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Bronchoscopy-guided radiofrequency ablation as a potential novel therapeutic tool

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Abstract

Background The aim was to assess the safety of bronchoscopy-guided radiofrequency ablation (RFA) and compare the effectiveness between new internal cooled-RFA and standard non-cooled-RFA.

Methods Normal lungs from sheep were used (n=6). Internal cooled-RFA and standard non-cooled-RFA were set to assess the most suitable RFA conditions such as power output, flow rate and ablation time. Internal cooled-RFA was then applied under the most optimal conditions of power output and flow rate for 15, 30, 60 and 120 seconds, and two flow water temperatures as room temperature (RT) water or cold water. Criteria for the most appropriate conditions are set over 15 seconds of ablation time and 50˚C of the tip's temperature.

Results Internal cooled-RFA had no complications. Standard non-cooled-RFA was complicated with bronchial bleeding after RFA. On the basis of the histologic findings, average temperature and average output, the most appropriate conditions of the cooled-RFA were a power output of 30 W and flow rate of 30 or 40 mL/min. The cooled-RFA using cold water caused a smaller, more discrete lesion compared with that using RT water.

Conclusion Bronchoscopy-guided internal cooled-RFA was an effective, safe and feasible procedure that could become a potential therapeutic tool in managing lung pathology.

Word count: 199

Keywords: radiofrequency ablation, internal cooled-RFA, standard non-cooled-RFA, fiberoptic bronchoscopy.

Introduction

Radiofrequency ablation (RFA) uses an electromagnetic wave with a frequency band the same as an electric scalpel used in surgery and a radiofrequency interchange electric current. RFA is a new treatment offered as a minimally invasive treatment and is most commonly used to treat patients with liver tumors [1], kidney cancer [2], breast cancer [3] or lung cancer [4]. Tumor cells are generally more susceptible to heat than normal cells. This procedure is safe, technically feasible and suitable for use with imaging guidance technologies such as ultrasonography, X-ray and computed tomography (CT).

Mortality from lung cancer remains high and establishment of new therapeutic modalities are needed. RFA has been described as a new technique for the treatment of lung cancer, and Miao *et al*. suggested that cooled-RFA is an effective alternative to lobectomy, in certain patients, for minimally invasive treatment of lung cancer [5]. In the United States standard RFA has been more widely used than percutaneous imaging-guided therapy [6]. Complications from this method include pain, pneumothorax, hemothorax, and pleural effusion [7]. Tsushima *et al*. reported the fiberoptic bronchoscopy guidance under real-time CT fluoroscopy for the diagnosis of peripheral lung lesions [8]. A critical aspect is that this procedure may reduce the above complications if we can apply RFA using real-time chest CT images under fiberoptic bronchoscopy.

We have developed a new internal cooled electrode (Japan Application No. 2006-88228) suitable for forceps channel bronchoscopy. The initial aim of this study was to compare the effective differences between the new internal-cooled electrode and the standard non-cooled electrode and to assess the feasibility and safety of bronchoscopy-guided RFA using normal sheep lungs.

Methods

Ethical considerations

The study protocol was approved by the Institutional Review Board for the care of animals at Shinshu University. The care and handling of animals was in accordance with the guidelines of the National Institute of Health. The animals had free access to commercial food and drinking water.

Preparation

Ex vivo RFA was performed on six male sheep (weight 35–50 kg) in the Shinshu University animal care facility. They were fasted for 8 hours before fiberoptic bronchoscopy to prevent aspiration pneumonia. The sheep were anesthetized using intravenous probocol (10 ml bolus) and an 8.0-mm tracheal tube was inserted after cutting part of the anterior trachea. Their limbs were fixed to the table in the supine position and spontaneous breathing was maintained under anesthesia with probocol (0.5 ml/min). RFA was performed in the animal operation room under X-ray fluoroscopy (BV-25 GOLD PHILIPS, USA).

Fiberoptic Bronchoscopy procedure

After airway anesthesia with 2% lidocaine hydrochloride, the sheep underwent fiberoptic bronchoscopy. Supplemental oxygen during the procedure was not needed. A flexible fiberoptic bronchoscope (Olympus; Tokyo, Japan), BF 1T20

(outer diameter; 5.0 mm, forceps channel; 2.2 mm) was inserted via the tracheal cannula route under local anesthesia.

Radiofrequency ablation (RFA) preparation

We prepared two kinds of electrodes for RFA, an internal cooled-electrode with a 4-mm active tip (Figure 1A) (ablation tip: 4-mm, diameter: 1.67-mm) (Shinshu University, Nagano, Japan) and a standard non-cooled-electrode with a 4-mm active tip (Figure 1B) (ablation tip: 4-mm, diameter: 1.67-mm) (Shinshu Univ., Nagano, Japan). These electrodes were attached to a monopolar radiofrequency generator (Shinshu Univ. Nagano, Japan) able to produce 50 W as the maximum output. Tissue impedance was monitored continuously by a generator, and an impedance-controlled radiofrequency algorithm was used. During the RFA procedure, a thermometer embedded within the electrode tip measured continuously the temperature and its upper limit was set at 70˚C. Grounding was achieved by attaching one or two standard steel mesh dispersive electrodes to the sheep's abdomen. A peristaltic pump (Shinshu Univ. Nagano, Japan) was used to infuse water into the internal lumen of the catheter electrode at several rates (20-50ml/minute). When the desired power output could not be applied as a result of the elevation of impedance due to tissue boiling, the generator automatically switched off the electrode. Current pulsing was also performed manually to avoid

charring local tissue caused by the rapid increase of impedance, which limited further heat diffusion.

Radiofrequency ablation (RFA) procedure

We set some conditions to assess the most suitable RFA condition according to the methods of cardiac conduction abnormality for procedure 1 [9][10][11]. An X-ray fluoroscopic image was obtained to correlate the location of the electrode tip in peripheral lung lesions with approximately 1-cm margin from pleura to prevent pneumothorax complications. Once the appropriate peripheral location of the electrode tip was confirmed, impedance less than 300Ω, RFA was used. We have settings regarding the areas which were ablated as follows.

Procedure 1: To compare between standard non-cooled-RFA and internal cooled-RFA, standard non-cooled-RFA (power output; 30 W) was ablated each right lobe only one time, and internal cooled-RFA (power output; 30W, flow rate 30ml/miniutes) was ablated each left lobe only one time. RFA was initially applied for 120 seconds under several conditions of power output and flow rate (Table 1). Lung from 1 sheep were harvested to assess ablated areas macroscopically and for histology immediately after ablation.

Procedure 2-1: To obtain an optimal output of 30 W, we performed several sets of flow rates. Internal cooled-RFA for 20, 30 and 40 ml/minutes of flow rates were ablated in the upper, middle and lower lobes once time, respectively. One

sheep were harvested immediately and 1 sheep were harvested at 7 days after ablation.

Procedure 2-2: We set the different conditions of output (20 W and 40 W) and flow rate (20, 40 and 50 ml/minutes) to compare to the data of 30 W. Internal cooled-RFA (power output; 20W) was ablated in each right lobe once and power output of 40W was ablated in each left lobe once. Lungs obtained from 1 sheep were harvested at 7 days after ablation.

Procedure 3: Internal cooled-RFA was applied under the most optimal conditions of power output and flow rate for 15, 30 and 60 seconds, using two different temperatures of flow water at different days (room temperature water or 4˚C water (cold water)). Internal cooled-RFA for 15, 30 and 60 seconds were ablated in the upper, middle and lower lobes once time, respectively. Two sheep were harvested at 7 days after ablation. Internal cooled-RFA was performed on the bronchial mucosa using the same methods as described above.

Histopathological analysis

Sheep were sacrificed immediately (n=2) and 7 days (n=4) after RFA procedure using an overdose of ketamine. Their lungs were then harvested. Gross examination was performed on all sheep for such as bronchial hemorrhage, atelectasis and perforation. For microscopic examination, two observers measured the central discolored region of coagulation necrosis in each pathologic specimen

with calipers and the average was calculated. Tissues were fixed in 10% formalin for routine histologic processing with paraffin sectioning and hematoxylin-eosin (HE) staining for light microscopic examination.

Data analysis

Technical assessment, therapeutic efficacy, and RFA complications were analyzed. Changes in the morphology and attenuation of the lesion after RFA were recorded. Optimal conditions were based on complications, local tissue temperature, histology, and procedure time in conjunction with power output, flow rate and impedance data. The above criteria were assessed with over 15 seconds of ablation time and 50˚C of the temperature of the electrode as a prolonged ablation exposure could be have denatured lung tissue due to generation of high temperatures.

Results

As shown in Figure 2, a standard non-cooled-RFA was continued for up to 120 seconds. It was complicated with bronchial bleeding immediately after RFA. Impedance increased from 770 to 999Ω. Macro findings showed bronchial hemorrhage and necrosis of 25 mm x 15 mm. Standard non-cooled-RFA showed diffuse bronchial bleeding from all ablated lobes. All histological findings showed diffuse alveolar hemorrhage, lung edema and destruction of the alveolar space. We concluded that this electrode was not suitable for lung ablation because of the increase of impedance and bronchial hemorrhage despite achieving a sufficient area of coagulation necrosis.

Internal cooled-RFA had no complications immediately after RFA. As shown in Figure 3, the average temperature of 20 W power output decreased slightly according to the flow rate. With a power output setting of 20 W and a flow rate of 20 ml/minute, impedance increased from 300 to 999 Ω. Histological findings showed diffuse alveolar hemorrhage and preserved structure of the alveolar space. With a flow rate of 40 ml/minute, histologic findings did not differ from the ones with a flow rate of 20 ml/minute.

As shown in Figure 4, with a power output setting of 30 W and a flow rate of 40 ml/minute, impedance decreased from 174 to 97 Ω. Macro findings showed necrosis of 15 mm x 15 mm, and no bronchial bleeding. Histological findings showed diffuse alveolar hemorrhage and necrosis. With 30 W power output and a

flow rate of 20 ml/minute, sufficient power output could not be achieved because of the rapid increase of the tip's temperature; however, pathohistological findings showed the same lesion and size as with a flow rate of 40 ml/minute. The findings between a flow rate of 30 and 40 ml/minute were almost identical. Although the data did not show, by using 40 W power output, the temperature of the electrode tip reached 60˚C; therefore, the flow rate remained high because the tip temperature rapidly increased with a low flow rate. Impedance decreased from 245 to 189 Ω. Histological findings showed diffuse alveolar hemorrhage, lung edema and destruction of the alveolar space. Power output of 40 W could achieve almost the same size of coagulation necrosis as 30 W; therefore, we suggest that 40 W power output was not necessary to ablate the lung tissue for clinical safety. On the basis of these histologic findings, and the average temperature and output, the most appropriate conditions for the cooled electrode were 30 W power output and a flow rate of 30 or 40 mL/min. In addition, the temperature of the electrode tip needed to ablate the lung tissue was about 50˚C based on the histologic findings.

As shown in Figure 5, internal cooled-RFA was applied under the most appropriate conditions of 30 W power output and a flow rate of 40 ml/min for 15, 30 and 60 seconds. The electrode tip temperature reached over 50˚C within 10 seconds at both water temperatures. The cooled-RFA with cold water achieved coagulation necrosis of approximately 7 mm in diameter after 15 seconds of ablation. There was a major difference histologically between cold water and room

temperature water. The macro findings of room temperature water showed larger burn lesions (40 mm x 45 mm) than cold water (20 mm x 15 mm) after 60 seconds of ablation; however, after 30 seconds of ablation, the burn size was almost identical between room temperature water (11 mm x 7 mm) and cold water (7 mm x 5 mm). From these histological results, a 30-second exposure of RFA affected deeper lung tissues similarly independently from water temperature used.

On ablation of the bronchial membrane, sufficient necrosis effect was achieved with white denaturation of the mucous membrane within 10 seconds using a cooled-RFA with cold water. No bronchial perforation was observed within 30 seconds of ablation; however, since impedance increased faster compared to the peripheral lung tissue, RFA could not continue over 30 seconds. We assumed that this was due to contact resistance around the electrode tip.

Discussion

Percutaneous guided-RFA has found clinical applications for lung cancer with good results reported [4][5][6][7][12]. Since the electrode is placed percutaneously directly into the tumor under cross-sectional imaging guidance such as chest CT, complications such as pneumothorax occur with frequency. The frequency of pneumothorax or hemothorax using percutaneously directly electrode was 47% on rabbit model [13]. Clinical complications occurring in percutaneously directly RFA showed 16-35% [6][7]. However, it is possible to avoid these complications using our fiberoptic bronchoscopy guidance; this is the greatest advantage of our internal cooled electrode. Our fiberoptic bronchoscopy-guided cooled-RFA is safe, technically feasible as we are confirming the tip of electrode in CT or X-ray imaging guidance. As this report has shown, cooled-RFA had no complications such as bronchial bleeding, pneumothorax and can be used with CT or X-ray imaging guidance technologies. Therefore, to our knowledge, this is the first report showing fiberoptic bronchoscopic guided cooled-RFA as a potential therapeutic tool.

The peripheral lung is referred to as the safety zone; however, the anatomically central and middle bronchi are accompanied by the pulmonary artery branches. A complication anticipated with bronchoscopy is bronchial bleeding. Although the data are not shown, we tried to ablate several areas of lesions from peripheral lung tissues to central lung tissues using power output of 30 W and flow

rate of 40 ml/minutes. On day 7 after ablation there were no complications of macro bronchial hemorrhage from the middle or central artery or atelectasis. Therefore, we could confirm that our cooled-RFA achieved coagulation and hemostasis in the lung normal tissues although we need to assess the safety in other lung tissues that could bleed more than normal lungs.

This internal cooled-RFA is constructed as a thin catheter (diameter: 1.67mm) because it passes through the bronchoscopy channel. The necrotic size obtained by this electrode is a critical consideration for this method. To achieve higher power output from the electrode and sufficient coagulation necrosis, we needed to increase the power output and to reduce impedance around the electrode tip. Using the standard non-cooled electrode, the temperature around the tip rose rapidly and the pop phenomenon occurred in the lung tissues. This phenomenon means that coagulated necrotic tissue is formed around the electrode tip and tissue impedance increases rapidly. To avoid this phenomenon, the electrode tip should be cooled using water. On the basis of these results using a cooled-RFA for cardiac conduction disease [14] [15], it is predicted that the lesion occurs in lung tissues away from the cooled-RFA. The cooled-RFA enables greater power output for a longer time compared with the standard non-cooled-RFA, resulting in larger coagulation necrosis area. The electrode tip is cooled down by circulating water in the electrode catheter. As the result, the tissue temperature just around the electrode tip does not reach an excessive high temperature. Based on this theory,

the cooled-RFA can reach deeper and wider areas of ablation using the same power output. Therefore, as shown in our results, we suppose that the cooled-RFA could obtain coagulation necrosis compared with the standard non-cooled-RFA, and the cooled-RFA circulating room temperature water could obtain larger burn lesions than that circulating cold water.

Lung cancer is regarded as suitable for RFA as the radiofrequency energy to a tumor relies on the insulation effect by the existence of normal surrounding lungs [5]. However, surgery is recognized to be the standard treatment for patients with localized primary lung cancer and metastatic resectable lesions. A minimally invasive procedure such as RFA is used when considering the generally poor outcome of patients treated with systemic chemotherapy and radiotherapy or with a poor cardiopulmonary status or coexistent medical problems for surgery. There have been some reports of RFA applied clinically for lung tumors [16][17]. The role of RFA in lung cancer is not sufficiently clear. However, bronchoscopy-guided RFA achieves only local coagulation necrosis and is likely to minimize injury to lung tissues and perhaps have a good effect on a patient's condition. When institutions use RFA percutaneously, an epidural anesthetic consisting of lidocaine, fentanyl, or both as needed, needs to be administered percutaneously with an epidural tube [7]. If we could apply this procedure to human advanced lung cancer, we would be able to use cooled-RFA with the same method as usual biopsy forceps under topical lidocaine anesthesia only.

Bronchoscopy-guided cooled-RFA advantages could include the ability to administer treatment non-surgically as well as a short hospital stay for the patient. From our results, we suggest that RFA for advanced lung cancer might have numerous benefits over systemic chemotherapy or radiation therapy, although trials would be needed to confirm potential risk/benefits.

This study's limitation was that a potential tumor to be ablated most likely would have a different behavior and data obtained in normal lungs cannot be extrapolated to tumor bearing lungs since RFA effect was tested in normal lungs. As VX2 tumor strains have strong malignant potential, some studies using RFA have been reported [13]. Since we needed to perform bronchoscopy-guided RFA, we needed bigger animals such as sheep, dogs or pigs. We tried to inject VX2 tumor cells into the right or left lower lung of sheep, but VX2 tumors cells did not grow in the lung. Secondly, as sheep skin is covered with wool, initial impedance was high compared with human lungs (initial impedance of human: 130-200Ω). Therefore, the size of coagulation necrosis may be underestimated because the rapid increase of impedance could not achieve sufficiently long ablation time and power output. As shown in Figure 5, we could not achieve an average power output of 30 W although we set 30 W power output. However since this method could achieve adequate coagulation necrosis, if it were applied in humans, larger coagulation necrosis would be achieved under the same conditions as the sheep lung with 30 W power output and a flow rate of 40 ml/minute. As we did not

achieve excessive coagulation necrosis on the surface of ablated sheep lung tissues, we should be able to perform RFA circulating cold water in the electrode tip in humans.

In conclusion, internal bronchoscopy-guided cooled-RFA was safe, effective and feasible procedure without major complications. The ideal power output of 30W and a flow rate of 40ml/minute were assessed as safe and technically feasible conditions for bronchoscopy-guided cooled-RFA for this normal sheep lung.

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Figure Legends

Figure 1: (A) This model is an internal cooled radiofrequency ablation electrode. (B) Top of the electrode. Only a 4 mm-top electrode produced power output, and the tip temperature and impedance were measured.

Figure 1

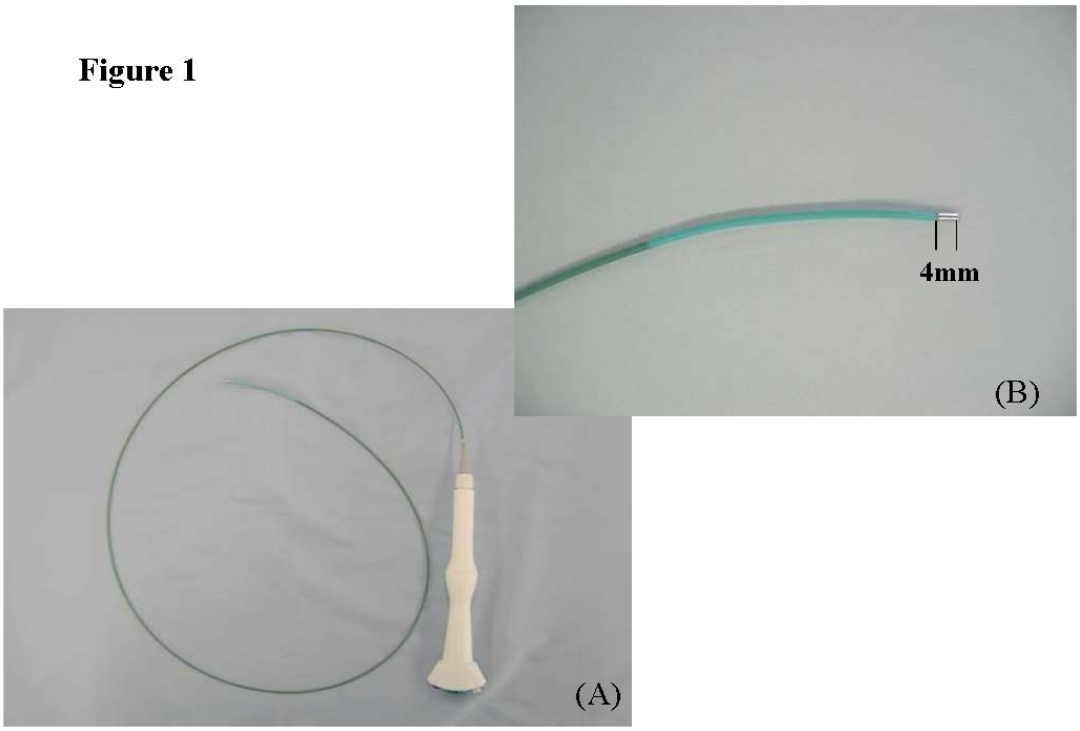
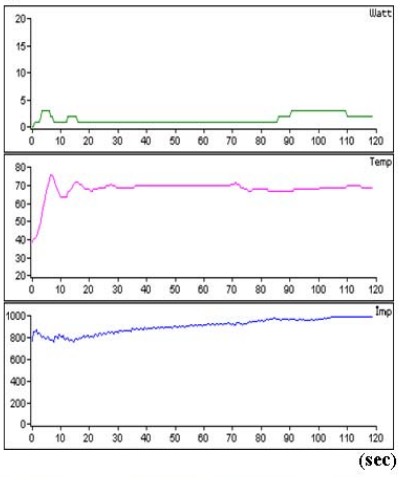


Figure 2: the data of standard non-cooled electrode of power output: 30 W. (A) Power output, temperature and impedance. Power output was low and mean temperature was 76˚C. Impedance increased from 770 to 999Ω. (B) Macro findings showed large coagulation necrosis. (C) Micro findings showed diffuse alveolar hemorrhage, destruction of alveolar space (hematoxylin-eosin stain, x 10). (D) This showed the data of two sets of power output.

Figure 2

(A)



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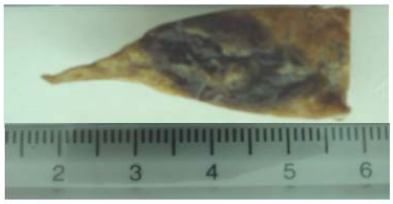

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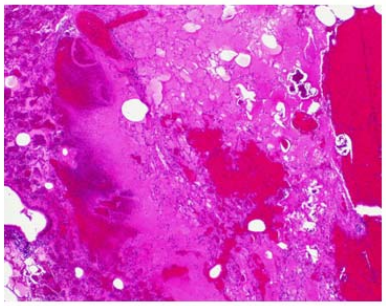


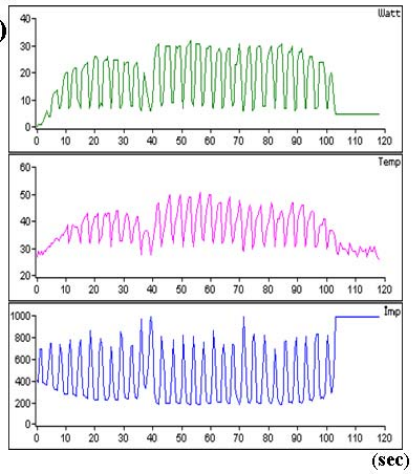
(D)

Power output (W)	Ablation time (sec)	Average output (W)	Maximum output (W)	Average temperature (℃)	Maximum temperature (℃)
20	120	2	4	66	74
30	120	1	3	68	76

Figure 3: Internal cooled electrode. Power output of 20 W and flow rate of 20 ml/minute. (A) Mean power output showed 16 W, and mean temperature was 43˚C. Impedance increased from 300 to 999Ω. Wide wave range meant changes accompanied with deep breathing. (B) Macro findings showed a ring burn and normal central area. (C) Micro findings showed some hemorrhage, maintenance of alveolar space (hematoxylin-eosin stain, x 10). (D) This showed the data of two sets of flow rate under 20 W power output.

Figure 3

(A)



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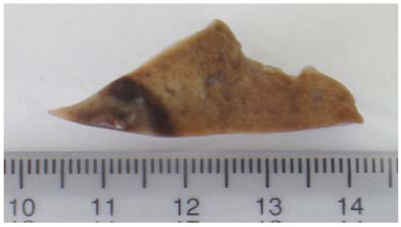

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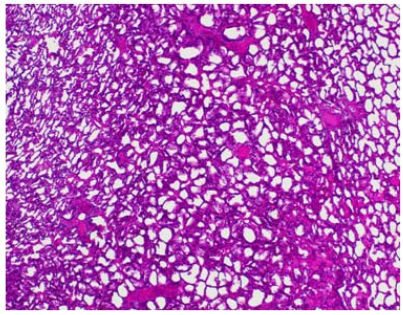


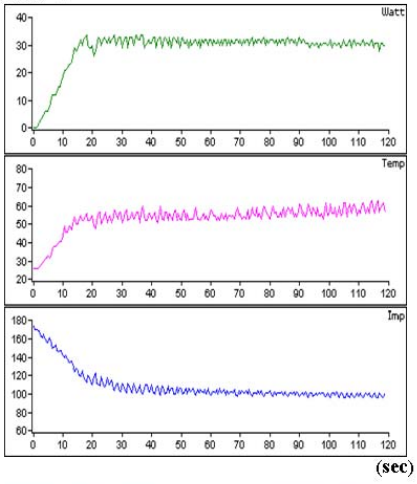
(D)

Power output (W)/ Flow rate (ml/min)	Ablation time (sec)	Average output (W)	Maximum output (W)	Average temperature (℃)	Maximum temperature (℃)
20/20	120	16	18	43	56
20/40	120	16	32	37	51

Figure 4: Internal cooled electrode. Power output of 30 W and flow rate of 40 ml/minute. (A) Mean power output showed 23 W, and mean temperature was 51˚C. Impedance increased from 245 to 189Ω. Power output and temperature maintained a plateau. Impedance showed decrease. (B) Macro findings showed a ring burn with central necrosis. (C) Micro findings showed hemorrhage in the central area and diffuse alveolar destruction (hematoxylin-eosin stain, x 10). (D) This showed the data of three sets of flow rate under 30 W power output.

Figure 4

(A)



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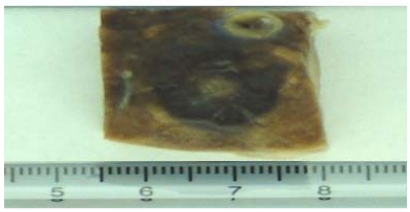
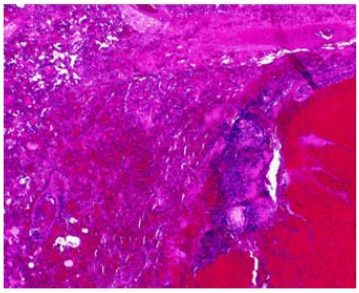


(C)



(D)

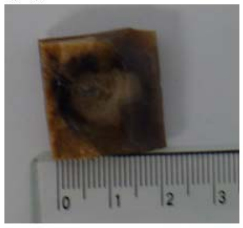
Power output (W)/ Flow rate (ml/min)	Ablation time (sec)	Average output (W)	Maximum output (W)	Average temperature (℃)	Maximum temperature (℃)
30/20	120	14	32	41	62
30/30	120	28	34	53	63
30/40	120	23	39	51	64

Figure 5: Internal cooled electrode. Power output of 30 W, flow rate of 40 ml/minute and 60 seconds of ablation time. Cold water and room temperature water were used as an internal flow. (A) Cold water showed coagulation necrosis of 15 mm in diameter and a burn area of 20 mm in diameter. (D) Room temperature water showed coagulation necrosis of 15 mm in diameter and a burn area of approximately 40 mm in diameter. The necrotic size was as twice as large as with cold water. (B) and (E) Micro findings showed the borderline between infiltration zone and normal lung zone; hemorrhage in the alveoli and diffuse alveolar destruction (hematoxylin-eosin stain, x 40). (C) and (F) These showed the data of three sets of ablation seconds under 30 W power output and 40 ml/minutes of flow rate.

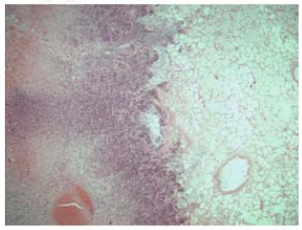
Figure 5

Cold water

(A)



(B)

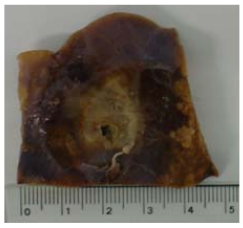


(C)

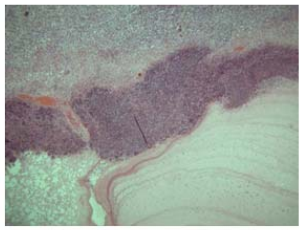
Condition (Power output: 30 W, Flow rate: 40 mL/min)	Average output (W)	Maximum output (W)	Average temperature (℃)	Maximum temperature (℃)
15 seconds	7	21	20	29
30 seconds	6	21	44	61
60 seconds	8	25	51	60

Room temperature

(D)



(E)



(F)

Condition (Power output: 30 W, Flow rate: 40 mL/min)	Average output (W)	Maximum output (W)	Average temperature (℃)	Maximum temperature (℃)
15 seconds	7	16	54	71
30 seconds	16	29	55	67
60 seconds	18	28	57	64

Table 1. Procedures of radiofrequency ablation (RFA)

Procedure 1. Compare to standard non-cooled-RFA and internal cooled-RFA

Power output: 30 W fixed, Flow rate: 30 ml/minutes, ablation time: 120seconds

Lung histology was obtained immediately after ablation

Procedure 2-1. Settings of internal cooled-RFA

Power output: 30 W fixed, ablation time: 120 seconds

Flow rate: 20, 30, and 40 ml/minutes

Lung histology was obtained immediately and at 7 day after ablation

Procedure 2-2. Settings of internal cooled-RFA

Power output: 20 and 40 W fixed, ablation time: 120 seconds

Each flow rate: 20, 40 and 40, 50 ml/minutes

Lung histology was obtained at 7 day after ablation

Procedure 3. Settings of internal cooled-RFA

Power output: 30 W fixed, Flow rate: 40 ml/minutes fixed

Compare to room temperature water flow and cold water flow

Lung histology was obtained at 7 day after ablation