

Radiofrequency Ablation with Epinephrine Injection: In Vivo Study in Normal Pig Livers¹

Hyoung Jung Kim, M.D., Dong Hoo Lee, M.D., Joo Won Lim, M.D.,
Young Tae Ko, M.D., Youn Wha Kim, M.D.², Bong Keun Choi, M.D.³

Purpose: We wanted to evaluate whether epinephrine injection prior to radiofrequency (RF) ablation can increase the extent of thermally mediated coagulation in vivo normal pig liver tissue.

Materials and Methods: Eighteen RF ablation zones were created in six pigs using a 17-gauge internally cooled electrode under ultrasound guidance. Three RF ablation zones were created in each pig under three conditions: RF ablation alone, RF ablation after the injection of 3 mL of normal saline, and RF ablation after the injection of 3 mL of epinephrine (1:10,000 solution). After the RF ablation, we measured the short and long diameters of the white zones in the gross specimens.

Results: Three of the RF ablations were technically unsuccessful; therefore, measurement of white zone was finally done in 15 RF ablation zones. The mean short and long diameters of the white zone of the RF ablation after epinephrine injection ($17.2 \text{ mm} \pm 1.8$ and $20.8 \text{ mm} \pm 3.7$, respectively) were larger than those of RF ablation only ($10 \text{ mm} \pm 1.2$ and $12.2 \text{ mm} \pm 1.1$, respectively) and RF ablation after normal saline injection ($12.8 \text{ mm} \pm 1.5$ and $15.6 \text{ mm} \pm 2.5$, respectively) ($p < .05$).

Conclusion: RF ablation with epinephrine injection can increase the diameter of the RF ablation zone in normal pig liver tissue.

Index words : Animals

Experimental study

Liver, interventional procedures

Radiofrequency (RF) ablation

Previous studies have demonstrated that radiofrequency (RF) ablation is a safe and effective treatment for focal metastatic and primary liver tumors (1 - 3). However, despite the technological advances and electrode modifications that have effectively increased the

delivery of RF energy and tissue heating, several recent studies have reported inadequate treatment as a clinical problem for malignant liver tumors greater than 3 cm in diameter (4 - 6). It has been suggested that this inadequate treatment was due to gross insufficient ablation of the tumors and the failure to create an adequate tumor free-margin (7). Therefore, the focus of recent studies has been on creating greater volumes of coagulation necrosis with performing just one RF ablation procedure.

The "bio-heat" equation that governs RF-induced heat

¹Departments of Diagnostic Radiology, ²Pathology and ³Preventive Medicine, Kyung Hee University Medical Center, Seoul 130-702, Korea
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Address reprint requests to : Hyoung Jung Kim, M.D., Department of Diagnostic Radiology, Kyung Hee University Medical Center, 1, Hoegi-dong, Dongdaemun-gu, Seoul 130-702, Korea
Tel. 82-2-958-8209 Fax. 82-2-968-0787 E-mail: radhjkim@khu.ac.kr

transfer through tissue has been previously described by Pennes (8) and this equation was simplified to a first approximation by Goldberg et al. (9) as "coagulation necrosis = energy deposited X local tissue interaction - heat loss". Energy deposition can be increased by modifying the RF electrode, such as making an umbrella RF electrode with multiple hooks (10) or by making an internally cooled electrode (4), and also by modifying the electrical conductivity via saline injection (11, 12). However, performing high-current ablation may increase the risk of grounding-pad burns, and the maximum generator output also has to be increased (13). Reducing the hepatic blood flow may be another option to increase the coagulation necrosis. There are several ways to reduce the hepatic blood flow. One is to occlude the hepatic artery and portal vein by using interventional procedures (14). The other way is pharmacologic modulation with using halothane (15); however, problems exist for applying these methods during ultrasound guided RF ablation because the former requires the assistance of interventional radiologists and the latter requires general anesthesia.

We hypothesized that RF ablation with percutaneous transhepatic epinephrine injection might increase the extent of ablation as epinephrine can be expected to induce vasoconstriction in the hepatic vessels and also increase the electrical conductivity because it is diluted with normal saline (11, 12). Furthermore, epinephrine injection and RF ablation can be performed at the same time under ultrasound guidance. The purpose of our study is to determine whether epinephrine injection prior to RF ablation can increase the extent of thermally mediated coagulation necrosis in normal pig liver tissue.

Materials and Methods

Animal Preparation

We obtained the approval of the institutional committee on research animal care before this study was initiated. Eight Yorkshire pigs (all were males, weight range: 10.0 - 13.5 kg) were used for the experiments. Six pigs were used for the RF ablations and two were used for demonstrating the hemodynamic change via percutaneous epinephrine injection into the liver.

All the pigs were anesthetized using an intramuscular injection of 35 mg/kg ketamine hydrochloride (Ketamine ; Yuhan, Seoul, Korea) and 5 mg/kg xylazine (Rompun ; Byer Korea, Ansan, Korea). A 20-gauge intravenous catheter was inserted into the ear vein of the

pig and the anesthesia was maintained with an intravenous injection of 15 mg/kg of ketamine hydrochloride every 60 minutes. Booster intravenous injections of up to one-half of the initial dose were administered as needed. For the six pigs used for RF ablations, the pig's epigastrium and back were shaved and sterilized, and one foil grounding pad (9.8 × 21.5 cm) was affixed to the lower back.

RF Ablation Protocol Design and the RF Ablation Setting

All RF ablations were performed by one radiologist. A total of 18 RF ablation procedures in six pigs were classified into three groups: group A was the standard RF ablation alone, group B was the RF ablation with 3 mL of 0.9% NaCl injection and group C was RF ablation with 3 mL of epinephrine (1:10,000 solution) injection. Three RF ablations (standard RF ablation alone, RF ablation with 0.9% NaCl injection and RF ablation with epinephrine injection) were done in each pig. For preventing any cardiovascular effect via the epinephrine injection, the RF ablations were performed following the sequence of RF ablations alone, then RF ablation with normal saline injection and finally RF ablation with epinephrine injection. A fifteen minute interval was employed between completion of RF ablation alone and the normal saline injection, and an additional 15 minute interval was also employed between completion of RF ablation with normal saline and that with the epinephrine injection. RF ablation started immediately after saline or epinephrine injection.

To the best of our knowledge, there has been only one report on percutaneous epinephrine injection into the liver (16). Leung et al. used epinephrine at up to 1 mg per treatment; however, they used cisplatin-epinephrine gel instead of a solution (16). In clinical practice, epinephrine has been commonly used to achieve control of bleeding peptic ulcer (17, 18). Epinephrine (1:10,000 solution) can be used up to 13 - 20 mL in the adult patient (18). The minimum weight of the pigs in this experiment was 10 kg, so 3 mL of diluted epinephrine (1:10,000) was injected into the target area. Although previous studies have shown that the concentration of NaCl solution that maximizes electrical conductivity during RF ablation is 38.5% (11), epinephrine is usually diluted with 0.9% NaCl solution when it is used to control bleeding peptic ulcer (17, 18). Thus, we used 3 mL of epinephrine (1:10,000 solution), diluted with 0.9% NaCl solution.

A 480-kHz RF generator (series CC-1; Radionics,

Burlington, MA., U.S.A.) capable of producing 200W of power was used for creating the RF ablation zones. An internally cooled, 17-gauge electrode (Radionics; Burlington, MA., U.S.A.) with a 1-cm active tip was placed percutaneously in the target area of the liver under ultrasound guidance. The needle tip was placed at least 2 cm away from the liver capsule, 2 cm away from the large vessels (vessels more than 3 mm in diameter), and 3 cm away from the previously created RF ablation lesion (19). After placing the electrode, a 21-gauge PEIT (Percutaneous Ethanol Injection therapy) needle (Hakko; Hanishina, Japan) was inserted with using the tandem technique for which the needle is closely attached to the electrode. The distal tip of the needle was placed 3mm posterior to the tip of electrode. Prior to applying RF energy, 3 mL of epinephrine or 0.9% NaCl solution was slowly injected (for about 30 seconds) manually in small boluses (0.1 - 0.2 mL) under ultrasound guidance.

RF was applied for 12 minutes at an initial generator output of 2,000 mA (200W). When an increase of impedance was observed, the current output was automatically reduced in accordance with a previously designed pulsing algorithm that optimizes energy deposition and tissue coagulation (20). The parameters of RF ablation, such as tissue impedance and current, were monitored by the generator during the RF ablation procedure, and they were recorded at 60-second intervals for the duration of the RF application (11).

CT Examination

The CT examinations of the six pigs were performed with using MDCT (multi-detector CT) (LightSpeed Pro; GE Medical Systems, Milwaukee, Wisconsin) immediately after the ablation procedures. The MDCT parameters were as follows: a detector configuration of 1.25 mm \times 16, a gantry rotation speed of 0.5 second and a table feed speed of 20 mm per gantry rotation. For all the pigs, 40 mL of iopromide (Ultravist 370; Schering, Berlin, Germany) was injected through a 20-gauge intravenous catheter that was inserted into an ear vein with a flow rate of 2 mL/sec by using a mechanical injector. The post-contrast CT scans were acquired 15, 40 and 90 seconds after contrast administration. Continuous 5-mm-thick sections and 5-mm intervals were used for the PACS (picture archiving and communicating system) (PiView, Infinitt, Seoul, Korea).

Two radiologists interpreted the dynamic CT images of the six pigs and they reached a consensus in each

case. Each RF ablation zone was evaluated in terms of its location, its relationship with the large vessels and the presence of complication such as hemorrhage or bowel injury.

Measurement of the Ablation Zones and the Pathologic Review

The six pigs were sacrificed with an overdose injection of ketamine and xylazine on the day of the procedures. For the gross examination, the two radiologists measured the short and long diameters (perpendicular to the electrode axis) of the white zone and the red zone in each pathologic specimen with using a caliper, and then they reached a consensus (20, 21). The areas of the white zone and red zone were defined as $\frac{\pi \times \text{long diameter}^2}{4} - \frac{\pi \times \text{short diameter}^2}{4}$. The shape of the RF ablation zone was also analyzed and expressed as the ratio between the long and short diameters (22). All the RF ablation zones were then fixed in 10% formalin for routine histologic processing, and the samples were finally processed with paraffin sectioning and hematoxylin-eosin (HE) staining for the light microscopic examination. The tissues from all the RF ablation zones were analyzed for their histologic appearance and their demarcation from the surrounding viable tissue. A pathologist and a radiologist evaluated the microscopic findings of each RF ablation zone and a consensus was then reached.

Demonstration of the Hemodynamic Change by Percutaneous Epinephrine Injection into the Liver

Two pigs were used in order to demonstrate the hemodynamic change via percutaneous epinephrine injection into the liver. For one pig, a dynamic CT examination was performed after both injecting percutaneous epinephrine (3 mL, 1:10,000 solution) into right side of the liver and injecting saline (3 mL, 0.9%) into the left side of the liver, without performing RF ablation, with using a same CT protocol as was described above. For the other pig, hepatic arteriography was obtained before and after both percutaneous epinephrine injection (3 mL, 1:10,000 solution) into the right side of the liver and the saline injection (3 mL, 0.9%), without RF ablation, into left side of the liver. For performing the hepatic arteriography, the right femoral artery was punctured using the Seldinger technique, and a 5F cobra catheter (Cook; Bloomington, U.S.A.) was advanced to the celiac trunk. There was a short delay (about 1 minute) between completion of the epinephrine and saline injection.

tions, and the dynamic CT and hepatic arteriography.

Two radiologists evaluated the dynamic CT and hepatic arteriography and they reached a consensus. The presence of an attenuation difference after the epinephrine injection and saline injection without RF ablation was evaluated on the dynamic CT scans. The hepatic arteriography was also evaluated for the presence of spasm or narrowing of the hepatic artery after the epinephrine or saline injection.

Statistical Evaluation

SPSS 10.0 computer software (SPSS Inc., Chicago, Ill., U.S.A.) was used for all the statistical analysis. One-way analysis of variance using the Tukey test was performed to compare the findings obtained with the epinephrine injection and with those obtained without the epinephrine injection. For all the statistical analysis, *p* values of less than 0.05 were considered statistically significant.

Results

General Aspect

None of the pigs died during the anesthesia or RF ablation procedures. There was one pig that suffered with cardiopulmonary complications associated with the anesthesia, and this pig recovered after cardiopulmonary resuscitation. Three RF ablation zones were excluded from the analysis because they were identified as technically unsuccessful on the CT and autopsy find-

ings. Two of the RF ablation zones included a large branch of the portal vein: one was created with RF ablation after injection of normal saline and one was created with RF ablation after epinephrine injection. The remaining RF ablation zone that was created by RF ablation only was made adjacent to the hepatic surface and this zone was associated with localized perihepatic hematoma. Finally, 15 RF ablation zones were included in the analysis: five in group A, five in group B and five in group C.

RF Ablation Parameters

The mean tissue impedance in groups A, B, and C were 125.2 ± 9.5 , 119.4 ± 11.4 and 107.9 ± 16.3 , respectively (Table 1). The mean tissue impedance of group C was the lowest among the three groups; however, the difference in the mean tissue impedance value for each group was statistically insignificant (*p* > 0.05). The mean current in groups A, B and C were 566.2 ± 29.6 mA, 618.2 ± 23.5 mA and 638.0 ± 48.2 mA, respectively. The mean current value of group C was the highest among the three groups and the difference in the mean current value between groups A and C was statistically significant (*p* < 0.05).

Measurement of the Ablation Zones and the Microscopic Findings

The long diameters of the white zones in groups A, B and C were 12.2 ± 1.1 mm, 15.6 ± 2.5 mm and $20.8 \pm$

Table 1. The Effect of Epinephrine Injection on the Tissue Impedance and Current in Normal Pig Liver

	RF Ablation only	RF Ablation with Saline Injection	RF Ablation with Epinephrine Injection	<i>p</i> value
Mean Tissue Impedance ()	125.2 ± 9.5	119.4 ± 11.4	107.9 ± 16.3	>0.05
Mean Current (mA)	566.2 ± 29.6	618.2 ± 23.5	638.0 ± 48.2	<0.05*

Data are means \pm SDs. Analyses of variance were used to compare the mean tissue impedance and mean current.

*Differences in mean current between group A and group C.

Table 2. The Effect of Epinephrine Injection on the Diameters and Areas of the White Zone and Red Zone in Normal Pig Liver

		RF Ablation only	RF Ablation with Saline Injection	RF Ablation with Epinephrine Injection	<i>p</i> value
White Zone	Long Diameter (mm)	12.2 ± 1.1	15.6 ± 2.5	20.8 ± 3.7	<0.05*
	Short Diameter (mm)	10.0 ± 1.2	12.8 ± 1.5	17.2 ± 1.8	<0.05 [†]
	Area (mm ²)	96.1 ± 16.1	158.3 ± 41.2	285.0 ± 78.8	<0.05*
Red Zone	Long Diameter (mm)	15.2 ± 0.8	18.8 ± 2.5	23.8 ± 3.7	<0.05*
	Short Diameter (mm)	12.8 ± 0.4	16.0 ± 2.2	20.8 ± 1.6	<0.05 [†]
	Area (mm ²)	152.6 ± 7.3	237.5 ± 53.1	391.9 ± 83.6	<0.05*

Data are means \pm SDs. Analyses of variance were used to compare the long and short diameters of white and red zones.

*Differences in diameters between group A and C, and group B and C.

[†] Differences in diameter of all the groups.

3.7 mm, respectively, (Table 2). The short diameters of the white zones in groups A, B and C were 10.0 ± 1.2 mm, 12.8 ± 1.5 mm and 17.2 ± 1.8 mm, respectively (Fig. 1 - 3). The differences between the long and short diameters of the white zones in group C and those of the other groups were statistically significant ($p < 0.05$). The long diameters of the white zones in groups A and B showed no statistical significance ($p > 0.05$). The long diameters of the red zones in groups A, B and C were 15.2 ± 0.8 mm, 18.8 ± 2.5 mm and 23.8 ± 3.7 mm, respectively. The short diameters of the red zones in groups A, B and C were 12.8 ± 0.4 mm, 16.0 ± 2.2 mm and 20.8 ± 1.6 mm, respectively. The differences be-

tween the long and short diameters of the red zones in group C and those of the other groups were statistically significant ($p < 0.05$). The long diameters of the red zones in groups A and B didn't show statistical significance ($p > 0.05$). The area of the white zones in groups A, B and C were 96.1 ± 16.1 mm², 158.3 ± 41.2 mm² and 285.0 ± 78.8 mm², respectively. The area of the red zones in groups A, B and C were 152.6 ± 7.3 mm², 237.5 ± 53.1 mm² and 391.9 ± 83.6 mm², respectively. The differences between the areas of the white and red zones in group C and those of the other groups were statistically significant ($p < 0.05$). The area of white and red zones in groups A and B didn't show statistical sig-

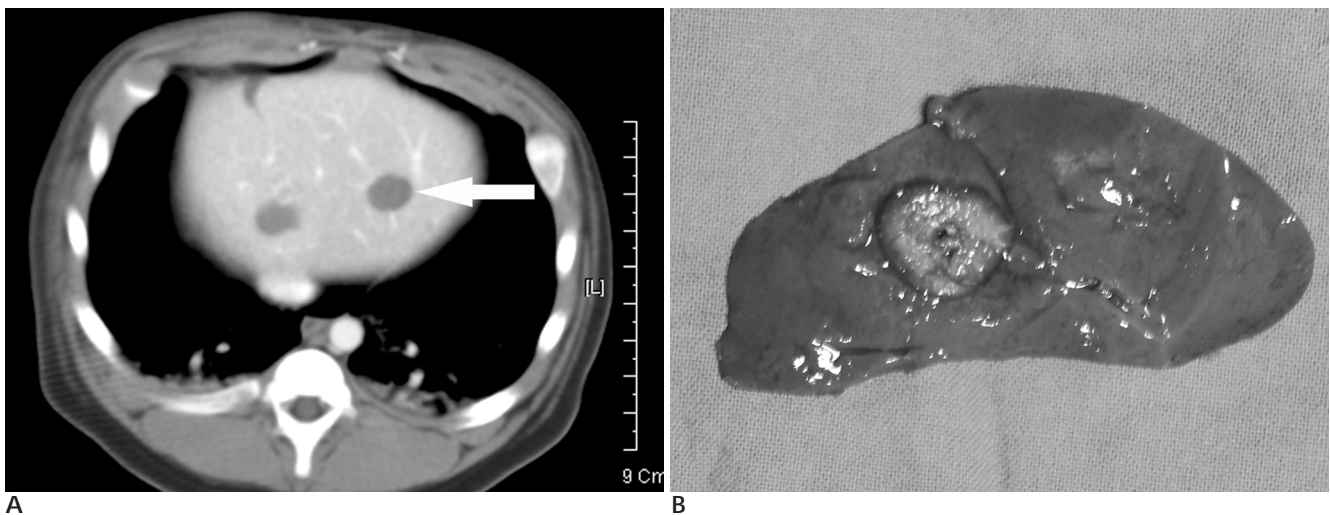


Fig. 1. RF ablation without use of normal saline or epinephrine.
A. On CT examination, a round perfusion defect (arrow) is noted.
B. The gross specimen shows a round white zone (10 × 12 mm) surrounded by a peripheral hemorrhagic rim

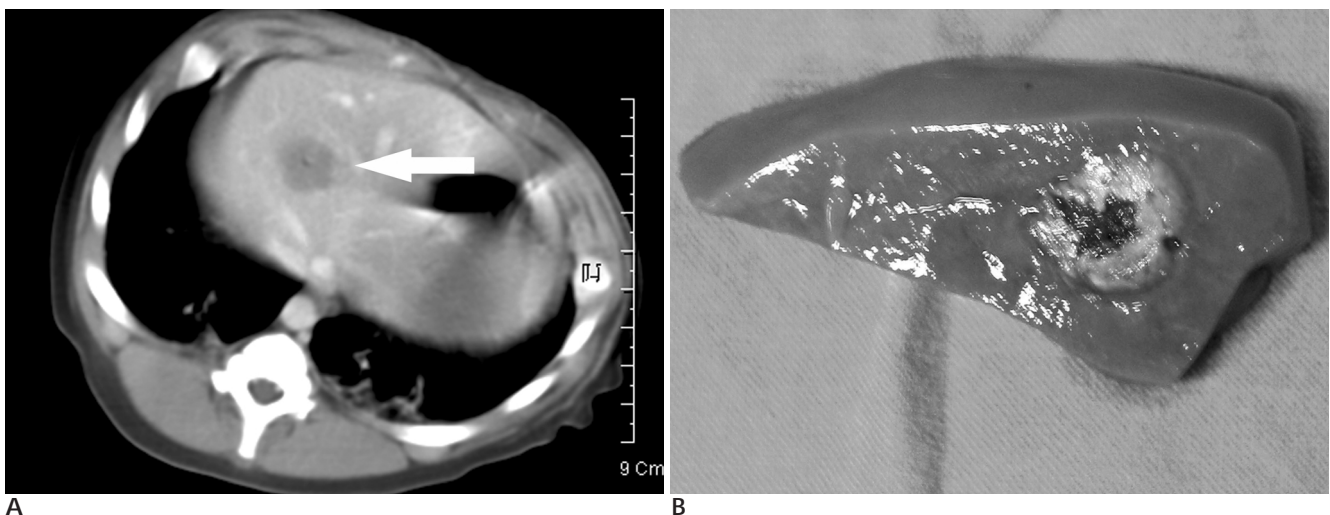


Fig. 2. RF ablation with normal saline injection.
A. On the CT examination, a round perfusion defect (arrow), containing small gas bubbles is noted.
B. The gross specimen shows a round white zone (13 × 15 mm) surrounded by a peripheral hemorrhagic rim

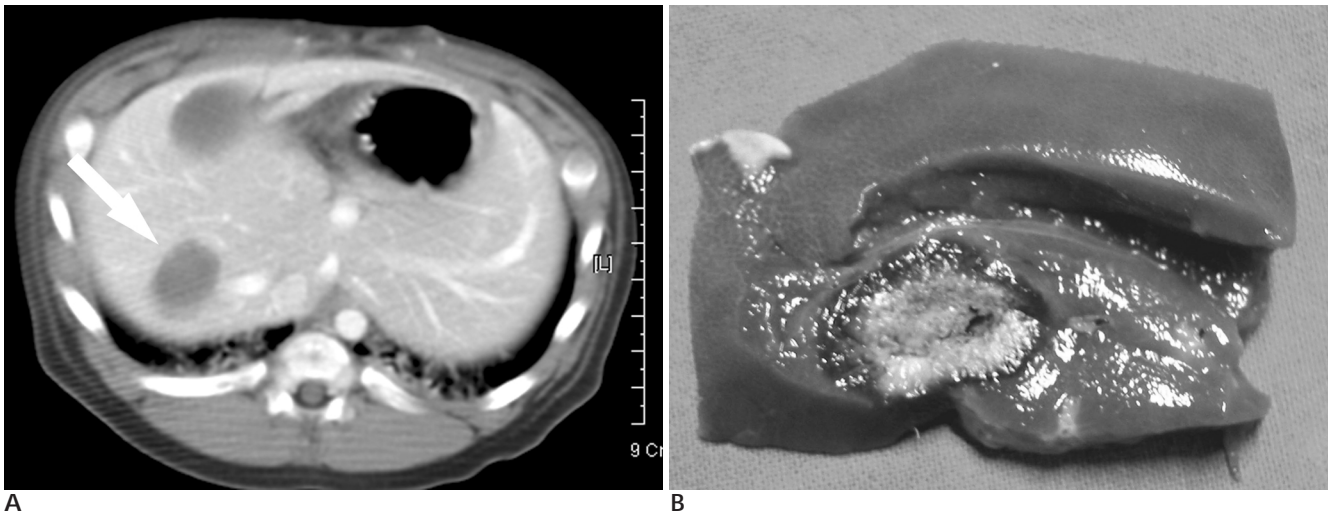


Fig. 3. RF ablation with epinephrine injection.

A. On CT examination, an ovoid perfusion defect (arrow) is noted.

B. The gross specimen shows an ovoid white zone (19 × 16 mm) surrounded by a peripheral hemorrhagic rim

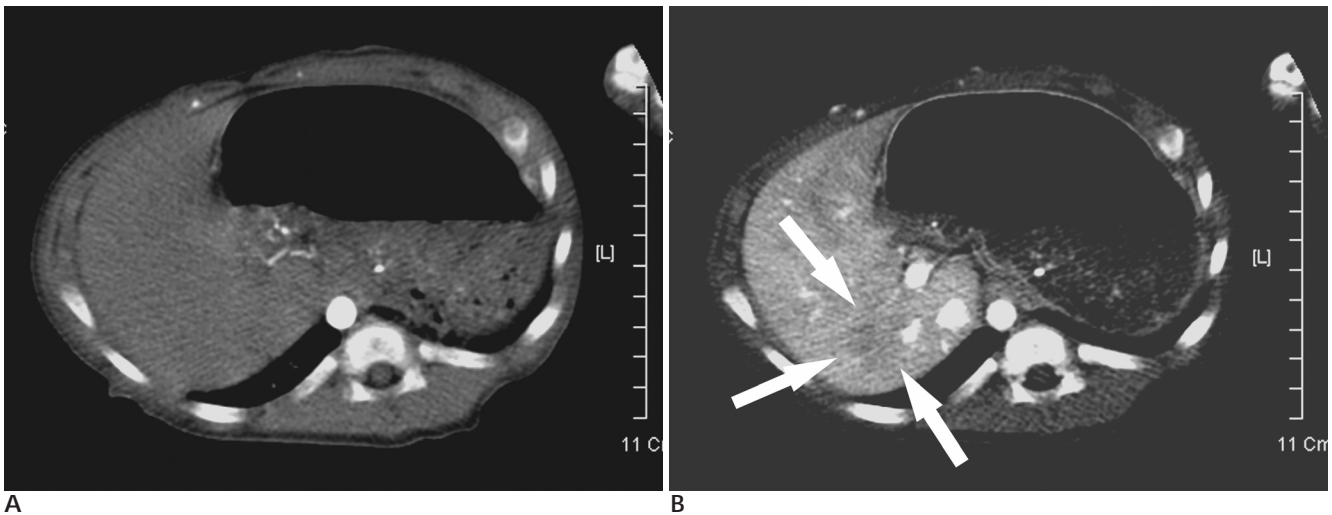


Fig. 4. Dynamic contrast-enhanced CT after epinephrine injection without RF ablation.

A. The 15-second delay image shows no specific abnormality.

B. The 40-second delay image shows ill-defined low density lesion (arrows).

C. An ill-defined low density lesion seen on (B) is not noted on the 90-second delay image



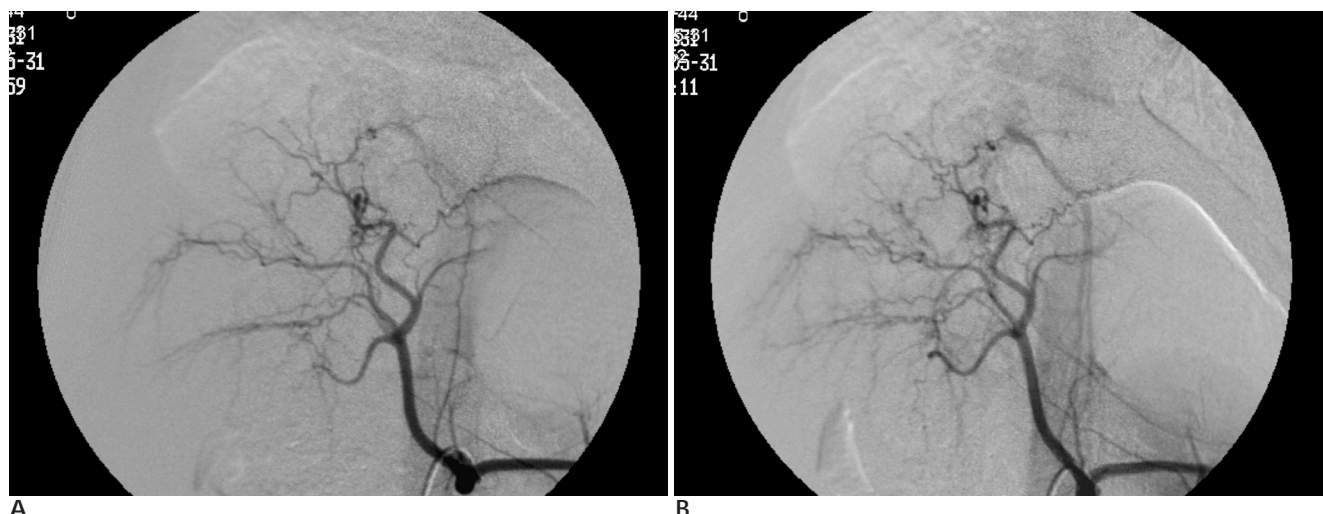


Fig. 5. Hepatic arteriography before (A) and after (B) epinephrine injection without RF ablation. Although epinephrine was injected in the right lobe of the liver after acquisition of the image (A), there is no evidence of constriction of the hepatic artery on the image (B)

nificance ($p > 0.05$).

The mean ratios between the long and short diameters of the white zone and the red zone were in the range of 1.14 and 1.22, and they didn't show any statistically significant difference among the three groups ($p > 0.05$).

Histopathologic examination of the RF ablation lesions revealed a central charred zone with altered cellular morphology that consisted of degenerated and shrunken hepatocytes, and this was characterized as being due to a heat effect. This central charred zone was surrounded by sinusoidal congestion and a hemorrhagic zone. There was a sharp cut-off between the ablation lesions and the areas of normal liver. The above microscopic findings were similar in groups A, B and C.

Hemodynamic Change by Percutaneous Epinephrine Injection into the Liver

The dynamic CT after epinephrine and saline injection without RF ablation showed an ill-defined low density lesion at the epinephrine injection site on the 40-second delay image (Fig. 4). This ill-defined low density lesion was not noted on the 15-second delay images or on the 90-second delay images. Any attenuation difference was not noted at the saline injection site. The hepatic arteriography that was done after epinephrine and saline injection without RF ablation showed no evidence of vascular narrowing or spasm at both the epinephrine and saline injection sites (Fig. 5).

Discussion

Our study showed that RF ablation with epinephrine

injection can induce a larger ablation zone than can RF ablation with saline injection or RF ablation only in normal pig liver tissue. Direct percutaneous injection of epinephrine into the liver tissue may have two effects on RF ablation. First, it might decrease the heat loss by reducing the hepatic blood flow at the target site. Second, the epinephrine injection might increase the deposition of heat because the epinephrine was diluted with normal saline. Two mechanisms have been proposed to account for the improved tissue heating and the increased RF ablation zone with using simultaneous saline injection (11): NaCl alters such tissue properties as the electrical conductivity to permit greater deposition of RF energy, or the infusion of fluid during RF application improved the thermal conduction within the tissues by allowing more rapid and effective heat convection over a larger tissue volume.

We performed hepatic arteriography and dynamic CT to demonstrate our assumption that percutaneous epinephrine injection into the liver might decrease the hepatic blood flow. Definite vasoconstriction of the hepatic artery was not noted on the hepatic arteriography that was obtained after percutaneous epinephrine injection into the liver. However, the dynamic CT examination after percutaneous epinephrine injection into the liver demonstrated an ill-defined low density area at the injection site. There is a possibility that the volume and concentration of epinephrine we used in our study were insufficient to cause constriction of the hepatic artery on conventional arteriography, but the volume and concentration of epinephrine were sufficient to cause an attenuation difference of the liver via constriction of the

small vessels that were not visible on conventional arteriography.

A previous report suggested that alteration of tissue conductivity might occur after sudden hemodynamic changes (14). This hypothesis is supported by the fact that during RF procedures and after the occlusion of arterial flow, the mean impedance values in the HCC were unexpectedly lower than those in the HCC tissue without occlusion of arterial blood flow (14, 23). In our study, the impedance in group C was lower than the impedance in group B, although any statistical significance was not found. The decreased hepatic blood flow via epinephrine might have lowered the impedance of group C as compared with group B.

There were several limitations of our study. First, the number of RF ablations we performed was somewhat small. In our results, the mean tissue impedance didn't show statistical significance among all three groups. This might be due to the small number of RF ablations in each group. Second, we used young, small pig livers instead of adult, large pig livers. Three RF ablation zones were inadvertently made although we cautiously inserted the electrode under ultrasound guidance and we used a 1-cm active tip electrode; therefore, we excluded these cases in the analysis. Third, we used only two animals for demonstrating the hemodynamic change via percutaneous epinephrine injection. This small number of animals may lower the value of this additional experiment for demonstrating hepatic hemodynamic change via percutaneous epinephrine injection. Fourth, the expected systemic effect and the maximum and minimum dosages of epinephrine were not studied in this experiment. Further experiments are needed before applying this technique to humans. Fourth, measurements of RF ablation zones were not made on the CT examination because respiratory artifacts were commonly observed on the CT images.

In conclusion, RF ablation with epinephrine injection may be more effective for achieving coagulation necrosis than is RF ablation with saline injection or RF ablation only in normal pig liver tissue. If the large volume of coagulation necrosis created by epinephrine injection is reproducible in tumors, it may increase the clinical utility of RF ablation by allowing the successful treatment of larger tumors or by reducing the number of sessions needed for achieving adequate treatment.

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