Received:
27 May 2014

Revised:
22 July 2014

Accepted:
19 August 2014

doi: 10.1259/bjr.20140374

Cite this article as:

Zhu J, Zhu H, Mei Z, Zhang L, Jin C, Ran L, et al. High-intensity focused ultrasound ablation: an effective and safe treatment for secondary hypersplenism. *Br J Radiol* 2014;87:20140374.

FULL PAPER

High-intensity focused ultrasound ablation: an effective and safe treatment for secondary hypersplenism

¹J ZHU, MD, ^{1,2}H ZHU, MD, ³Z MEI, MD, ²L ZHANG, MD, ²C JIN, PhD, ¹L RAN, MD, ²K ZHOU, PhD and ¹W YANG, MD

¹State Key Laboratory of Ultrasound Engineering in Medicine Co-founded by Chongqing and the Ministry of Science and Technology, Chongqing Key Laboratory of Ultrasound in Medicine and Engineering, College of Biomedical Engineering, Chongqing Medical University, Chongqing, China

²Clinical Center for Tumor Therapy, the Second Clinical College and Affiliated Hospital, Chongqing Medical University, Chongqing, China

³Department of Digestive Diseases, the Second Clinical College and Affiliated Hospital, Chongqing Medical University, Chongqing, China

Address correspondence to: Hui Zhu

E-mail: cqhifu@163.com

Objective: Hypersplenism is a common disease. The conventional treatment is splenectomy and partial splenic embolization; however, both of them have high complication rates and technical defects. Therefore, safer and more effective techniques should be considered for the treatment of hypersplenism. High-intensity focused ultrasound (HIFU) may provide an effective and safe way for treatment of hypersplenism. Therefore, we conducted this study to assess the safety and efficacy of HIFU in treatment of secondary hypersplenism.

Methods: A total of 28 patients who suffered from secondary hypersplenism were treated with HIFU ablation. All patients who underwent HIFU were closely followed-up over a year. MRI scan was performed, and the spleens were observed. Blood counts and liver function tests were also carried out.

Results: In the follow-up process, the levels of white blood cells and platelets in the blood after HIFU were significantly higher than those before HIFU, liver function also improved after HIFU treatment. In addition, the symptoms were ameliorated significantly or even disappeared. The MRI showed that the ablation area had turned into a non-perfused volume, and after 12 months of HIFU ablation, the ablated area shrank evidently; the sunken spleen formed a lobulated shape and the splenic volume decreased.

Conclusion: HIFU ablation is a safe, effective and non-invasive approach for secondary hypersplenism.

Advances in knowledge: For the first time we used HIFU ablation to treat secondary hypersplenism. It not only expands indications of HIFU but also provides better choice for the treatment of secondary hypersplenism.

Hypersplenism is a common manifestation in cirrhotic patients with portal hypertension. Liangpunsakul et al¹ reported that 70–80% of cirrhotic patients with portal hypertension have different degrees of splenomegaly and hypersplenism. Hypersplenism is a clinical syndrome characterized by splenomegaly, a variable combination of anaemia, leucopenia and/or thrombocytopaenia, compensatory bone marrow hyperplasia, reduced immunity and improvement after splenectomy.¹ The conventional treatment for patients with hypersplenism is splenectomy. However, after the first report of overwhelming post-splenectomy infection, clinical practitioners started realizing the important immunological function of the spleen. What is more, splenectomy is associated with increased risk of splenic vein thrombosis, secondary thrombocythemia and infection, particularly with encapsulated micro-organisms.² Several studies have shown that the spleen is an organ with a variety of important functions such as anti-infection and anti-tumour immunity. Therefore, it is important to retain the

splenic function as much as possible when using splenomegaly treatment. Recently, partial splenic embolization (PSE) has been used in the treatment of splenomegaly and hypersplenism, but it has high incidence of complications. Local ablation therapies, such as radiofrequency ablation (RFA) and microwave ablation, also have marked improvement for hypersplenism treatment. However, since secondary hypersplenism often occurred with hyperkinesis of the portal vein and fragile spleen tissues, thus, in the process of puncture, the risk of splenic injury is high. Therefore, safer and more effective techniques that can preserve splenic tissue and function should be considered for the treatment of hypersplenism.

High-intensity focused ultrasound (HIFU) may provide an effective and safe way for treatment of hypersplenism. HIFU is a new emerging non-invasive therapy for the treatment of solid tumours, which has also been found to be applicable to manage some splenic symptoms. Noble et al³ and Vaezy

*et al*⁴ have shown that HIFU was effective in achieving haemostasis in the haemorrhagic spleen models of pigs and rabbits. An experimental study on HIFU ablation of the porcine spleen for the treatment of hypersplenism has also shown that HIFU is feasible and effective in treating animal splenomegaly and hypersplenism.⁵ However, to the best of our knowledge, no clinical study on HIFU ablation of secondary hypersplenism has been reported before. In this present study, patients with secondary hypersplenism were treated by splenic HIFU ablation. The safety, efficacy and clinical prospects of HIFU for secondary hypersplenism were evaluated.

METHODS AND MATERIALS

Patients

The study was approved by the Ethics Committee at Chongqing Medical University, Chongqing, China. A written informed consent was obtained from each patient before every procedure.

From September 2008 to September 2012, a total of 28 patients with severe secondary hypersplenism who refused to have surgical operation were recruited in this study. Severe secondary hypersplenism was defined as splenomegaly, leucopenia [white blood cell (WBC) count $<3 \times 10^9 \text{ l}^{-1}$] and thrombocytopenia [platelets (PLTs) count $<50 \times 10^9 \text{ l}^{-1}$]. All patients had portal hypertension, and among them, 9 patients also had 13 hepatocellular carcinoma (HCC) lesions. 15 were male and 13 were female, the median age was 53 years (range, 26–71 years). In these patients, the average WBC count was $(2.05 \pm 0.68) \times 10^9 \text{ l}^{-1}$, PLT count was $(33.43 \pm 11.02) \times 10^9 \text{ l}^{-1}$ and red blood cell (RBC) count was $(3.45 \pm 0.59) \times 10^9 \text{ l}^{-1}$. According to the Child–Pugh classification, 19 out of 28 patients had liver function in class A, 8 in class B and 1 in class C. For the aetiological agent, the liver cirrhosis was caused in 23 patients by the chronic hepatitis B virus; in 2 by autoimmune hepatitis; in 2 by drug hepatitis; and in 1 by alcoholic hepatitis. Among these patients, 11 had a history of oesophageal and gastric variceal bleeding.

Therapeutic method

The treatment was performed with the Model-JC Focused Ultrasound Tumour Therapeutic System (Chongqing Haifu® Medical Technology Co., Ltd, Chongqing, China). This system consists of ultrasound therapy transducer with an ultrasound generator, a real-time diagnostic ultrasound, a HIFU treatment table and a degassed water circulation unit. The 12-cm diameter PZT-4 piezo-ceramic transducer (Beijing Cheng-Cheng Weiye Science and Technology Co., Ltd, Beijing, China) was employed to produce therapeutic ultrasound energy. An ultrasound imaging probe with 2.5–3.5 MHz (Esaote DU3, Genova, Italy) was situated in the centre of the transducer as a real-time imaging guidance unit. The integrated transducer was then placed in a tank filled with degassed water. Figure 1 shows the simulated diagram of HIFU ablation on the spleen for treatment of hypersplenism (Figure 1).

HIFU treatment was performed after patients were given general anaesthesia. The patient was then positioned in the left lateral recumbent position, the skin overlaying the spleen was in contact with the degassed water. With the six-direction movement

Figure 1. Examples of high-intensity focused ultrasound (HIFU) regions. HIFU delivers large amounts of energy to the tissue of interest—the splenic tissue. The high intensity of the ultrasound beam can easily lead to temperatures in excess of 100 °C at the focus after a few seconds of HIFU application. These high temperatures can result in coagulation necrosis of splenic tissue and the occlusion of sinusoids and small vessels.

of the integrated transducer, the location, size, shape of the spleen and relation to adjacent organs were clearly identified on the ultrasound imaging device. The lower pole and the hilum of the spleen were selected as the primary ablation area. The treatment started from the middle layer, and a linear scanning mode of HIFU exposure was selected as an ablative scheme. The 200 W of test power was first used, and then gradually increased up to 300–400 W. One sonication lasted for 5 s. With the help of provisional therapeutic parameters based on the depth and vascular supply of the target region, the process was repeated slice by slice to achieve ablation of all planned slices. Greyscale changes (echogenicity) on the diagnostic images within the focus after each HIFU exposure were analysed to identify and monitor the extent of treatment. The main parameters of the splenic ablation were configured as follows: a therapy frequency of 0.85 MHz, a focal length of 140 mm, a diameter of the transducer surface of 200 mm, a therapy power of 300–400 W and an average ablation time of 3242.0 ± 1677.3 s (range, 600–7000 s). Moreover, among nine patients with HCC, all of them underwent simultaneous liver HIFU and splenic HIFU ablation.

Clinical observation and follow-up

Body temperature and other vital signs, symptoms and complications were closely observed after HIFU treatment. Peripheral blood cells included WBC, RBC and PLTs, and conventional liver function parameters included alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB) and albumin (ALB) that were closely observed in the 1st, 3rd, 6th and 12th month after HIFU treatment. Generally, the postoperative complications indicate the safety of treatment; the change of peripheral blood cells and symptoms both reflect the therapeutic effect of HIFU; ALT and AST are representative of a hepatocellular injury; and ALB indicates the liver capacity for protein synthesis, whereas TB is an indicator of bilirubin metabolism and cholestasis.

Figure 2. Contrast MRI obtained from a 58-year-old patient before and 2 weeks after a high-intensity focused ultrasound (HIFU) treatment. (a) Splenomegaly was observed before HIFU; (b) the ablation mass was observed in the spleen after HIFU treatment: the signal of ablation area increased or remained the same on T_1 weighted imaging (b1), reduced on T_2 weighted imaging (b2) and coronal section (b4), and no enhancement was found in dynamic contrast-enhanced MRI (b3). The ratio of ablation area of this cross-sectional view in the spleen was 37.1%.

In order to observe the change of splenic tissue, abdominal ultrasound and abdominal contrast-enhanced MRI were also evaluated at the follow-up time points. Although the abdominal volumes of the whole spleen and the ablated splenic zones were calculated by the software program “HIFU-3DT PS”, which was programmed by the engineers from Chongqing Haifu (HIFU) Tech Co., Ltd.

Statistical analysis

All the data were recorded as median or mean $\pm$ standard deviation. Data were analysed by computer with SPSS® (SPSS Inc., Chicago, IL) using Student's *t*-test. Statistical significance was defined as $p < 0.05$.

RESULTS

Imaging evaluation and stereometry of ablation in spleen

In order to observe the ablation results on the spleen, patients received the abdominal contrast-enhanced MRI at the follow-up time points after HIFU treatment. Compared with those before treatment, the signal increased, reduced or remained the same on T_1 weighted imaging (T1WI) and reduced on T_2 weighted imaging (T2WI) after HIFU treatment. Dynamic contrast-enhanced MRI showed the ablation area had turned into a non-perfused volume (NPV) in the spleen, which was larger than those on T1WI and T2WI (Figures 2–4). These changes accorded with the occurrence of coagulation necrosis. In conclusion, T1WI showed no specificity, and T2WI showed some specificity in demonstrating coagulation necrosis after HIFU ablation, while dynamic contrast-enhanced MRI displayed higher sensitivity in demonstrating the ablation area, by demonstrating the blood supply of the lesion and enhancement

characteristics. 12 months after HIFU ablation, the abdominal contrast-enhanced MRI showed that the ablated area shrank evidently, the sunken spleen formed a lobulated shape and the splenic volume decreased (Figure 4). Spleen volume and ablated volume of the spleen were calculated by the software program “HIFU-3DT PS”, which was programmed by the engineers from Chongqing Haifu (HIFU) Tech Co., Ltd, to contour and to calculate the non-perfused region in every slice of MRI. The NPV ratio of the spleen = (the NPV/the volume of spleen) $\times 100\%$. The average splenic volume before operation was $1307.30 \pm 177.79 \text{ cm}^3$. The average splenic volume was $949.50 \pm 130.86 \text{ cm}^3$ at 12 months after HIFU, and the average NPV ratio was $27.20 \pm 6.07\%$ (range, 16.90–42.34%). It was significantly smaller than the pre-treatment volume ($p < 0.001$) (Figure 5).

The changes of peripheral blood cells and liver function

Trends of average values of the peripheral blood cell are shown in Figure 6. The WBC counts reached a peak $(4.12 \pm 1.73) \times 10^9 \text{ l}^{-1}$ on the second day post-HIFU owing to post-operative reaction and then decreased to $(2.76 \pm 1.05) \times 10^9 \text{ l}^{-1}$ on the third day post-HIFU. After 1 week, it increased again and remained higher than the baseline $(2.05 \pm 0.68) \times 10^9 \text{ l}^{-1}$ at 12 months $[(2.96 \pm 0.69) \times 10^9 \text{ l}^{-1}; p < 0.001]$ post-HIFU. The PLT counts decreased slightly on the third day post-HIFU, but then started to increase one week after HIFU. It reached a peak of $(57.92 \pm 9.04) \times 10^9 \text{ l}^{-1}$ at 14 days post-HIFU and remained at $48.64 \pm 12.98 \times 10^9 \text{ l}^{-1}$ at 12 months after HIFU. It was significantly higher than the baseline levels $[(33.43 \pm 11.02) \times 10^9 \text{ l}^{-1}; p < 0.001]$. There was no significant difference in RBC counts.

Figure 3. Contrast MRI of a 48-year-old patient 2 weeks and 12 months after high-intensity focused ultrasound (HIFU) treatment. (a1) The signal of ablated lesions remained the same or decreased on T_1 weighted imaging. (a2) The signal of ablated lesions decreased on T_2 weighted imaging. (a3) No enhancement was found on dynamic contrast enhanced MRI, the ratio of ablation area of this cross-sectional view in the spleen was 25.3%. (b) 12 months after HIFU ablation, from the dynamic contrast enhanced MRI, the ablation area had obviously shrunk, the local outline of spleen had a depression and a lobulated shape, the splenic volume decreased.

Changes in ALT, AST and TB before and after HIFU treatment are presented in Figure 7. ALT, AST and TB decreased significantly and remained lower than baseline at 1 month after HIFU (ALT, 43.50 ± 11.11 vs 25.21 ± 7.89 U l^{-1} ; $p < 0.001$; AST, 46.61 ± 10.76 vs 32.18 ± 8.39 U l^{-1} ; $p < 0.001$; TB, 33.18 ± 12.04 vs 22.63 ± 7.18 $\mu\text{mol l}^{-1}$; $p < 0.001$). There was no significant difference with ALB between baseline and 1 week after HIFU (ALB, 49.10 ± 18.71 vs 41.14 ± 13.95 U l^{-1} ; $p > 0.05$). After 1 month, a significant difference was observed in ALB (ALB, 49.10 ± 18.71 vs 40.06 ± 10.25 ; $p < 0.05$). No significant differences were observed in ALT, AST, ALB and TB at 12 months post-HIFU compared with the baseline (ALT, 38.82 ± 16.68 vs 25.21 ± 7.89 U l^{-1} ; AST, 46.61 ± 10.76 vs 32.18 ± 8.39 U l^{-1} ;

ALB, 53.11 ± 31.03 vs 41.14 ± 13.95 U l^{-1} ; TB, 33.18 ± 12.04 vs 22.63 ± 7.18 $\mu\text{mol l}^{-1}$; $p > 0.05$ for all comparisons).

Adverse effects and symptom changes

All patients tolerated the procedure well. There was no death or severe complications, such as gastrointestinal perforation, peritonitis, splenic rupture or splenic abscess, in this study. The post-operative complications and possible causes are shown in Table 1. All the adverse events were transitory and disappeared after the expectant treatment. During the follow-up period, no other complications were observed. In addition, the symptoms of epistaxis and gingival bleeding were ameliorated significantly

Figure 4. Changes in the splenic volume, pre-operative spleen volume (1307.3 ± 177.79 cm^3) vs post-operative spleen volume (949.5 ± 130.86 cm^3); $p < 0.001$.

Figure 5. Trends of average values of white blood cell (WBC) and platelet (PLT) counts. $p < 0.001$ compared with pre-high intensity focused ultrasound (HIFU) baseline, at all post-HIFU time points.

Figure 6. Dynamic changes of average values of alanine aminotransferase (ALT), aspartate aminotransferase (AST) (a), albumin (ALB) and total bilirubin (TB) (b). The liver function improved significantly after the treatment.

or even eliminated. The quality of life improved in all cases, which chiefly manifested through improved appetite, physical strength and weight.

DISCUSSION

Hypersplenism is a well-known complication of portal hypertension in cirrhosis, which can result in thrombocytopenia and/or leucocytopenia. Surgical splenectomy can eliminate hypersplenism-induced blood cell destruction, but the morbidity of severe complications after splenectomy remains high. In addition, splenectomy is often associated with an increased long-term risk of septic events.⁶ As a non-invasive modality, HIFU may provide a better choice for the treatment of hypersplenism. HIFU has been clinically used in the treatment of malignant and benign tumours. Several studies have shown that the homogeneous coagulative necrosis with an irreversible tumour cell death and severe damage to tumour blood vessels occurred after HIFU. The processes of necrotic tissue absorption and granulation tissue replacement were observed.⁷⁻⁹ In consideration of the role of vascular occlusion by HIFU, many studies demonstrated that HIFU could stop the bleeding from injuries of different organs.¹⁰⁻²⁰ Spleen haemostasis is one of the clinical issues we often face. HIFU is effective in achieving haemostasis in

haemorrhagic spleen models of pigs and rabbits,^{3,4} and no major adverse effects were observed.^{7,21,22} Another study has shown that HIFU is feasible and effective in the treatment of experimental splenomegaly and hypersplenism.⁵ We reported that HIFU may be an effective and safe alternative for treatment of HCC that is complicated by hypersplenism.²³ However, no clinical results of HIFU for secondary hypersplenism have been reported. Because of the particularities of secondary hypersplenism, such as abundant blood sinus and vessels in spleen tissues, hyperkinesis of portal vein, fragile spleen tissues and poor liver function, leucopenia and/or thrombocytopenia and depressed immune function, it is important to investigate the safety and efficiency of HIFU treatment for patients with secondary hypersplenism.

Our results showed that HIFU treatment for secondary hypersplenism was safe. No major complications, such as gastrointestinal perforation, peritonitis, splenic rupture and splenic abscess, were observed. Minor adverse events such as abdominal pain and the dermal ecchymosis were recorded in some cases and eliminated in a short time after treatment. Our study also showed that HIFU treatment is effective for patients with secondary hypersplenism. We found that the peripheral WBC counts, RBC counts and PLT counts increased after HIFU, and most of them remained at a higher level for at least 1 year. Meanwhile, symptoms such as epistaxis and gingival bleeding were significantly ameliorated. In this study, eight patients had the peripheral blood cell counts decline again after 1 year. The cause of declined peripheral blood cells may be related to the insufficient percentage of ablated splenic volume and the severity of hypersplenism. For these patients, additional HIFU treatment can be considered. Moreover, we also found that the liver function improved after HIFU treatment, which was consistent with splenectomy.²⁴ Liu et al²⁵ reported that the splenic and portal venous flow decreased, but hepatic arterial flow (HAF) and the total oxygen supply increased dramatically after the RFA procedure for hypersplenism, and the resultant increase in HAF may improve liver function and induce liver regeneration.²⁶ We assume that HIFU may play the same role.

Compared with those before treatment, the signal increased, reduced or remained the same on T1WI and reduced on T2WI after HIFU treatment. Dynamic contrast-enhanced MRI showed the ablation area had turned into a NPV in the spleen, which was larger than those on T1WI and T2WI. Through the imaging data, we observed that coagulation necrosis occurred in the spleens, the ablation area shrank and the splenic volume decreased. These results were consistent with the pathological results.^{5,27} The results may explain that the coagulative necrosis in spleen parenchyma that was caused by HIFU is just like PSE, which may impair the splenic ability to phagocytize blood cells, weaken the function and capacity of the spleen and produce the effect of splenectomy. The thermal effect induced by HIFU ablation leads to the temperature of the splenic increasing to 65–100 °C within seconds, resulting in coagulation necrosis of the tissue and the occlusion of sinusoids and small vessels. It may directly damage the target tissue and vessel. Mechanical effects such as cavitation are believed to cause PLT activation and aggregation,²⁸ resulting in blood coagulation and tissue homogenization. Tissue

Table 1. Post-operative complications and possible causes of high-intensity focused ultrasound (HIFU) ablation for secondary hypersplenism

Complications	Number of cases	Incidence (%)	Possible causes
Abdominal pain	7	25.0	A common reaction in post-procedure without the need for special treatment
Low fever	3	10.7	The absorbed necrosis substance of spleen mass
Hydrothorax	2	7.1	Hypoproteinaemia and the stimulation of the diaphragm muscle in HIFU treatment
Pleural and peritoneal effusions	1	3.6	Hypoproteinaemia and the stimulation of the diaphragm muscle in HIFU treatment
Dermal ecchymosis of the treated area	2	7.1	Severity of hypersplenism and long treatment time
Gastrointestinal perforation	0	0	
Splenic rupture	0	0	
Splenic abscess	0	0	
Peritonitis	0	0	
Death case	0	0	

homogenization seems to provide an effective seal, especially for the spleen, which may enhance and expedite clot formation and coagulation so as to enhance the ablation effect.²⁹ A recent study also demonstrated that the vascular effects induced by microbubble-enhanced, high-pressure ultrasound can slow down or block blood perfusion in the rabbit spleen.³⁰

Compared with surgery and other thermal ablation technologies, HIFU has its advantages as it being less invasive and can be considered as an option for repeat treatment; moreover, for

patients of HCC complicated by hypersplenism, HIFU is also an effective and safe alternative treatment. Therefore, based on our results, HIFU ablation is effective and safe in achieving therapeutic aim for hypersplenism. With comprehensive researches, HIFU ablation could play a role in the treatment of secondary hypersplenism. However, there are still issues to resolve in future studies, for example, the dosimetry, such as the ideal treatment parameter, the appropriate ablated volume, the relationship between the ablated volume and efficacy, and safety of treatment etc. The mechanisms still need to be clarified in further studies.

REFERENCES

- Liangpunsakul S, Ulmer BJ, Chalasani N. Predictors and implications of severe hypersplenism in patients with cirrhosis. *Am J Med Sci* 2003; **326**: 111–16.
- Sangro B, Bilbao I, Herrero I, Corella C, Longo J, Belouqui O, et al. Partial splenic arterial embolization for the treatment of hypersplenism in cirrhosis. *Hepatology* 1993; **18**: 309–14.
- Noble ML, Vaezy S, Keshavarzi A, Paun M, Prokop AF, Chi EY, et al. Spleen hemostasis using high-intensity ultrasound: survival and healing. *J Trauma* 2002; **53**: 1115–20.
- Vaezy S, Martin R, Kaczkowski P, Keilman G, Goldman B, Yaziji H, et al. Use of high-intensity focused ultrasound to control bleeding. *J Vasc Surg* 1999; **29**: 533–42.
- Shi B, Zhu H, Liu YJ, Lü L, Jin CB, Ran LF, et al. Experimental studies and clinical experiences on treatment of secondary hypersplenism with extracorporeal high-intensity focused ultrasound. *Ultrasound Med Biol* 2012; **38**: 1911–17. doi: [10.1016/j.ultrasmedbio.2012.07.010](https://doi.org/10.1016/j.ultrasmedbio.2012.07.010)
- Kojouri K, Vesely SK, Terrell DR, George JN. Splenectomy for adult patients with idiopathic thrombocytopenic purpura: a systematic review to assess long-term platelet count responses, prediction of response, and surgical complications. *Blood* 2004; **104**: 2623–34.
- Wu F, Chen WZ, Bai J, Zou JZ, Wang ZL, Zhu H, et al. Pathological changes in human malignant carcinoma treated with high-intensity focused ultrasound. *Ultrasound Med Biol* 2001; **27**: 1099–106.
- Wu F, Chen WZ, Bai J, Zou JZ, Wang ZL, Zhu H, et al. Tumor vessel destruction resulting from high-intensity focused ultrasound in patients with solid malignancies. *Ultrasound Med Biol* 2002; **28**: 535–42.
- Chen L, Rivens I, ter Haar G, Riddler S, Hill CR, Bensted JP. Histological changes in rat liver tumours treated with high-intensity focused ultrasound. *Ultrasound Med Biol* 1993; **19**: 67–74.
- Vaezy S, Martin R, Schmiedl U, Caps M, Taylor S, Beach K, et al. Liver hemostasis using high-intensity focused ultrasound. *Ultrasound Med Biol* 1997; **23**: 1413–20.
- Vaezy S, Noble ML, Keshavarzi A, Paun M, Prokop AF, Cornejo C, et al. Liver hemostasis with high-intensity ultrasound: repair and healing. *J Ultrasound Med* 2004; **23**: 217–25.
- Delon-Martin C, Vogt C, Chignier E, Guers C, Chapelon JY, Cathignol D. Venous thrombosis generation by means of high-intensity focused ultrasound. *Ultrasound Med Biol* 1995; **21**: 113–19.
- Vaezy S, Martin R, Yaziji H, Kaczkowski P, Keilman G, Carter S, et al. Hemostasis of punctured blood vessels during high-intensity focused ultrasound. *Ultrasound Med Biol* 1998; **24**: 903–10.
- Martin RW, Vaezy S, Kaczkowski P, Keilman G, Carter S, Caps M, et al. Hemostasis of

- punctured vessels using Doppler-guided high-intensity ultrasound. *Ultrasound Med Biol* 1999; **25**: 985–90.
15. Zderic V, Keshavarzi A, Noble ML, Paun M, Sharar SR, Crum LA, et al. Hemorrhage control in arteries using high-intensity focused ultrasound: a survival study. *Ultrasonics* 2006; **44**: 46–53.
 16. Lim JH, Chung DJ, Lim YT, Cho SH, Lee JM, Hahn ST. High-intensity focused ultrasound treatment of abnormal vaginal bleeding secondary to uterine myoma. *J Ultrasound Med* 2011; **30**: 397–401.
 17. Vaezy S, Zderic V, Karmy-Jones R, Jurkovich GJ, Cornejo C, Martin RW. Hemostasis and sealing of air leaks in the lung using high-intensity focused ultrasound. *J Trauma* 2007; **62**: 1390–5.
 18. Sanghvi NT, Foster RS, Bihle R, Casey R, Uchida T, Phillips MH, et al. Noninvasive surgery of prostate tissue by high intensity focused ultrasound: an updated report. *Eur J Ultrasound* 1999; **9**: 19–29.
 19. Madersbacher S, Schatzl G, Djavan B, Stulnig T, Marberger M. Long-term outcome of transrectal high-intensity focused ultrasound therapy for benign prostatic hyperplasia. *Eur Urol* 2000; **37**: 687–94.
 20. Brentnall MD, Martin RW, Vaezy S, Kaczowski P, Forster F, Crum L. A new high intensity focused ultrasound applicator for surgical applications. *IEEE Trans Ultrason Ferroelectr Freq Control* 2001; **48**: 53–63.
 21. Zderic V, O’Keefe GE, Foley JL, Vaezy S. Resection of abdominal solid organs using high-intensity focused ultrasound. *Ultrasound Med Biol* 2007; **33**: 1251–8.
 22. Vaezy S, Zderic V. Hemorrhage control using high intensity focused ultrasound. *Int J Hyperthermia* 2007; **23**: 203–11.
 23. Zhu J, Zhu H, Mei Z, Jin C, Ran L, Zhou K, et al. High-intensity focused ultrasound ablation for treatment of hepatocellular carcinoma and hypersplenism: preliminary study. *J Ultrasound Med* 2013; **32**: 1855–62. doi: [10.7863/ultra.32.10.1855](https://doi.org/10.7863/ultra.32.10.1855)
 24. Cai JQ, Hu JQ, Bi XY, Zhao JJ, Che X, Xie SL, et al. Long-term effect of united hepatectomy and splenectomy on treatment of hepatocellular carcinoma complicated with cirrhosis and hypersplenism. [In Chinese.] *Natl Med J China* 2004; **84**: 6–8.
 25. Liu Q, Ma K, Song Y, Zhou N, He Z. Two-year follow-up of radiofrequency ablation for patients with cirrhotic hypersplenism: does increased hepatic arterial flow induce liver regeneration? *Surgery* 2008; **143**: 509–18. doi: [10.1016/j.surg.2007.11.016](https://doi.org/10.1016/j.surg.2007.11.016)
 26. Ma KS, Wu Q, Liu QD, Bie P, Dong JH. Clinical research on radiofrequency ablation for hypersplenism. [In Chinese.] *Zhonghua Wai Ke Za Zhi* 2004; **42**: 944–6.
 27. Zhu J, Zhu H, Mei Z, She C. Enhanced magnetic resonance imaging for evaluation of hypersplenism after high-intensity focused ultrasound ablation. [In Chinese.] *Nan Fang Yi Ke Da Xue Xue Bao* 2012; **32**: 1415–18.
 28. Poliachik SL, Chandler WL, Mourad P, Ollos RJ, Crum LA. Activation, aggregation and adhesion of platelets exposed to high-intensity focused ultrasound. *Ultrasound Med Biol* 2001; **27**: 1567–76.
 29. Vaezy S, Martin R, Crum L. High intensity focused ultrasound: a method of hemostasis. *Echocardiography* 2001; **18**: 309–15.
 30. Liu J, Xiao S, Wu S, Ou W, He J, Gao S, et al. Disruption of splenic circulation using microbubble-enhanced ultrasound and prothrombin: a preliminary study. *Ultrasound Med Biol* 2012; **38**: 1930–7. doi: [10.1016/j.ultrasmedbio.2012.07.012](https://doi.org/10.1016/j.ultrasmedbio.2012.07.012)