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Temperature Isotherms during Pulmonary Cryoablation and their Correlation with the Zone of Ablation

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Abstract

PURPOSE—To determine the expected ablation zone size and associated isotherms when using clinically available percutaneous cryoprobes for pulmonary cryoablation in a porcine lung model.

MATERIALS AND METHODS—Seven ablations were performed in the lungs of three adult pigs using clinically available 2.4-mm cryoprobes (Endocare, Inc, Irvine, California) and a 10-minute double-freeze protocol. Five 18-gauge thermocouples were positioned at 5-mm increments (ie, 5, 10, 15, 20, and 25 mm) from the cryoprobe. Real-time tissue temperatures were recorded during the cryoablation. The isotherms obtained during the ablation and the pathological ablation zones were measured.

RESULTS—The pathologic zone of complete necrosis had a mean diameter of 2.4 ± 0.2 cm, with a mean area of 4.6 ± 0.6 cm² and a circularity of 0.95 ± 0.04 . In comparison, the mean diameter ($\pm$ standard deviation) of the 0°C, -20°C, and -40°C isotherms were 3.1 ± 0.2 cm, 2.3 ± 0.3 cm, and 1.8 ± 0.4 cm, respectively. The -20°C isotherm was most closely related to the pathologic zone of ablation.

CONCLUSIONS—This study establishes the temperature isotherms and associated ablation zone size that can be expected with modern percutaneous cryoprobes in an in vivo porcine lung model.

IMAGE-GUIDED pulmonary ablation is a rapidly developing technique that has potential applications for both primary lung cancer and pulmonary metastatic disease (1–6). To date, the greatest clinical and experimental experience has been with pulmonary radiofrequency (RF) ablation. However, RF ablation has significant technical limitations, when it is applied in the lung. These limitations are related to the heat sink effects of both blood flow and air movement as well as to the elevated electrical resistance of air, all of which limit energy deposition (7–11). To overcome these limitations, devices that increase the surface area of the electrodes (ie, deployable array electrodes) and adjuncts such as saline infusion have been used (12). However, both of these interventions are associated with increased procedural risks. Because freezing is an entirely thermal process, cryoablation does not have the same limitations related to electrical impedance but is likely to have similar limitations related to heat sink effects. Although there are several clinical series in which cryoablation was applied in the lung, there has been minimal critical scientific evaluation of the underlying process, limitations, and possible advantages. As a result, many questions remain regarding its efficacy and applicability in the lung.

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There are two in vivo pulmonary cryoablation studies in the literature that have evaluated the ablation zone attained with modern cryoprobes (13,14). One was an evaluation of cryoablation in the lung, kidney, and liver using an identical ablation protocol (14). This study revealed two issues that limit the applicability of the results. First, the placement of the thermocouples was at the same depth as the tip of the cryoprobe, which does not accurately reflect the size of the iceball; and second, the temperature isotherms obtained and the ablation zones reported do not have the expected relationship based on previous findings (eg, iceball size of 35.5 ± 3.6 mm with ablation zone of only 11.6 ± 1.48 mm in the lung and similar large discrepancies in the other tissues). These findings suggest that there may be an issue with the pathology. The other study is an evaluation of the ablation zone sizes and configurations seen during multiprobe cryoablation in kidney, liver, and lung (13). Although this study is useful in that the findings suggest that closer spacing or optimized freeze thaw protocols may be needed for pulmonary cryoablation, it does not identify the isotherms that can be expected when using currently available percutaneous cryoprobes. Thus, neither study provides conclusive data regarding the use of cryoablation in the lung.

Some promising early clinical results with pulmonary cryoablation exist as well, but the isotherms created by percutaneous cryoprobes have not been well characterized (2). Because temperature isotherms (-20°C and -40°C isotherms) have been shown to correlate to the final zone of necrosis, isotherm mapping is a critical step to establish the applicability of cryoablation in the lung (15). This study is designed to determine the thermal isotherms that can be produced by modern percutaneous cryoprobes and establish the relationship between the isotherms and associated cellular necrosis in a normal porcine lung model.

MATERIALS AND METHODS

Study approval was obtained from the Research Animal Care and Use Committee of our institution, and all husbandry and experimental studies were compliant with the National Research Council's Guide for the Care and Use of Laboratory Animals.

Three female domestic swine (approximate weight 68 ± 4.5 kg) were used for our study. Preanesthetic sedation was achieved with intramuscular tiletamine hydrochloride/zolazepam hydrochloride, 7 mg/kg (Telazol, Fort Dodge, Iowa), and xylazine hydrochloride, 2.2 mg/kg (Xyla-Ject; Phoenix Pharmaceutical, St. Joseph, Missouri). Atropine, 0.05 mg/kg (Phoenix Pharmaceutical), was provided to facilitate intubation. Endotracheal intubation was performed in the standard fashion. Anesthesia was then induced and maintained with inhaled isoflurane (Halocarbon Laboratories, River Edge, New Jersey). Clinically available 2.4-mm percutaneous cryoprobes with a 4-cm active tip were used for all ablations (Endocare, Inc., Irvine, California). Once the pigs were stabilized on the operating table, a thoracotomy was performed, including take down of the diaphragms bilaterally, exposing the lungs. Cryoprobes were inserted into the lower and middle lobes bilaterally under direct visualization. In some cases, the middle lobe was not thought to be large enough to use without possible overlap between the two ablations, and in these lungs, only a single ablation was performed. Thermocouples were positioned at 5-mm increments from the cryoprobe. The cryoprobes were positioned with the tips approximately 4–5 cm into the lung parenchyma. Thermocouple tips were positioned at a depth 1.5 cm proximal to the tip of the cryoprobe where the iceball would be expected to be largest (Fig 1). A custom-machined plastic template was used to ensure consistent positioning of the temperature sensors relative to the cryoprobe. The cryoprobes were positioned at least 4 cm apart in a portion of the lung that had adequate parenchyma so that an approximately 3-cm iceball would be fully encased by lung parenchyma. Once positioning was optimized, a 10-5-10 double freeze-passive thaw-freeze cycle was performed. The ablations were performed sequentially, so that we were able to appropriately monitor the temperatures. Cryoprobe and thermocouple

temperatures were recorded digitally every minute during the ablation. All ablation procedures were performed by a single operator who had more than 5 years of clinical and laboratory experience with ablation techniques and this cryoablation system. A total of seven ablations were performed for this study.

Immediately after the ablations, animals were sacrificed by an intravenous injection of Beuthanasia-D (390 mg/mL pentobarbital sodium and 50 mg/mL phenytoin sodium at 0.2 mL/kg intravenous; Schering-Plough, Kenilworth, New Jersey). The lungs were removed, and the ablation zones were sectioned transverse to the cryoprobe insertion track in approximately 5-mm increments. Sections were scanned optically as electronic files for later measurement. A representative slice (largest diameter at the approximate midpoint of the ablation zone thought to be at the approximate depth of the thermocouples) from each ablation zone was measured by consensus between two of the authors using the software ImageJ (National Institute of Mental Health, Bethesda, Maryland). Measurements included minimum and maximum diameter, area, and circularity (measure of how closely the ablation zone approximates a circle). The lung samples were subsequently stained with both hemotoxylin and eosin and vital stain for histological and pathological evaluation by a board-certified pathologist specializing in ablation technologies.

Continuous data were expressed as means with standard deviations. A nonlinear interpolation was used to determine the approximate isotherms.

RESULTS

A total of seven cryoablations were performed with thermocouple temperature measurements. An analysis of the thermocouple temperature measurements as a function of the distance from the cryoprobe was consistent across the ablations. The mean ($\pm$ standard deviation) low temperatures achieved 0, 5, 10, 15, 20, and 25 mm from the probe were $-117.5^{\circ} \pm 13.6^{\circ}\text{C}$, $-70.8^{\circ} \pm 29.1^{\circ}\text{C}$, $-24.3^{\circ} \pm 9.9^{\circ}\text{C}$, $0.3^{\circ} \pm 6.1^{\circ}\text{C}$, $24.1 \pm 6.3^{\circ}\text{C}$, and $31.3^{\circ} \pm 3.3^{\circ}\text{C}$, respectively (Fig 2). Based on a nonlinear interpolation of the individual temperature readings, the mean ($\pm$ standard deviation) diameter of 0°C , -20°C and -40°C isotherms was 3.10 ± 0.23 cm, 2.36 ± 0.31 cm, and 1.78 ± 0.38 cm, respectively (Table 1). When the temperature is plotted versus time, it is seen that the rate of temperature decrease during the initial freeze was rapid initially (4.7 , 11.7 , and $8.8^{\circ}\text{C}/\text{min}$ between the first and fourth minute at 0, 0.5, and 1.0 cm from the cryoprobe, respectively), but decreased later in the freeze (0.5° , 1.3° , and $0.1^{\circ}\text{C}/\text{min}$ between the fourth and tenth minute at 0, 0.5, and 1.0 cm from the cryoprobe, respectively). However, even at the end of the second freeze cycle, the temperature of the iceball is still decreasing slowly, as shown by the declining slope of the temperature profile at the end of the ablation (0.7° , 1.4° , and $1.9^{\circ}\text{C}/\text{min}$ over the final 3 minutes at 0, 0.5, and 1.0 cm from the cryoprobe, respectively) (Fig 3). The mean diameter of the ablation zone identified on pathology (2.4 ± 0.2 cm) (Fig 4) (16) was most closely related to the mean diameter of the -20°C isotherm (2.3 ± 0.3 cm) (Table 2), suggesting that the critical temperature for inducing cellular death in lung parenchyma is approximately -20°C . In the transverse plane, the ablation zones were highly circular and consistent (circularity = 0.95 ± 0.04).

DISCUSSION

This study directly measures the temperature isotherms of the largest part of the iceball created by percutaneous cryoprobes in normal porcine lung and shows a direct relationship between those temperature isotherms and the ablation zone. The ablation zones were consistent and reproducible with a close relationship identified between the -20°C isotherm and the zone of coagulative necrosis. This finding is in agreement with that of previous

studies, which have found that the critical isotherm is between -20 and -40°C depending on the tissue type (15,17). Also, the results show that clinically relevant ablation zone sizes can be achieved in the lung with percutaneous cryoprobes. In our study, the mean ablation zone diameter was 2.4 ± 0.2 cm.

The application of RF ablation in the lung has associated limitations related to the very high electrical resistance inherent to air. Even if the electrode is completely encased by the tumor after placement (a situation that is likely to be associated with incomplete ablation), the deposited RF energy still has to traverse aerated lung to return to the ground pads to complete the electrical circuit. Thus, the overall resistance of the circuit remains high. Several different innovations have been used to try and overcome this limitation. One is to use expandable array or “cluster” electrodes that have a larger surface area, thus increasing the amount of current that can be deposited. However, the profile of these electrodes is also significantly larger (12–14 gauge) than single percutaneous electrodes (15–17 gauge); therefore, the trauma of placement and risk for complications is greater. Infusion electrodes have also been used (12). With these electrodes, saline is infused into the tissues, augmenting the electrical conductivity of the tissues, thus increasing the current that can be deposited in the tissues. However, this method is also associated with reduced control of the ablation zone because the saline is unpredictable in its distribution and can extend the ablation zone to sites distant from the target. Thus, although RF is a robust modality, there are reasons to continue to evaluate other techniques for image-guided ablation in the lung, including cryoablation and microwave ablation.

Cryoablation is not dependent on current deposition and is a purely thermal event. As a result, the deposition of energy should be related primarily to the thermal conductivity of the tissue, and the air within the lung should not have as large of an impact on ablation zone size. In fact, in a previous study, it was found that unlike RF ablation, selective intubation and control of ventilation in the lung to be ablated has minimal if any effect on the resulting zone of ablation (18). Cryoablation has not been a viable alternative for percutaneous use in the past because of the prohibitively large cryoprobes. However, with the development of argon-based cryoablation systems, cryoprobes as small as 17 gauge have become available. This has expanded the utilization of cryoablation into percutaneous applications, particularly in the kidney and liver, where it has proven to be both safe and efficacious (19–23). Cryoablation has been used in a more limited fashion in the lung, but to date, there is a dearth of in vivo animal studies to evaluate and establish its efficacy and applicability in the lung. This study shows that relatively large, clinically relevant zones of necrosis can be produced in the lung with modern percutaneous cryoprobes.

There are several limitations of our study. First, the ablations were performed in the setting of open thoracotomy, which may have unexpected effects on the inflation pattern and physiology of the lungs. However, previously described work with RF ablation has also been performed with an open thoracotomy, and that work appears to be valid as it is translated into the clinical setting (8,24). This finding suggests that the open model is reasonably valid. However, percutaneous ablations will need to be performed to confirm these findings, and this is already underway at our institution. A second limitation is the study size. The relatively small numbers are justified by the need to limit the number of animals sacrificed in a pilot study. Subsequent studies will use larger sample sizes. In addition, our isotherm measurements occurred on one radius and depth and assumed an isotropic profile. Actual ablations will be more oblate and are never circular, and we did not account for the length of the ablation zone. However, the circularity was consistently high, and the length that we did not account for is actually the largest dimension of the ablation zone, so this should not detract substantially from the results. Last, a tumor model was not used because a large animal tumor model is not readily available or reproducible. However,

because the thermal conductivity of soft tissue is greater than that of air, there may be a “freezer effect” associated with cryoablation of soft tissue tumors embedded in the lung similar to the “oven effect” previously described in the setting of RF ablation of hepatocellular carcinoma in a cirrhotic liver. Therefore, this study may actually underestimate the isotherms that can be achieved during pulmonary cryoablation of a tumor.

Our study was designed to establish the expected temperature isotherms and associated zones of necrosis for pulmonary cryoablation utilizing modern percutaneous cryoprobes. In our study, the zone of necrosis was most closely related to the -20°C isotherm, and a relatively robust ablation zone was established with a mean ablation zone of 2.4 cm utilizing a single cryoprobe. This work will need further validation in a larger study cohort but is certainly promising and validates already ongoing clinical work.

Abbreviation

RF radiofrequency

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Figure 1.

The experimental setup involved placement of the cryoprobe centrally, with thermocouples in a radial array at 5-mm increments. Note that the depth of the thermocouples was controlled so that the tip of the thermocouple was at the expected depth of the largest diameter of the iceball.

Figure 2.

A plot of the temperature versus the distance from the cryoprobe shows the expected extreme cold at the cryoprobe with a gradient of temperatures within the iceball.

Figure 3.

Because of the extreme cold of the cryoablation, the temperatures in the tissues adjacent to the cryoprobe decreased rapidly. During the second freeze, there was both an increase in size of the iceball and a decrease in temperatures within the iceball. Both are important for cellular necrosis.

Figure 4.
The ablation zone can be seen easily on gross pathology (arrows). The relationship of the gross findings to the histopathology has been described previously.

Table 1

Isotherm Diameters

Isotherm	Diameter (mean $\pm$ SD)
0°C (iceball)	3.1 $\pm$ 0.2
−20°C*	2.3 $\pm$ 0.3
−40°C	1.8 $\pm$ 0.4

* Note the relatively large diameter of the −20°C isotherm (2.3 cm), which generally results in cellular necrosis.

Table 2

Ablation Zone Parameters

Measurement	Mean $\pm$ SD
Diameter (cm) *	2.4 $\pm$ 0.2
Area (cm ²)	4.6 $\pm$ 0.6
Circularity	0.95 $\pm$ 0.04

* Note that the ablation zone size (2.4 cm) is most closely related to the -20°C isotherm identified on the temperature measurements.