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Ex Vivo Experiment on Radiofrequency Liver Ablation with Saline Infusion through a Screw-Tip Cannulated Electrode

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Purpose: To investigate whether radiofrequency (RF) therapy with hypertonic saline infusion through a hollow screw-tip electrode can cause a lesion size suitable for liver tumor ablation. Materials and methods: RF tissue ablation of 180 sites was performed by using a hollow screw-tip electrode in 40 freshly excised swine livers. Under both power and temperature control modes, the ablation effects with and without various regimes of 5% hypertonic saline (1 ml/min) prior to and/or during the procedure were compared by measuring the size of lesions at dissection and confirmed by T1 and T2 weighted magnetic resonance (MR) imaging. Results: The maximal lesion diameter of 5.5 cm was reached at 30 W with saline infusion 1 min prior to and during 12 min of ablation. The smaller sizes ($P < 0.01$) between 0.3 and 2.5 cm in diameter were met with noninfusion or preinfusion-only groups. The RF ablation lesions appeared as hyper- and hypointense areas on T1 and T2 MR images, respectively. Conclusions: RF ablation in combination with present hollow screw-tip electrode and saline infusion allows for necrotic development of suitable size for liver tumor ablation. Such ablated lesions can be visualized with MR imaging. © 1997 Academic Press

INTRODUCTION

Radiofrequency (RF) catheter ablation techniques have shown promise for treatment of either primary or metastatic solid neoplasms in the liver [1, 2]. However, the maximum size of a lesion that can be treated effectively is still limited by impedance rise from the electrode–tissue interface, secondary to tissue desiccation and charring [1, 2]. A proposed approach to solve this limitation is to irrigate the electrode with cooling liquid [3–5]. By the cooling effect, the tip of the electrode is maintained at low temperature, thereby increasing the conductivity of the electrode–tissue interface and preventing an impedance rise. The effectiveness of this approach has been shown in the ablation of abnormal muscle and liver [3–5]. Another approach is to infuse saline into the tissue through the hollow electrode tip [6–8]. The conductivity of normal saline is 3 to 5 times higher than that of the blood and 12 to 15 times higher than that of tissues. Infused saline produces a liquid electrode in the tissue to be ablated and spreads the applied RF energy away from the metal electrode. The resultant lower current density at the metal electrode–tissue interface reduces tissue desiccation [6]. When room temperature saline is infused, some convective cooling also occurs at the tip. The purpose of this study was to evaluate whether the RF ablation size of liver tissue (eventually in liver tumors) can still be increased by interstitial infusion of 5% hypertonic saline through a newly developed screw-tip hollow electrode (Medtronic, Minneapolis, MN).

MATERIALS AND METHODS

Ablation protocol. RF tissue ablation of 180 sites was performed in 40 freshly excised swine livers. Four to 12 applications of RF current were delivered to separate sites per excised liver. RF current was produced by a modified RF generator (Medtronic, San Jose, CA); the maximal energy output is 50 W into a 50–250 Ω load of 475 ± 20 kHz RF current continuously with an automatic high impedance shutoff at 250 Ω. Impedance, tip electrode temperature, and power output values are recorded along with the time of ablation. A luminal screw catheter (5 French) with one end hole and four side holes (0.12 mm in diameter) at its tip, which is 1.7 mm in screw diameter and 10 mm in length (Fig. 1), was inserted into the tissue at a depth of 1.5 to 3 cm. This catheter permits infusion of fluid and delivery of RF current. RF current was delivered between the catheter tip electrode and an adhesive electrosurgical pad placed on the opposite side of the liver. The delivery was controlled using both power and temperature mode. An additional thermocouple (Type K, Omega Engineering, Stamford, CT) was inserted in contact with the distal electrode to monitor tip temperature. In the power control mode, 30 W was chosen because of the match between power and saline infusion rate (1 ml/min). In the temperature control mode, the RF generator output was adjusted to the greatest level of power without increasing electrode temperature beyond 90°C. Hypertonic saline (5% NaCl, Baxter N.V., Lessines, Belgium) at room temperature (20°C) was infused at 1 ml/min by using an infusion pump (Ismatic, Switzerland). The experimental regimes were designed as both power and temperature control modes. Each mode was further divided into three subgroups:

Power control mode (energy output fixed at 30 W): Group A (Ap), no infusion, $n = 10$; Group B (Bp), 1 min preinfusion only (1 ml), n

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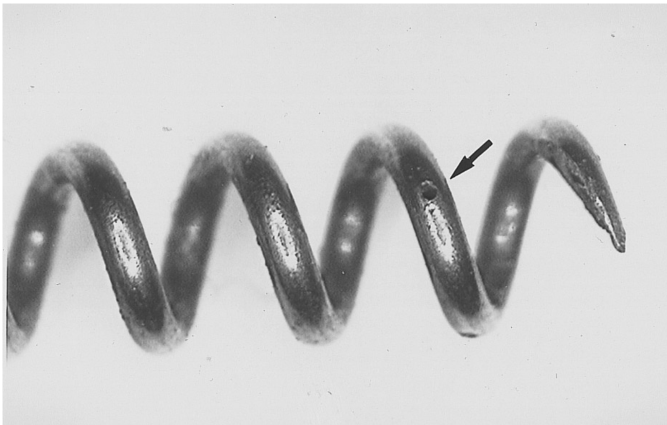

FIG. 1. Photograph of a screw-tip cannulated electrode. Arrow indicates one of the four side holes.

= 10; and Group C (Cp), preinfusion (1 ml) and continuous infusion during ablation (1 ml/min), $n = 40$ ($n = 10$ in duration of 2, 4, 8, and 12 min each).

Temperature control mode ($n = 120$ in total, $n = 40$ in each group, and $n = 10$ in duration of 2, 4, 8, and 12 min each): Group A (At), no infusion; Group B (Bt), 1 min preinfusion only (1 ml); Group C (Ct), preinfusion (1 ml) and continuous infusion during ablation (1 ml/min).

Measurement of lesion size. The sites of ablation were sectioned along the longitudinal (both *X* and *Y*) and transverse (*Z*) axes. The maximal transverse diameter of the lesions was measured.

Magnetic resonance imaging (MRI). To assess whether a RF-induced lesion can be visualized with MRI, T1 (TR/TE = 450/12 msec) and T2 (TR/TE = 3000/90 msec) weighted spin echo images were obtained in 11 ablated lesions using a 1.5 T Magnetom Vision (Siemens, Erlangen, Germany). The size of the lesion was measured on the images with monitor-defined distance measurement function and compared with that on the tissue section.

Statistical analysis. The power output, impedance of RF delivery, temperature of the electrode–tissue interface, and lesion diameter were compared and correlated among groups with or without saline infusion. The values are expressed as means ± SD. Student's *t* test was used and a probability of <0.01 was considered significant.

This experiment complied with the current guidelines for use and care of laboratory animals of this institute.

RESULTS

General Appearance

After RF treatment, a very well-defined circular lesion with pale discoloration can be seen on the surface of the liver section (Fig. 2A). On T1 weighted MRI, in contrast to normal liver parenchyma, the RF-ablated lesion appears as a circular hyperintense area with a hypointense rim around the track of the electrode tip (Fig. 2B). On T2 weighted images, the lesion is hypointense relative to the hyperintense liver tissue. The dimension of lesion measured on MR images was conformable with that measured on the sample by gross inspection. In some liver samples, the small cave was found in the center of the lesion around the electrode tip.

Quantitative Measurement

Power control mode. The mean tip electrode temperature, impedance, and lesion size are compared among the three groups in Figs. 3a–3c. Without saline infusion (in Group Ap), the temperature of the electrode–tissue interface exceeded 100°C. Impedance rose abruptly within a mean of 3.9 ± 1.1 sec accompanied with an audible pop in the treated site, which prematurely terminated the RF application. This short duration resulted in a small mean diameter of 0.45 ± 0.1 cm in all 10 lesions which prevented the scheduled test durations of 2, 4, 8, and 12 min RF in this group.

In the preinfusion-only group (Group Bp), a similar pattern but with slightly longer duration (23.3 ± 5.3 sec) was observed, leading to a mean diameter of 1.05 ± 0.2 cm of 10 lesions. Again, the RF delivery for duration of 2, 4, 8, and 12 min could not be realized as designed.

In the group with saline preinfusion and continuous infusion during RF treatment (Group Cp), the mean temperatures of the electrode–tissue interface were 58.6 ± 17.6, 71.4 ± 18.7, 79.2 ± 13.3, and 86.1 ± 12.3°C for the duration of respectively 2, 4, 8, and 12 min of 10 lesions each. These temperatures were lower than those seen in Groups Ap and Bp ($P < 0.01$). The values of the mean impedance were 110.9 ± 30.1, 100.2 ± 24.6, 90.1 ± 18.5, and 101.5 ± 34.0 Ω for the above-mentioned four duration settings, respectively, which were lower ($P < 0.01$) than those in Groups Ap (210.5 ± 17.4 Ω) and Bp (163.8 ± 30.6 Ω). An abrupt impedance rise with an audible pop or steaming, which interrupted the procedure, occurred in 7 of 40 applications in this group, probably caused by a disruption of saline infusion. The lesion diameters in Group Cp were 2.01 ± 0.30, 2.77 ± 0.61, 4.28 ± 0.49, and 4.50 ± 0.75 cm for the duration of 2, 4, 8, and 12 min respectively and were significantly larger than those in other groups ($P < 0.01$).The maximal lesion diameter was greater than 5.5 cm (Fig. 4).

Temperature control mode. The maximal temperature of the electrode–tissue interface was set at 90°C for all four time settings of each group. The mean temperature of the electrode–tissue interface, impedance, power output, and lesion size are compared among the three groups in Figs. 5a–5d.

In the noninfusion group (Group At), the mean impedance values were 140.5 ± 20.9, 130.0 ± 20.2, 125.9 ± 21.5, and 127.7 ± 29.9 Ω for the treatment of 2, 4, 8, and 12 min, respectively. Although the initial value was high (about 50 W) within the first second, the power output progressively decreased and stayed at a relatively low level with 4.6 ± 0.5, 3.7 ± 0.8, 3.1 ± 0.7, and 2.6 ± 0.5 W, resulting in the lesion diameters at 0.84 ± 0.13, 0.92 ± 0.10, 1.04 ± 0.08, and 1.12 ± 0.14 cm respectively in the above-mentioned four groups.

In the preinfusion-only group (Group Bt), the values of mean impedance of four time settings were somewhat lower than those in Group At, allowing a slightly higher power output and larger lesion size.

In the group with infusion prior to and during RF delivery (Group Ct), the temperature of the electrode–tissue interface was lower ($P < 0.01$) than those in

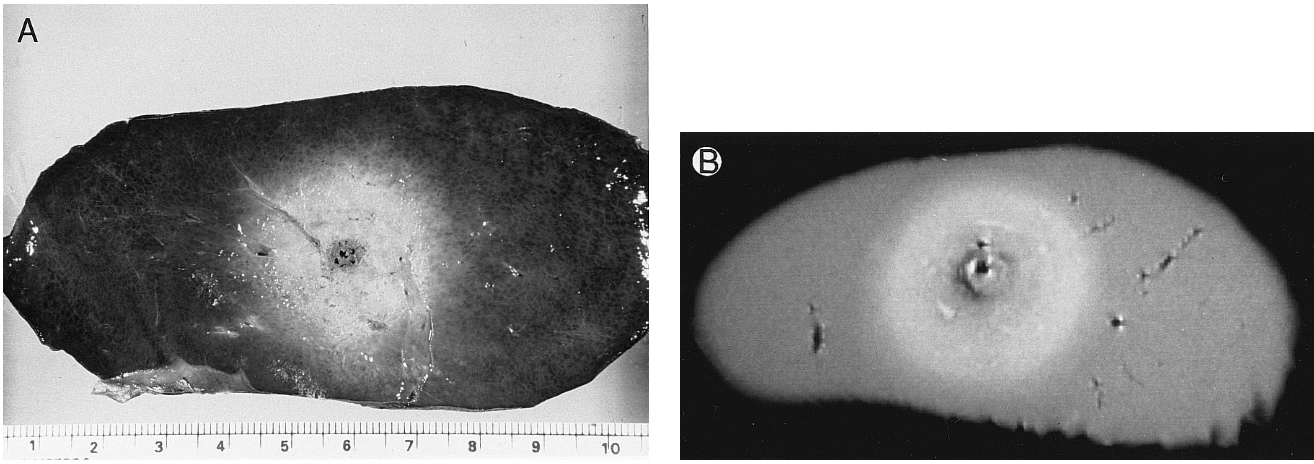

FIG. 2. The transverse section (A) of the liver with a RF ablated lesion and corresponding T1 weighted MR image (B).

Groups At and Bt during the first 2 min. The power output was more than three times higher than that in the other two groups ($P < 0.01$). The lesion diameters were 1.94 ± 0.10, 2.13 ± 0.26, 3.03 ± 0.48, and 3.55 ± 0.37 cm for the durations of 2, 4, 8, and 12 min, respectively, and were significantly larger than those in other groups ($P < 0.01$) (Fig. 6).

DISCUSSION

Surgical resection of liver malignancies of either primary hepatoma or metastatic disease is still considered as the primary choice of treatment because it can improve the survival rate of the patients [9, 10]. However, some of these patients are not candidates for open sur-

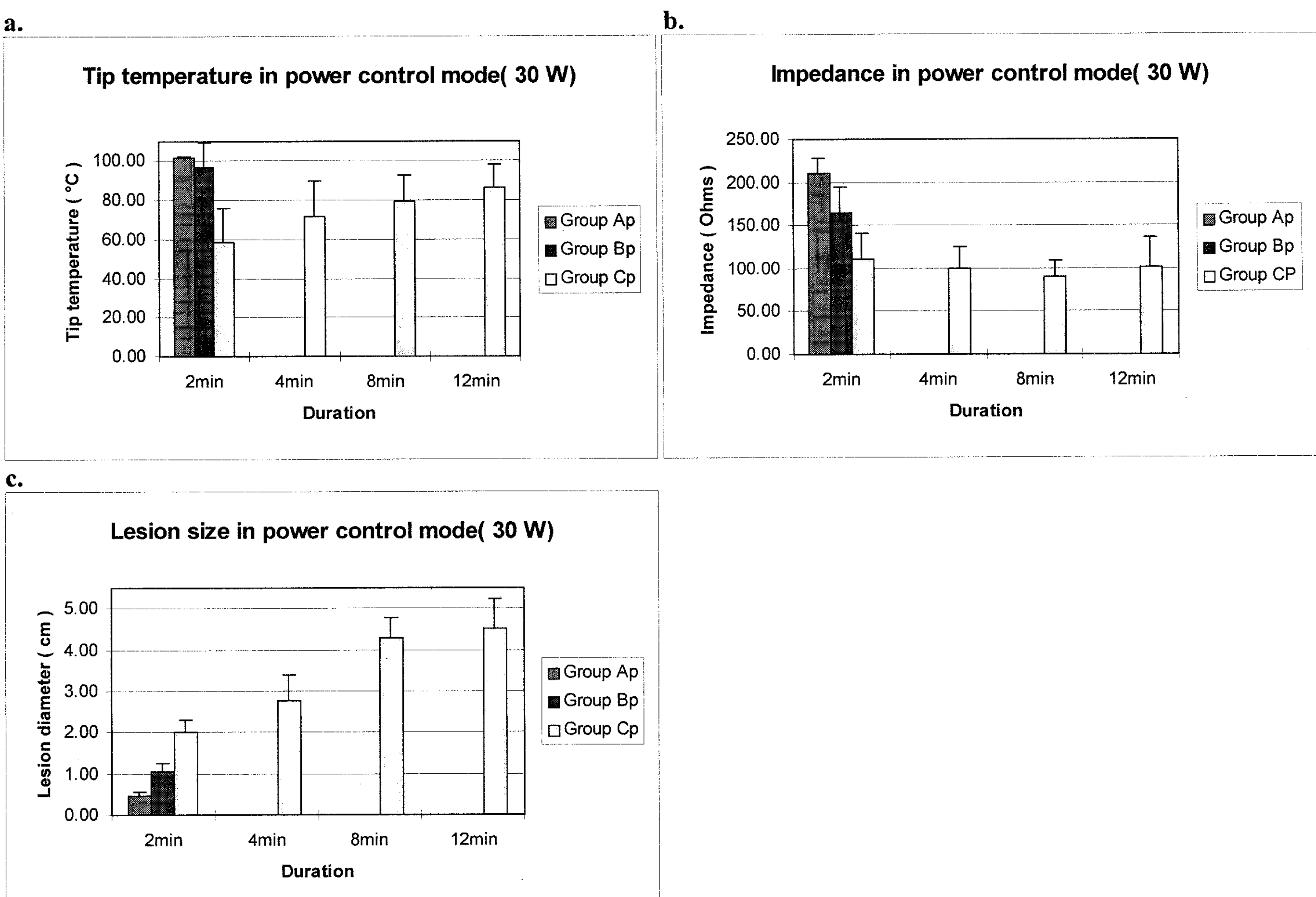

FIG. 3. Bar charts of tip temperature (a), impedance (b), and lesion size (c) in power control mode.

FIG. 4. Photograph of longitudinal section of the liver with a RF ablation lesion over 5 cm in diameter (power control mode, 30 W, 12 min, and 1 ml/min of infusion prior to and during ablation).

gery either because of multiple lesions that locate beyond a hepatic anatomic unit or because of the poor general conditions [11]. Several less invasive techniques have been developed as alternatives to surgical resection, such as intraoperative cryosurgery [12], local injection of ethanol [13], focused microwaves [14], interstitial laser therapy [15], and high focused ultrasound [16]. RF interstitial ablation has recently been introduced as another approach to treat liver tumors, although some limitations in this technique still remain to be overcome. One of them is the limited maximum lesion size, which was reported to be 2 cm or less [1, 2]. From a technical point of view, there are multiple factors that affect the size of the lesion, including tissue contact, impedance, temperature at the tissue–electrode interface, output power, duration of energy application, and the size of the electrode tip [17–22]. The most critical factor has been suggested to be the temperature at the electrode–tissue interface [23]. If the temperature of the electrode–tissue interface is above 100°C, the electric conduction will be reduced because of boiling, steaming, and tissue desiccation [18, 24, 25]. The RF energy delivery will be subsequently terminated as a result of an impedance rise, hence a limited lesion size. Several measures have been taken to prevent this phenomenon. One approach is called "temperature control mode" in which a thermocouple is installed within the electrode to monitor tip electrode temperature during the ablation procedure [18, 26]. An

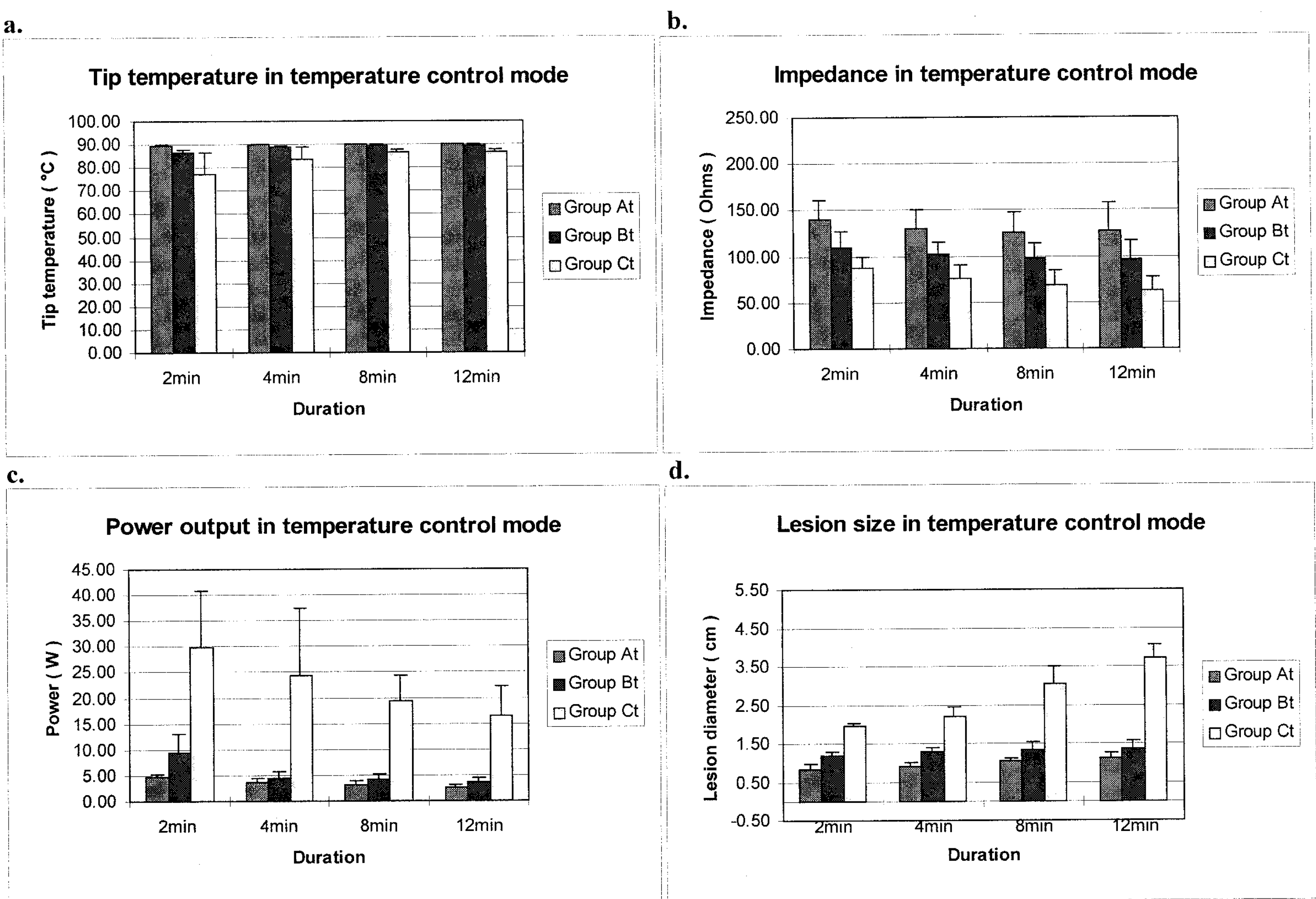

FIG. 5. Bar charts of tip temperature (a), impedance (b), power output (c), and lesion size (d) in temperature control mode.

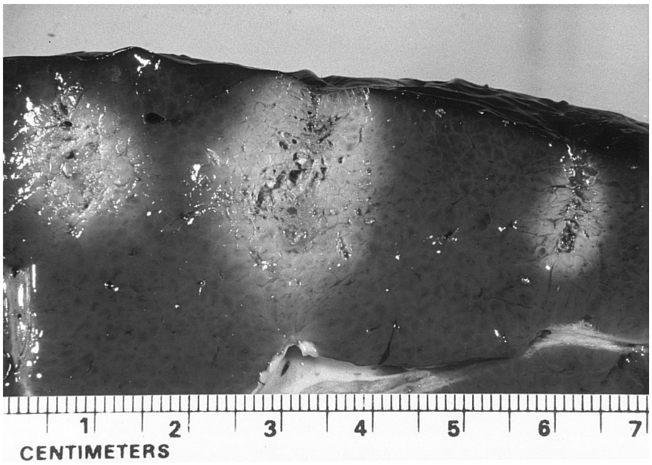

FIG. 6. Photograph of longitudinal liver section displaying the difference in lesion sizes after 2 min of RF ablation in temperature control mode: 1 ml of preinfusion only (left) and noninfusion (right) and 1 ml/min of infusion prior to and during ablation (middle).

alternative approach is to irrigate the electrode itself with cooling liquid to reduce the tip temperature [3–5]. Lorentzen and Goldberg used such a cooled needle electrode in liver tissue ablation and reported an enlarged lesion with transverse diameters of 3.7 [5] and 3.1 cm [4], respectively. However, even with this cooling mechanism, charring around the tip was still unavoidable when power output was above 50 W, leading to restrained lesion size [5]. The newest approach to solve this problem was introduced by Hoey *et al.* using the hollow screw-tip electrode to controllably produce a large lesion in the myocardium [27]. This technique was then adapted to the prostate [28, 29] and in this study to the liver. The screw-tip electrode provides greater surface area and active fixation to the tissue [6]. The longer needle track of the screw tip also reduces any possible saline reflux along the track. However, it may be more difficult to be introduced in the tissue. In practice, it can be inserted in a 7 French steerable needle sheath for guided placement. Normal saline is known to be more conductive than blood and other tissues [6, 29]. A interstitial infusion to conductive dielectric solution during RF application electrically couples RF energy to tissue and spreads RF current density away from the metal electrode tip. This promotes more uniform distribute throughout the saline which prevents overheating and high impedance at the metal electrode–tissue interface [6–8]. During the experiment in the power control mode of this study, in noninfusion and preinfusion-only groups or when infusion was insufficient (e.g., <1 ml/min), a poor energy spread and a loss of cooling effect allowed the electrode tip to overheat, causing tissue desiccation, local boiling and steaming, and increased impedance. Consequently, RF delivery was terminated prematurely resulting in limited lesion size. As shown in the groups with sufficient infusion, the tip temperature and impedance are lower than those with non- or insufficient infusion ($P < 0.01$) in both power and temperature control modes.

The lesion size is the most critical determinant of successful ablation. The present screw-tip-mediated RF technique with saline infusion proves to increase lesion size, e.g., the maximal lesion diameter was greater than 5.5 cm in the power control mode (Group Cp). Similar to the previous results using a "dry electrode" in myocardium [18, 26], the procedure of the temperature control mode in the present study was more practical and convenient than that of the power control mode by presenting a continuous RF delivery and improved efficiency. Furthermore, the temperature control mode in combination with saline infusion as applied here could be even more efficacious than the "dry tip" approach owing to improved cooling and conducting effects. The maximum allowable power output and eventually the lesion size could also be increased. In comparison with the groups without infusion or with insufficient infusion but higher temperature of the electrode–tissue interface, larger lesions were produced in groups with sufficient infusion but lower temperature. These observations are supportive to the theory advocated by Nakagawa *et al.* that resistive heating is more important than conductive heating in RF therapy [3].

The averaged lesion sizes of 3.7 and 4.5 cm caused by a 12-min RF delivery in temperature and power control modes might be sufficient for ablation of small metastatic and primary liver tumors. The therapy can be conducted either percutaneously or intraoperatively as alternatives to surgical resection when appropriate indications are met. However, liver contains a complex vessel system with flowing blood and bile. All these structures could be vulnerable to the RF injury due to current and/or heat dissipation. Therefore, precise targeting of the tumor is of importance. When MR-compatible materials become available, MR imaging can be used not only to guide the RF ablation procedure but also to monitor the effects of the therapy as suggested by our preliminary imaging data. Furthermore, noninvasive techniques of temperature mapping by using water proton chemical shift [30] and MR diffusion imaging [31] have been developed, which can be applied to detect local temperature change during RF ablation. A possible drawback of saline infusion into the tumor is that it may increase the intratumoral pressure and therefore may increase the chance of local and remote migration of tumor cell and cause metastasis. Since current experiment was performed in excised swine liver which is largely different from *in vivo* conditions, the above-mentioned problems should be further investigated in living animals.

CONCLUSIONS

RF ablation in combination with the screw-tip hollow electrode and saline infusion allows for necrotic development of suitable size for liver tumor ablation. The temperature control mode appears superior to the power control mode for delivery of RF current. A RF-ablated liver lesion can be visualized with MRI.

REFERENCES

1. Rossi, S., Fornari, F., and Buscarini, L. Percutaneous ultrasound-guided radiofrequency electrocautery for the treatment of small hepatocellular carcinoma. *J. Intervent. Radiol.* **8:** 97, 1993.
2. Buscarini, L., Rossi, S., Fornar, F., Stasi, M. D., and Buscarini, E. Laparoscopic ablation of liver adenoma by radiofrequency electrocauthery. *Gastrointest. Endosc.* **41:** 68, 1995.
3. Nakagawa, H., Yamanashi, W. S., Pitha, J. V., Arruda, M., Wang, X., Ohtomo, K., Beckman, K. J., McClelland, J. H., Lazzara, R., and Jackman, W. M. Comparison of in vivo tissue temperature profile and lesion geometry for radiofrequency ablation with a saline-irrigated electrode versus temperature control in a canine thigh muscle preparation. *Circulation* **91:** 2264, 1995.
4. Goldberg, S. N., Gazelle, G. S., Solbiati, L., Rittman, W. J., and Muelle, P. R. Radiofrequency tissue ablation: Increased lesion diameter with a perfusion electrode. *Acad. Radiol.* **3:** 636, 1996.
5. Lorentzen, T. A cooled needle electrode for radiofrequency tissue ablation: Thermodynamic aspects of improved performance compared with conventional needle design. *Acad. Radiol.* **3:** 556, 1996.
6. Hoey, M. F., Mulier, P. M., and Shake, J. G. Intramural ablation using radiofrequency energy via screw-tip catheter and saline electrode. *PACE* **18**(II): 917, 1995.
7. Mittleman, R. S., Huang, S. K., de-Guzman, W. T., Cuenoud, H., Wagshal, A. B., and Pires, L. A. Use of saline infusion electrode catheter for improved energy delivery and increased lesion size in radiofrequency catheter ablation. *PACE* **18:** 1022, 1995.
8. Goldberg, S. N., Gazelle, G. S., Solbiati, L., Monti, F., Livraghi, T., and Rittman, W. J. Saline-enhanced RF tissue ablation: Demonstration of efficacy and optimization of parameters. *Radiology* **197**(P):140, 1995.
9. Gallinger, S., and Langer, B. Primary and secondary hepatic malignancies. *Curr. Opin. Gen. Surg.* **1:** 257, 1993.
10. Wade, T. P., Virgo, K. S., Li, M. J., Callander, P. W., Longo, W. E., and Johnson, F. E. Outcomes after detection of metastatic carcinoma of the colon and rectum in a national hospital system. *J. Am. Coll. Surg.* **182:** 353, 1996.
11. Fuster, J., Garcia-Valdecasas, J. C., Grande, L., Tabet, J., Bruix, J., and Anglada, T. Hepatocellular carcinoma and cirrhosis: Results of surgical treatment in a European series. *Ann. Surg.* **223:** 287, 1996.
12. Poik, W., Fong, Y., Karpeh, M., and Blumgart, L. H. A technique for the use of cryosurgery to assist hepatic resection. *J. Am. Coll. Surg.* **180:** 171, 1995.
13. Livraghi, T., Lazzaroni, S., Meloni, F., Torzilli, G., and Vettori, C. Intralesional ethanol in the treatment of unresectable liver cancer. *World J. Surg.* **19:** 801, 1995.
14. Murakami, R., Yoshimatsu, S., Yamashita, Y., Matsukawa, T., Takahashi, M., and Sagara, K. Treatment of hepatocellular carcinoma: Value of percutaneous microwave coagulation. *AJR* **164:** 1159, 1995.
15. Hiele, M., Penninckx, F., Gevers, A. M., Van Eyken, P., Geboes, K., Ni, Y., Marchal, G., Van Trappen, G., Fevery, J., Frank, F., Hessel, S., and Rutgeerts, P. Interstitial thermotherapy for liver tumours: Studies of different fibres and radiation characteristics. *Lasers Med. Sci.* **8:** 121, 1993.
16. Yang, R., Kopecky, K. K., Rescorla, F. J., Galliani, C. A., Wu, E. X., and Grosfeld, J. L. Sonographic and computed tomography characteristics of liver ablation lesion induced by high-intensity focussed ultrasound. *Invest. Radiol.* **28:** 796, 1993.
17. Strickberger, S. A., Ravi, S., Daoud, E., Niebauer, M., Man, K. C., and Morady, F. Relation between impedance and temperature of accessory pathways. *Am. Heart J.***130:** 1026, 1995.
18. Haines, D. E. The biophysics of radiofrequency catheter ablation in the heart: The importance of temperature monitoring. *PACE* **16:** 586, 1993.
19. Calkins, H., Kim, Y-N., Schmaltz, S., Sousa, J., el-Atassi, R., Leon, R., Kadish, A., Langberg, J. J., and Morady, F. Electrogram criteria for identification of appropriate target sites for RF catheter ablation of accessory aterioventricular connections. *Circulation* **85:** 565, 1992.
20. Ring, M. E., Huang, S. K., Gorman, G., and Graham, A. R. Determinants of impedance rise during catheter ablation of bovine myocardium with radiofrequency energy. *PACE* **12:** 1502, 1989.
21. Goldberg, S. N., Gazelle, G. S., Halpern, E. F., Rittman, W. J., Mueller, P. R., and Rosenthal, D. L. Radiofrequency tissue ablation: Importance of local temperature along the electrode tip exposure in determining lesion shape and size. *Acad. Radiol.* **3:** 212, 1996.
22. Huang, S. K. Advances in applications of RF current to catheter ablation therapy. *PACE* **14:** 28, 1991.
23. Haines, D. E., and Verow, A. F. Observations on electrode–tissue interface temperature and effect on electrical impedance during radiofrequency ablation of ventricular myocardium. *Circulation* **82:** 1034, 1990.
24. Jackman, W. M., Wang, X. Z., Friday, K. J., Roman, C. A., Moulton, K. P., Beckman, K. J., McClellond, J. H., Twidale, N., Hazlitt, H. A., and Prior, M. I. Catheter ablation of accessory atrioventricular pathways (Wolff–Parkinson–White syndrome) by RF current. *N. Engl. J. Med.* **324:** 1605, 1991.
25. Saxon, L. A., Stevenson, W. G., Fonarow, G. C., Middlekauff, H. R., Yeatman, L. A., Sherman, C. T., and Child, J. S. Transesophageal echocardiography during radiofrequency catheter ablation of ventricular tachycardia. *Am. J. Cardiol.* **72:** 658, 1993.
26. Hoffmann, E., Mattke, S., Dorwarth, U., Muller, D., Haberl, R., and Steinbeck, G. Temperature-controlled radiofrequency catheter ablation of AV conduction: First clinical experience. *Eur. Heart J.* **14:** 57, 1993.
27. Hoey, M. F., Mulier, P. M., and Shake, J. G. Intramural ablation using screw-tip catheter and saline electrode produces predictable lesion sizes. *Circulation* **92**(Suppl.): 3818 , 1995.
28. Hoey, M. F., Leveillee, R. J., Hulbert, J. C., and Mulier, P. M. A new method to couple radiofrequency energy to prostate tissue using electrolyte solution to enhance ablation. *J. Endourol.* **9:** S125, 1995.
29. Leveillee, R. J., Hoey, M. F., Hulbert, J. H., Mulier, P., Lee, D., and Jessrun, J. Enhanced radiofrequency ablation of canine prostate utilizing a liquid conductor: The virtual electrode. *J. Endourol.* **10:** 5, 1996.
30. Ishihara, Y., Calderon, A., Watanabe, H., Okamoto, K., Suzuki, Y., Kuroda, K., and Suzuki, Y. A precise and fast temperature mapping using water proton chemical shift. *Magn. Reson. Med.* **34:** 814, 1995.
31. Samulski, T. V., MacFall, J., Zhang, Y., Grant, W., and Charles, C. Non-invasive thermometry using magnetic resonance diffusion imaging: Potential for application in hyperthermic oncology. *Int. J. Hyperthermia* **8:** 819, 1992.