CT assessment of liver hemodynamics in patients with hepatocellular carcinoma after argon-helium cryoablation

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BACKGROUND: **Assessment of tumor response after argon-helium cryoablation is critical in guiding future therapy for unresectable hepatocellular carcinoma. This study aimed to evaluate liver hemodynamics in hepatocellular carcinoma after argon-helium cryoablation with computed tomography perfusion.**

METHODS: **The control group comprised 40 volunteers without liver disease. The experimental group was composed of 15 patients with hepatocellular carcinoma treated with argon-helium cryoablation. Computed tomography perfusion parameters were measured: hepatic blood flow, hepatic blood volume, mean transit time, permeability of capillary vessel surface, hepatic arterial fraction, hepatic arterial perfusion, and hepatic portal perfusion.**

RESULTS: **After treatment, in the tumor foci, permeability of capillary vessel surface was higher, and hepatic blood flow, hepatic blood volume, hepatic arterial fraction, and hepatic arterial perfusion values were lower ($P<0.05$). In the liver parenchyma surrounding the tumor, hepatic arterial perfusion was significantly lower ($P<0.05$); however, there was no significant difference in hepatic blood flow, hepatic blood volume, mean transit time, permeability of capillary vessel surface, hepatic arterial fraction, or hepatic portal perfusion ($P>0.05$).**

CONCLUSION: **Computed tomography perfusion can evaluate tumor response after argon-helium cryoablation.**

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KEY WORDS: **ablation; computed tomography; cryosurgery; hepatocellular carcinoma; liver neoplasms; perfusion imaging**

Introduction

Hepatocellular carcinoma (HCC), a common malignant tumor in China, has become a major health problem worldwide due to its high mortality rate. Argon-helium cryoablation is often used for unresectable HCC in the middle and advanced stages of the disease.[1-3] Assessment of therapeutic response after argon-helium cryoablation is critical in determining the success of treatment and guiding future therapy. In recent years, computed tomography (CT) perfusion has been widely used clinically, because it provides information not only about tumor size but also about hemodynamic changes caused by the tumor. However, few studies have assessed perfusion changes in HCC after argon-helium cryoablation. This study was designed to use CT perfusion to quantitatively evaluate hemodynamic changes in HCC before and after cryoablation.

Methods

Patients

Twenty women and 20 men who were free of liver disease (average age 54.5 years) comprised the control group. The diagnosis of HCC was made according to the criteria from the European Association for the Study of the Liver.[4, 5] Six women and 9 men with HCC treated with argon-helium cryoablation comprised the

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experimental group. After giving their informed consent, both control and experimental subjects underwent plain CT, CT perfusion, and enhanced CT scanning. The experimental subjects had CT scans 1 week before and 4 weeks after argon-helium cryoablation.

Contrast-enhanced CT and CT perfusion protocol

Before the CT examinations, the patients drank 500-600 mL water in 15 minutes on an empty stomach to ensure that their digestive tract was full, differentiating it from other structures and organs in the abdomen. A 20-gauge catheter was inserted into an antecubital vein, and patients were told to breathe calmly, in synch with thoracic respiration, to avoid moving their abdomen during the scan. Using a GE LightSpeed® 64-slice CT scanner, a plain scan was first performed with the patient in a supine position to localize the central slice of the tumor. Next, a perfusion scan was performed on this slice, which was as close as possible to the porta hepatis. Non-ionic iodinated contrast agent (100 mL iohexol [Omnipaque, GE Healthcare, USA]) was injected intravenously as a bolus at 4.5 mL/sec using a binocular high-pressure syringe, and then 20 mL physiological saline was injected at the same rate.

The whole-liver perfusion scanning started about 5 seconds after injection of the contrast agent. The scanning parameters were: 5-mm slice thickness, 5-mm slice interval, 8 layers per revolution, acquisition field of view 40 mm, 60 mA, 120 kV, matrix size of 512×512 pixels, 360° revolution per second, 50 seconds of continuous scanning, and 320 layers of 5-mm slice thickness reconstruction images. Ten minutes after the perfusion scanning, conventional 3-phase enhancement scans were performed. The scanning time of the arterial phase was 15-20 seconds. The portal vein phase was 45 seconds, and the delayed scanning time was 120 seconds.

Argon super-cryosurgery of HCC

The Cryocare knife (Endocare, USA) comes in diameters of 2, 3, 5, and 8 mm. A color ultrasonic diagnostic instrument (GE, USA) was used for guidance and location. Cannulas of different capacities were prepared according to the size of the tumor. The cryoprobe was inserted into the tumor along with the cannula under ultrasound guidance. The tip of the Cryocare knife was inserted at least 1 cm away from the tumor border. The locations of the target and temperature probe were confirmed under ultrasound guidance. The cryoprobe was inserted into the tumor with the help of a pipe sheath and guidewire. The pipe sheath was drawn back 3-5 cm after fixing the cryoprobe. The operation was repeated when 2 or more probes were needed.

The cryosurgery module was activated in ultra-low temperature mode when all the cryoprobes were in place. The cryoprobe temperature reaches -100 ℃ within 10 seconds and, with time, temperatures can reach as low as -160 ℃. Each cycle consists of a 15- to 20-minute freeze followed by a rewarming through the heating system. Then the cycle is repeated. The Cryocare knife is extracted when rewarming is finished. Absorbable stanching satin was packed into the knife edge for hemostasis. Sterile gauzes were used to cover the wound, which was then secured with an abdominal belt.

Data processing

The CT images were transferred to a workstation (Advantage Windows 4.3, GE Medical Systems Ltd., Milwaukee, WI, USA). Liver tissue was considered a double-input system (hepatic artery and portal vein) to take into account the dual hepatic perfusion, with a single output (hepatic vein). The deconvolution algorithm allowed the calculation of 7 parameters, quantifying perfusion for each tissue region of interest (ROI). Hepatic blood flow (HBF) was expressed as mL/min/100 mg of body weight, hepatic blood volume (HBV) as mL/100 mg, mean transit time (MTT) in second, the permeability of capillary vessel surface (PS) as mL/min/100 mg, and hepatic arterial fraction (HAF) as the percentage of total blood flow of arterial origin. Hepatic arterial perfusion (HAP) and hepatic portal perfusion (HPP) were expressed as mL/min/100 mg. HBF was calculated using the following equation: HBF=HAP+HPP, where HAP=HBF×HAF and HPP=HBF×(1-HAF).

The ROIs were placed on a color map. Perfusion parameters were measured 3 times at each time point for each ROI, and the mean of the 3 measurements was used in the analysis. ROIs of 20-30 mm^2 were placed in the aorta, portal vein, and liver parenchyma. For liver tissue surrounding the tumor, an equivalent ROI was placed in an area of liver parenchyma surrounding the tumor, which did not show any abnormality on conventional contrast-enhanced CT. As controls, 2 or 3 ROIs were placed randomly in the liver parenchyma. To evaluate the HCC foci, 2 or 3 ROIs were placed in areas showing obvious enhancement on contrast-enhanced CT.

Statistical analysis

Data are expressed as mean±SD. SPSS v19.0 was used for data analysis. Student's *t* test was used to compare the different perfusion parameters before and after treatment. A *P* value of <0.05 was considered statistically significant.

Results

Contrast-enhanced CT showed the location, shape, and enhanced characteristics of liver parenchyma. The representative perfusion maps of liver tissues were created by CT perfusion software. The red area represents the highest perfusion value, while the yellow, green, blue, and black colors represent decreasing perfusion value, respectively (Fig. 1). The mean values of the perfusion parameters were also calculated for controls, HCC foci, and background liver tissues surrounding the tumor.

Before treatment, in HCC foci, the perfusion parameters (HBF, HAP, and HAF) were higher, but HPP and PS were lower than both the controls and background liver parenchyma adjacent to the HCC ($P<0.05$). There were no differences in HBV and MTT in HCC foci compared with the controls and background liver parenchyma adjacent to the HCC ($P>0.05$) (Table).

After treatment, HCC foci showed decreased enhancement in the arterial phase, and decreased perfusion was shown on HBF, HAP, HBV, and HAF ($P<0.05$); however, PS was significantly higher ($P<0.05$), and there was no difference in MTT and HPP (Figs. 2-4). For the liver parenchyma surrounding the HCC, HAP (mL/min/100 mg) was significantly lower after treatment (7.45±5.54 vs 17.07±4.31, $P=0.042$). There were no significant differences in HBF, HPP, HBV, MTT, PS, or HAF after treatment in liver parenchyma surrounding the HCC: HBF (mL/min/100 mg) was 52.98±9.20 vs 65.11±20.27, $P=0.234$; HPP (mL/min/100 mg) was 45.53±13.69 vs 48.04±16.17, $P=0.752$; HBV (mL/100 mg) was 12.37±4.32 vs 14.48±3.84, $P=0.523$; MTT (seconds) was 15.91±3.63 vs 18.71±8.47, $P=0.588$; PS (mL/min/100 mg) was 22.28±18.74 vs 19.98±5.68, $P=0.817$; HAF (%) was 0.15±0.13 vs 0.27±0.02, $P=0.088$.

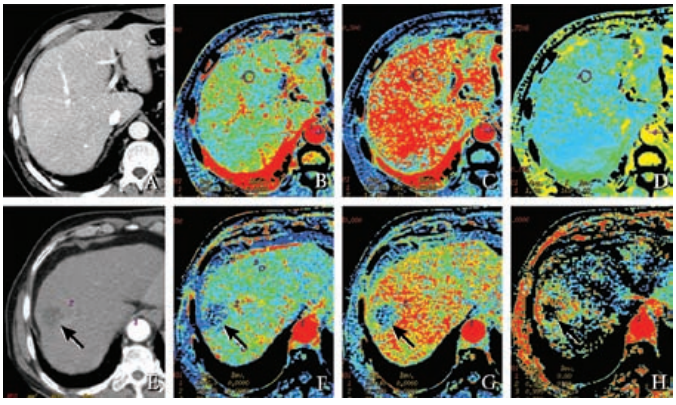

Fig. 1. Images of enhanced CT and CT perfusion of the controls and HCC foci. **A-D**: CT enhancement and CT perfusion performed in the controls. **E-H**: CT enhancement and CT perfusion performed in HCC foci. Black arrows show the delimitation of HCC foci in the hepatic right-lobe.

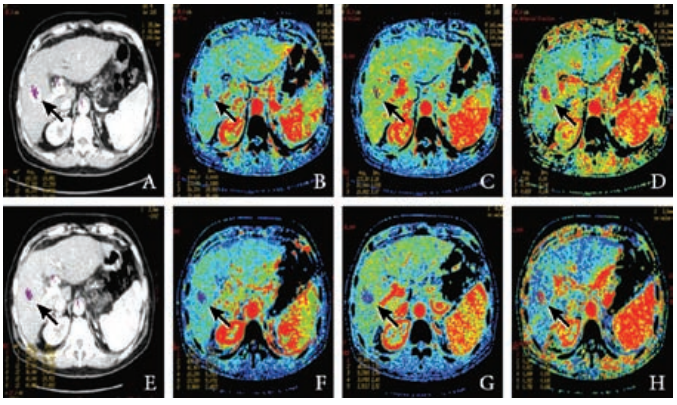

Fig. 2. Images of enhanced CT and CT perfusion of HCC foci in the hepatic right-lobe. **A-D**: Contrast-enhanced image and perfusion maps (HBF, HBV, and HAF) of HCC foci before treatment. **E-H**: Contrast-enhanced image and perfusion maps (HBF, HBV, and HAF) of HCC foci after treatment. The regions of interest are the aorta, portal vein and the focal lesion of HCC. Red regions indicate high blood perfusion, while yellow, green, blue, and black represent decreasing blood perfusion. Black arrows show the delimitation of HCC foci.

Table. CT perfusion in different regions of interest in background liver parenchyma adjacent to HCC, HCC foci and controls

Parameters	Background liver adjacent to HCC (n=15)	HCC foci (n=15)	Controls (n=40)
HBF (mL/min/100 mg)	65.11±20.27*	119.68±61.26	90.78±23.77
HAP (mL/min/100 mg)	17.07±4.31*	106.99±48.00	18.08±4.91*
HPP (mL/min/100 mg)	48.04±16.17*	12.69±20.80	72.69±21.08*
HBV (mL/100 mg)	14.48±3.84	15.62±1.68	17.91±9.19
MTT (sec)	18.71±8.47	15.41±5.45	14.03±4.43
PS (mL/min/100 mg)	19.98±5.68*	8.87±4.39	34.98±13.91*
HAF (%)	0.27±0.02*	0.91±0.11	0.20±0.04*

*: $P<0.05$, compared with the HCC foci. HBF: hepatic blood flow; HAP: hepatic arterial perfusion; HPP: hepatic portal perfusion; HBV: hepatic blood volume; MTT: mean transit time; PS: permeability of capillary vessel surface; HAF: hepatic arterial fraction.

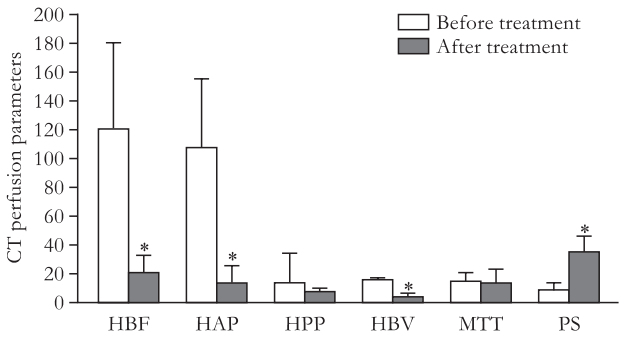

Fig. 3. CT perfusion parameters of HCC foci before and after treatment. *: $P<0.05$, compared with before treatment.

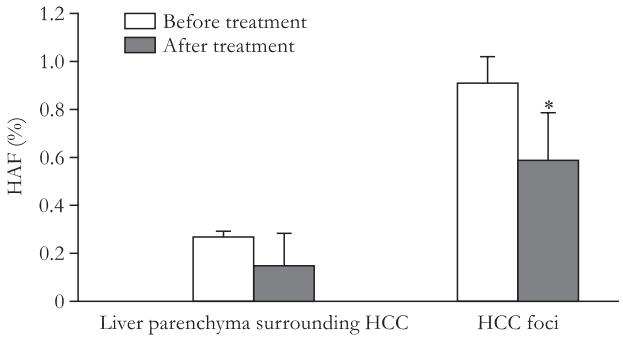

Fig. 4. HAF in liver parenchyma surrounding HCC and HCC foci before and after treatment. *: $P<0.05$, compared with before treatment.

Discussion

In the early stages of HCC, there are no obvious symptoms, so HCC is identified in many patients only at a late stage, when it is too late for successful surgery. Argon-helium cryoablation is effective and necessary for prolonging patient survival and improving quality of life. It can completely ablate some large tumors through multiple blade fusion, although some patients experience subclinical therapeutic effects. Even for patients with HCC with a poor blood supply, argon-helium cryosurgery can be curative.[1-3] Assessment of therapeutic response after argon-helium cryoablation is critical in determining the success of treatment and in guiding therapy.

Our results showed that the perfusion parameters were significantly different in HCC from both the controls and background liver parenchyma adjacent to the HCC. These findings indicate that CT perfusion is a good functional imaging technique to quantify multiple perfusion parameters in both normal and pathologic tissues. These findings are also comparable to results from our earlier experimental and clinical studies.[6, 7]

In the evaluation of argon-helium cryosurgery, conventional CT can be used to display the position of the puncture needle and detect the extent of ablation, providing anatomical information and accurately showing the size and range of the tumor for clinicians to determine or adjust the therapeutic plan.[8] However, conventional CT is not very useful in monitoring liver lesions with no obvious change in tumor size. In fact, hemodynamic changes occur before morphological transformation, so the observation of hemodynamic changes in HCC is particularly important.[9, 10] As a noninvasive functional imaging method, CT perfusion not only shows the anatomical position of liver lesions but also provides information on blood flow changes, which can be more accurate in evaluating tumor response to treatment.[11-15]

As shown above, in the HCC foci, the HAF value, representing the blood supply ratio of the hepatic artery, reflects the hemodynamics and degree of malignancy of the tumor.[16] The HAF decreased after treatment, suggesting that the degree of malignancy was reduced. In addition, some studies have shown that HAF can be used to determine tumor characteristics and guide clinical treatment.[17, 18] Our results showed that the HAP value was significantly lower after treatment, indicating that hepatic artery blood supply for HCC was reduced. The decrease of HAP validated that the cryoablation was effective.

The HBF and HBV reflect the blood supply of the HCC. Development of HCC is related to the formation of new arterial vessels. The increasing number of tumor vessels expands the access for the contrast agent in and out of the lesions, so HBF and HBV increase in the HCC foci. After treatment, the number of tumor vessels and the blood flow were decreased thus resulted in HBF and HBV decrease, approaching the normal quantitative index. Therefore, changes in CT perfusion parameters can be a valuable reference for the evaluation of treatment efficacy. The results are in line with reported experimental studies in which CT perfusion has been used to assess the response of HCC to treatment by evaluating perfusion changes.[12, 19]

However, this study has several limitations. First, measurements of CT perfusion parameters are influenced by many factors, such as gender, age, general health, cardiac output, contrast agent quantity and injection rate, and the choice of blood vessels and ROI, where subjectivity is possible. The effects of these various factors need further study. Second, the mathematical model and calculation methods differ in each model, and the liver perfusion indexes also need to be further unified to develop a CT perfusion technique for routine clinical application. Another limitation is that the perfusion parameters and pathological characteristics in a comparative study and the relationships between perfusion parameters, disease etiology, and biological characteristics need to be explored.

Despite these limitations, liver CT perfusion imaging may be effective in clinical application. We will use the perfusion parameters to evaluate the reserve function of patients with liver cirrhosis and assess the relationship between liver perfusion parameters and the severity of liver cirrhosis. Using CT perfusion, we will achieve the early qualitative diagnosis of small nodules in the liver and improve the accuracy of liver CT perfusion in the diagnosis of precancerous lesions. In addition, for patients after liver transplantation, CT

perfusion can monitor changes in blood flow at the microcirculation level and be used to evaluate liver function and hemodynamic changes.

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