hypertonic Saline into the Lung Parenchyma during Radiofrequency Ablation of the Lungs with Multitined Expandable Electrodes: Results Using a Porcine Model

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The present study was performed to clarify the effect of hypertonic saline infusion into the lung parenchyma on radiofrequency ablation (RFA) of the lungs. A total of 20 ablation zones were created in 3 pigs. The ablation zones were divided into 3 groups. Group 1 (n = 6) consisted of ablation zones created by applying smaller radiofrequency (RF) power without saline infusion; group 2 (n = 5) zones were created by applying greater RF power without saline infusion; and group 3 (n = 9) zones were created by applying greater RF power with saline infusion. The techniques of saline infusion included administration of hypertonic saline 1 ml before RFA, followed by continuous administration at a rate of 1 ml/min during the first 2 min after the initiation of RFA. The ablation parameters and coagulation necrosis volumes were compared among the groups. Group 3 had a tendency toward smaller mean impedance than group 1 ($p = 0.059$) and group 2 ($p = 0.053$). Group 3 showed significantly longer RF application time than group 2 ($p = 0.004$) and significantly greater maximum RF power than group 1 ($p = 0.001$) and group 2 ($p = 0.004$). Group 3 showed significantly larger coagulation necrosis volume (mean, 1,421 mm^3) than group 2 (mean, 858 mm^3, $p = 0.039$) and had a tendency toward larger necrosis volume than group 1 (mean, 878 mm^3, $p = 0.077$). Although this small study had limited statistical power, hypertonic saline infusion during RFA appeared to enlarge coagulation necrosis of the lung parenchyma.

Key words: radiofrequency ablation, lung, experimental study

Primary lung cancer is one of the most common malignancies in the world [1], and surgical resection offers the best opportunity for its cure. The lung is one of the most common organs to which metastatic deposits may adhere. Many surgeons believe that surgery offers the best potential for long-term survival in patients with a relatively small number of pulmonary metastases. However, some patients with primary or metastatic lung cancer are not candidates for surgery because of cardiopulmonary dysfunction, poor performance status, or advanced disease, and some refuse to undergo surgery. Thus, many studies have focused on less invasive therapies for lung cancer.

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Radiofrequency ablation (RFA) has been investigated as a less invasive local therapy for tumors mainly in the liver and the kidney [2, 3]. The favorable outcomes in those organs have encouraged the application of this therapy to lung tumors. Unlike other solid organs, however, the lungs possess unique tissue characteristics that considerably affect the outcome of RFA. Alveolar air may severely limit both the electrical and thermal conduction, thereby hindering the creation of an adequate ablative margin in the peritumoral lung parenchyma. Therefore, the microscopic extension of cancer cells to the marginal parenchyma may remain untreated, leading to subsequent local progression. Thus, attempts to minimize the alveolar air may be warranted. Balloon occlusion of the bronchus successfully facilitated the ablation of the lung parenchyma in an animal experiment [4]. However, this method does not seem practical in a clinical setting, partly because it requires general anesthesia. In the liver, saline infusion during RFA has been shown to enlarge the area of coagulation necrosis [5, 6]. If this technique was applied to the lung, the alveolar air could be replaced by saline. Given that saline possesses more electric and thermal conductivity than air, saline infusion may facilitate the ablation of the lung parenchyma. Therefore, the purpose of this study was to clarify the effect of hypertonic saline infusion into the lung parenchyma on RFA of the lungs.

Materials and Methods

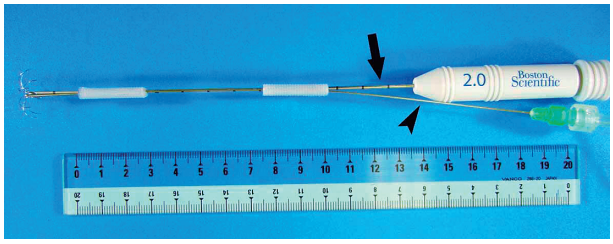
This animal study was approved by our institutional animal care committee in accordance with the National Institutes of Health guidelines for the use of laboratory animals. The experiment was performed at the Miyazaki Technology and Education Center of Boston Scientific Japan Inc. (Miyazaki, Japan).

Animals. The experiment was performed on 3 domestic female swine (mean weight, 83.0 kg; range 83.0–85.0 kg). The animals were tranquilized with an intramuscular injection of atropine 1.5 mg and intravenous injection of xylazine 420 mg and ketamine 450 mg, intubated, and ventilated with mechanical ventilation. Inhalation anesthesia was maintained with 1.3% halothane in 50% oxygen and 50% nitrous oxide. The animals were fixed on a table in the supine position, and 2 steel mesh grounding pads were placed on their shaved hips. Cardiac and respiratory parameters such as blood pressure, heart rate, and blood oxygen saturation were monitored continuously.

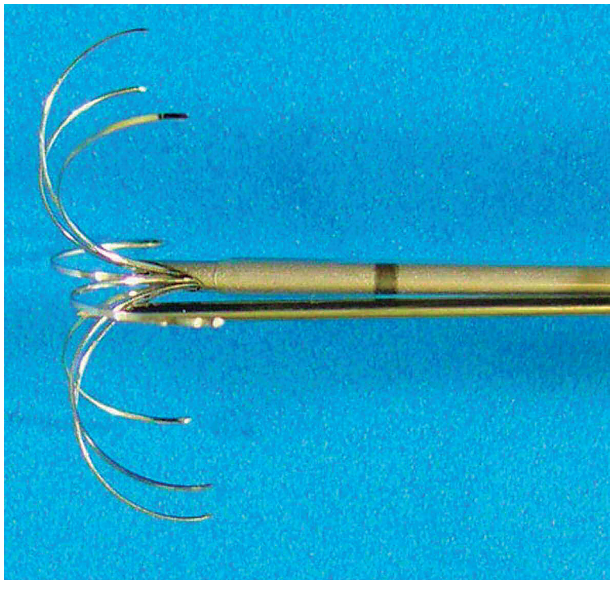
Techniques of RFA and saline infusion. The RFA system comprised a 17-gauge multitined expandable electrode (LeVeen; Boston Scientific, Natick, MA, USA) with arrays 2 cm in diameter and a generator (RF 3000; Boston Scientific). RFA was performed with direct visualization with bilateral thoracotomy. The electrode was inserted into the lung to a depth of 1–1.5 cm; the tines were then completely expanded. According to the manufacture's recommendations, radiofrequency (RF) energy was increased in incremental steps until a notable increase in impedance (so-called "roll-off"). The impedance and RF power were recorded at 15-sec intervals throughout the RF energy application.

RFA was performed with 3 different ablation techniques. First, RFA was performed without saline infusion with the initial RF energy set at 10 W and subsequently increased by 5 W/sec (group 1). Second, it was performed without saline infusion with the initial RF energy set at 30 W and subsequently increased by 10 W/sec (group 2). Third, it was performed during saline infusion with the initial RF power set at 30 W and subsequently increased by 10 W/sec. A total of 20 ablation zones were created in the 3 pigs. Groups 1, 2, and 3 comprised 6, 5, and 9 ablation zones, respectively.

The techniques of saline infusion were as follows. A 21-gauge needle (PEIT needle; Hakko, Tokyo, Japan) was used for infusion of saline. The tips of the needle and the RFA electrode, which fit together, were arranged in tandem and fixed together with plastic tape (Fig. 1A, B). To eliminate the possible bias introduced by the effect of the needle on RFA, the needle was inserted along with the electrode even in the case of RFA without saline infusion (group 1 and 2). The saline used was hypertonic saline solution (Otsuka sodium chloride injection 10%; Otsuka Pharmaceutical, Tokyo, Japan), which was heated to 40°C beforehand. Before RF energy application, 1 ml of the solution was administered gradually into the lung parenchyma through the needle. Immediately thereafter, RF energy application was initiated. Infusion of the solution was performed continuously with a syringe pump (TE-331; Terumo, Tokyo, Japan) at a rate of 1 ml/min during the first 2 min after



A



B

Fig. 1 Overview of the electrode (arrow) used for radiofrequency ablation and the needle (arrowhead) used for saline injection (A), along with a close-up of the tips (B). The electrode and the needle are lined in tandem as those tips fit and fixed together with plastic tape.

the initiation of RF energy application. Thus, a total of 3 ml of the solution was administered into the parenchyma unless "roll-off" occurred within 2 min.

Before the first ablation of this study, we examined how the aforementioned techniques distributed the solution in the parenchyma. As an alternative to saline, 3 ml (15 mg) of diagnogreen solution (Indocyanine green; Daiichi-Sankyo, Tokyo, Japan) was administered with the same techniques as above. Then, the lung was dissected along the path of the needle to allow for gross examination. The diagnogreen spread three-dimensionally around the needle, forming a nearly spherical zone with a diameter of 29.4 mm (Fig. 2). The parameters for saline infusion were set based on this result.

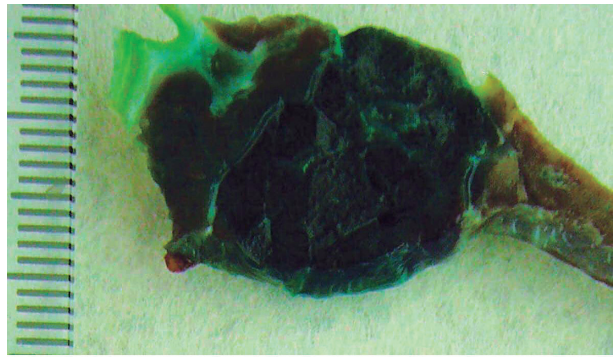


Fig. 2 Injection of indocyanine green. The indocyanine green spreads three-dimensionally, forming a nearly spherical zone with a diameter of 29.4 mm.

Gross and histologic examination. After RFA, the animals were sacrificed by intravenous injection of an overdose of potassium chloride solution (Shimizu Pharmaceutical, Shizuoka, Japan) under general anesthesia. The lungs and heart were removed en bloc, and the ablation zones were dissected along the electrode. After fixation in 10% buffered formalin, specimens were obtained by slicing the ablation zone completely at 3-mm intervals, and each slice was photographed.

All 20 ablation zones were evaluated macroscopically. The ablation zones always consisted of a central discolored zone and surrounding hyperemic zone. The discolored zones have been shown to correspond to coagulation necrosis on histologic examination [7, 8]. The size of the central discolored zones was measured by the following techniques. We did not measure the size of the entire ablation zones because the hyperemic zones surrounding coagulation necrosis were frequently limited by the pleura and poorly defined as a result of the congestion and intraalveolar hemorrhage of the underlying parenchyma (Fig. 3A, 3B). The area of coagulation was measured for every slice with Image J software (version 1.37v; National Institutes of Health, Bethesda, MD, USA), and the volume was calculated by multiplying the area by the thickness of the slice. Total coagulation volume was estimated as the sum of the volume of all slices.

The representative specimens were embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Histologic evaluation was performed by a pathologist (H.Y).

Statistical analysis. Ablation parameters,

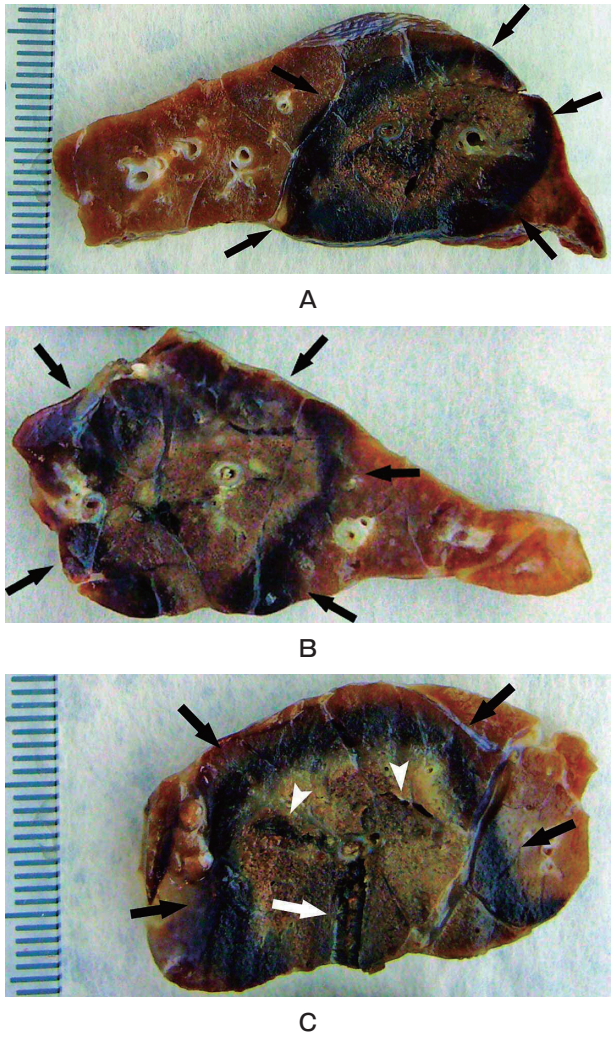


Fig. 3 Ablation zones in group 1 (A), group 2 (B), and group 3 (C). In all study groups, the ablation zones (black arrows) consisted of a central discolored zone and surrounding dark hyperemic zone. The size of the central discolored zone in group 3 was greater than that in group 1 and group 2. C shows that there was a loss of tissue in the central discolored zone, presumably due to the shaft of the electrode (white arrow) and its tines (arrowheads).

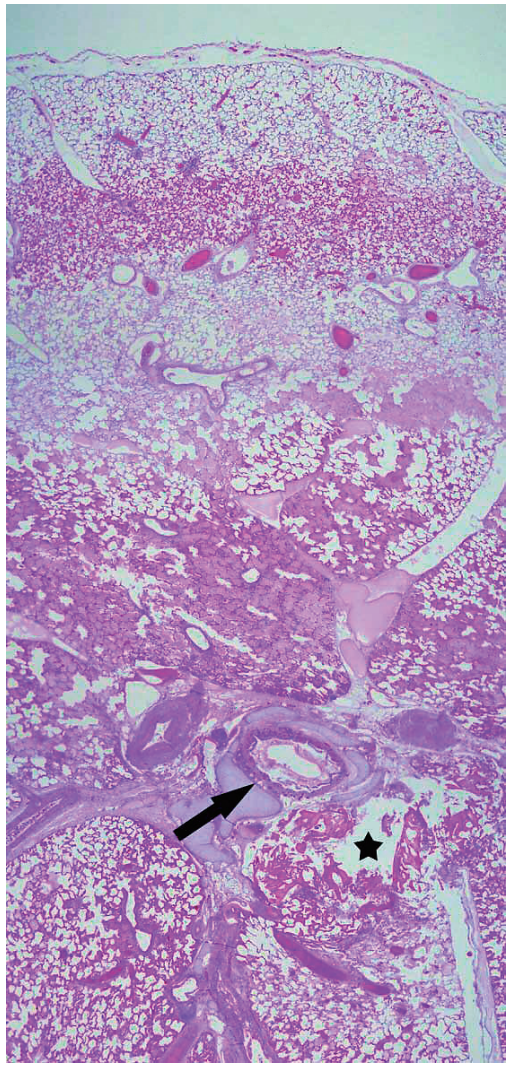


Fig. 4 Histologic section of the ablation zone in group 3. The ablation zone consists of the coagulation necrosis with varying degrees of alveolar infiltration with hypereosinophilic material and surrounding hyperemic zone. The ablation zone is clearly demarcated from the intact parenchyma. The arrow shows an injured bronchus with a detached epithelial lining with occasional disruption, which is located near the loss of structure (asterisk), presumably around the tine (hematoxylin and eosin staining).

including mean impedance, RF application time, and maximum RF power were compared among the groups. Mean impedance was the average of the impedances recorded at 15 sec intervals throughout the RFA. The total volumes of coagulation necrosis were also compared among the groups. These comparisons were performed with the Mann-Whitney U test. A p value less than 0.05 was considered to indicate a significant difference. Statistical analyses were performed with SPSS statistical software (version 11.0; SPSS, Chicago, IL, USA).

Results

Ablation parameters of each group are shown in Table 1. Group 2 showed significantly greater maximum power ($p=0.035$) and shorter application time (p

Table 1 Results of RFA in each group

	Mean Impedance (Ω)	Application Time (min)	Max. Power (W)	Coagulation Volume (mm^3)
1 (n=6)	100 ± 17	4.8 ± 1.4	29 ± 6	878 ± 502
2 (n=5)	125 ± 60	1.8 ± 1.0*	39 ± 7*	858 ± 722
3 (n=9)	82 ± 19	5.6 ± 1.8§	79 ± 19*§	1,421 ± 761§

*Significant difference at $p<0.05$ compared with the data of group 1.
§Significant difference at $p<0.05$ compared with the data of group 2.
Note. Data expressed as means ± standard deviation.

$=0.001$) than group 1. The volume of coagulation necrosis in group 2 was not significantly different from that in group 1. Group 3 showed significantly longer RF application time than group 2 ($p=0.004$) and greater maximum RF power than group 1 ($p=0.001$) and group 2 ($p=0.004$). As for mean impedance, there was a tendency toward smaller impedance in group 3 than in group 1 ($p=0.059$) and group 2 ($p=0.053$), but these differences did not reach the level of statistical significance.

Gross findings of the ablation zones were similar among the 3 groups, except for their sizes. The volume of coagulation necrosis in each group is shown in Table 1. Group 3 showed significantly larger coagulation volume than group 2 ($p=0.039$). Compared to group 1, there was a tendency toward larger coagulation in group 3, but the difference did not reach the level of statistical significance ($p=0.077$).

In histological examination, although the alveoli consisted of varying degrees of alveolar exudates and alveolar cells with basophilic nuclei and hypereosinophilic cytoplasm, the basic structure and cellular architecture of the lung parenchyma were generally intact in the central zone. This is similar to the "ghost phenomenon" that has been observed after RFA of liver tumors [9, 10], possibly as a result of sudden thermal coagulation. A dark zone indicated marked hyperemia with scattered intraalveolar hemorrhage. There was no difference in the aforementioned histological findings among the 3 groups.

Discussion

RFA has received considerable attention as a therapy for the local control of lung tumors. An international survey reported that RFA of lung tumors is a safe procedure with an extremely low mortality rate (0.4%) [11]. The most common complication is pneumothorax, but the majority of cases are treated conservatively [12, 13]. Regarding local tumor control by RFA, the outcomes in the lungs seem inferior to those in the livers and kidneys; several studies with mid-term follow-up have shown a primary local control rate of 60%–70% [14]. Lung cancer, whether primary or secondary, may show microscopic extension around the tumor [15, 16]. Thus, ablation of the surrounding parenchyma together with the tumor appears quite important for complete treatment. Nevertheless, the severely limited electrical and thermal conductivity of the air-containing lung tissue may interfere with acquisition of an adequate ablative margin, which probably contributes to the inferior outcome in the lungs.

Several strategies have been tested to enhance the effect of RFA of lung tumors. The combined use of external radiation therapy or systemic chemotherapy has proven successful in providing larger coagulation. In a clinical setting, RFA followed by conventional radiation therapy has achieved promising local tumor control (*i.e.*, a local progression rate of 8.3% (2/24) at the mean follow-up of 26.7 months) in 24 patients with stage I lung cancer [17]. Other methods, including minimizing perfusion [18] and ventilation [4], have also successfully enlarged the coagulation necrosis volume in animal experiments.

Another technique that may enlarge coagulation volume is fluid infusion into the target tissue during RFA. This method was first attempted in animal livers by Goldberg *et al.* [19]. They showed that saline infusion decreased tissue impedance, allowed greater RF power, and resulted in enlarged coagulation area. Thereafter, a number of studies clarified the enlarged coagulation by saline infusion in both the animal and human liver [20]. It is not surprising, therefore, that

saline infusion has been considered as a possible means of enlarging the coagulation area in the lung. Saline infused into the lung parenchyma is presumed to replace the alveolar air and spread to the surrounding alveoli through Kohn's pores and Lambert's duct.

The technique of saline infusion during RFA was first introduced in the lung by Lee *et al.* [21]. Similar to the results in the liver, infusion of 1.5 ml of 0.9% saline decreased tissue impedance and enlarged coagulation volume in rabbit lungs [21]. The same group also performed another *ex vivo* and *in vivo* study [22]. An *ex vivo* study using bovine lungs showed that coagulation was larger by infusion of 36% saline than by infusion of 0.9% saline; an *in vivo* study using rabbit lungs showed that the coagulation area was larger by infusion of 36% saline than by saline infusion [23]. In these studies, monopolar electrodes (Cool-tip electrode; Valleylab, Boulder, CO, USA) were used for ablation; Chiba needles were used for saline infusion [23]. Further, the same group performed RFA of the porcine lungs during saline infusion by using a specified monopolar electrode (HiTT 106; Berchtold, Tuttlingen, Germany); the electrode has side holes at the 1.5 cm-long active tip for saline infusion [23]. RFA during infusion of 0.9% saline using this electrode achieved larger coagulation than RFA using internally cooled electrodes (Cool-tip) with a 3 cm-long active tip or RFA using multitined expandable electrodes (Starburst XL; Rita Medical Systems, Mountain View, CA, USA) with a maximum diameter of 5 cm when fully expanded.

Gananadha *et al.* used a multitined expandable electrode (Starburst XLi; Rita Medical Systems) specified for RFA during saline infusion; this electrode consists of 11 hollow needles with open ends for saline infusion. RFA during saline infusion using this electrode has been shown to achieve larger coagulation than RFA without saline infusion using multitined expandable electrodes (Starburst XL) [24].

The Starburst XLi and Berchtold electrodes are currently unavailable in Japan. The Cool-tip electrode is available in Japan, but our previous clinical study on RFA for lung tumors showed that an LeVeen electrode was significantly more effective for local tumor control than a Cool-tip electrode based on multivariate analysis [14]. Therefore, we used LeVeen electrodes in this study. Other unique methodologies in this study were the use of PEIT needles for infusion of heated hypertonic (10%) saline. PEIT needles were used because they are thin and thus may minimize the risks of pneumothorax and bleeding. In addition, they have three equally spaced holes at the tip, and thus were expected to facilitate a uniform, three-dimensional spread of the infused saline. The results of the diagnogreen infusion supported this expectation. During RFA, coagulation necrosis is induced by heat friction resulting from ionic agitation. Based on this fact, it is reasonable to assume that hypertonic saline achieves a greater increase in tissue ionicity and thus a greater enlargement of coagulation area than nonionic fluid or normal saline. This was the rationale for using hypertonic saline in this study. Further, we heated the saline to 40°C, since it was considered that cold saline might hinder heat conduction by decreasing the tissue temperature. Thus, one of the important findings of this study was that these novel methodologies were successful in achieving larger coagulation.

Comparing the results of group 2 with those of group 1, it can be seen that application of greater RF power did not result in larger coagulation in RFA without saline infusion. This is probably because greater RF power resulted in earlier roll-off (*i.e.*, shorter RF application time). That is, the effect of greater RF power was compensated for by shortening the RF application time, and presumably, the total RF energy delivered was not increased by application of greater RF power. In RFA with saline infusion (group 3), on the other hand, greater RF power did not result in shorter RF application time. We assume that early "roll-off" was avoided by saline infusion, because the improved thermal conductivity delayed heat accumulation and tissue charring around the electrode. In any case, saline infusion simultaneously enabled greater RF power and longer RF application time. These 2 results, together with the lower impedance, enhanced the heat generation from the electrode, which may explain the larger coagulation area in RFA during saline infusion. In addition, the heating or even boiling of saline by RF energy could have contributed to the enhancement of thermal damage and thus the increase in coagulation area.

This study suffered from several limitations. The number of animals used in each group was quite small, which limited the statistical power. In addition, our

study was performed in the normal lungs of pigs with mechanical ventilation under open thoracotomy, and tissue impedance may be higher under open thoracotomy than under a percutaneous approach [24]. Mechanical ventilation may result in forceful respiration and thereby enhance the cooling effect of the airway. These effects may in turn affect the area of coagulation. Therefore, the data on coagulation volume in this study cannot be directly applied to a clinical setting in which lung tumors are ablated using a percutaneous technique under spontaneous breathing. Nevertheless, we suggest that these methodological issues did not interfere greatly with the goal of this study (*i.e.*, evaluation of the effect of saline infusion on RFA), because they were common to both the groups with and without saline infusion.

The use of this technique in a clinical setting could have the potential to decrease the risk of local progression by achieving an adequate ablative margin. However, the preferred needle to use for the saline infusion and the preferred electrode type remain to be determined, along with the ideal saline density, volume and speed of saline infusion, and ablation algorithm. In consideration of a previous clinical case in which RFA during saline infusion resulted in excessive necrosis [25], it is hoped that optimization of this methodology would not only increase the coagulation, but also make it more predictable and controllable.

In conclusion, although this small study had limited statistical power, hypertonic saline infusion into the lung parenchyma during RFA appeared to enhance coagulation necrosis.

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