

Targeted Vessel Ablation for More Efficient Magnetic Resonance-Guided High-Intensity Focused Ultrasound Ablation of Uterine Fibroids

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Received: 16 September 2011 / Accepted: 4 November 2011 / Published online: 7 December 2011
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Abstract

Purpose To report the first clinical experience with targeted vessel ablation during magnetic resonance-guided high-intensity focused ultrasound (MR-HIFU) treatment of symptomatic uterine fibroids.

Methods Pretreatment T1-weighted contrast-enhanced magnetic resonance angiography was used to create a detailed map of the uterine arteries and feeding branches to the fibroids. A three-dimensional overlay of the magnetic resonance angiography images was registered on 3D T2-weighted pretreatment imaging data. Treatment was focused primarily on locations where supplying vessels entered the fibroid. Patients were followed 6 months after treatment with a questionnaire to assess symptoms and quality of life (Uterine Fibroid Symptom and Quality of Life) and magnetic resonance imaging to quantify shrinkage of fibroid volumes.

Results In two patients, three fibroids were treated with targeted vessel ablation during MR-HIFU. The treatments resulted in almost total fibroid devascularization with nonperfused volume to total fibroid volume ratios of 84, 68, and 86%, respectively, of treated fibroids. The predicted ablated volumes during MR-HIFU in patients 1 and 2 were 45, 40, and 82 ml, respectively, while the nonperfused volumes determined immediately after treatment were 195, 92, and 190 ml respectively, which is 4.3

(patient 1) and 2.3 (patient 2) times higher than expected based on the thermal dose distribution. Fibroid-related symptoms reduced after treatment, and quality of life improved. Fibroid volume reduction ranged 31–59% at 6 months after treatment.

Conclusion Targeted vessel ablation during MR-HIFU allowed nearly complete fibroid ablation in both patients. This technique may enhance the use of MR-HIFU for fibroid treatment in clinical practice.

Keywords Magnetic resonance-guided high-intensity focused ultrasound · MR-HIFU · Uterine fibroids · Vessel occlusion

Introduction

Magnetic resonance-guided high-intensity focused ultrasound (MR-HIFU) is a noninvasive outpatient treatment option for symptomatic uterine fibroids [1–3]. A limitation of MR-HIFU in clinical practice is its long treatment time. Fibroids are generally large tumors, and a single sonication yields a treatment volume of only a few milliliters. Cooling time between subsequent sonications also extends treatment duration [4]. Another limitation is that, in most patients, only part of the fibroid volume can be treated with MR-HIFU as a result of treatment safety margins. In clinical studies, ablated tissue, defined as nonperfused volume (NPV)—that is, the nonenhancing area on contrast-enhanced T1-weighted magnetic resonance images (MRI) acquired immediately after treatment—ranged 2–100% of the fibroid volume, with a mean of 43% [4–16].

However, because the ablated volume correlates linearly with relief of clinical symptoms, treatment should be aimed

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at ablating as much fibroid tissue as possible within acceptable treatment times [7, 8, 12].

We present a novel method of MR-HIFU ablation in two patients with uterine fibroids, which allowed ablation of larger volumes. The method is called targeted vessel ablation because MR-HIFU is intentionally aimed at the uterine artery supplying the fibroid.

Materials and Methods

We treated two patients who both participated in a prospective clinical study investigating the efficacy of volumetric MR-HIFU treatment for uterine fibroids in our hospital. The ethics committee approved this study, and informed consent was obtained. Postmenopausal status and desire for pregnancy were exclusion criteria, as were extensive scarring of the lower abdomen, MRI contraindications, and major comorbidities. Diagnostic contrast-enhanced MRI with a 1.5 T magnetic resonance (MR) scanner (Achieva; Philips Healthcare, Best, The Netherlands) was performed with the patient in prone position to evaluate patient suitability for MR-HIFU. Interposition of bowel between fibroid and abdominal wall, hyperintense signal of the fibroid on T2-weighted MRI, total number of fibroids ≥ 10 , and a fibroid size of >10 cm in diameter were other exclusion criteria [4]. MRI included T2-weighted imaging in three orthogonal planes, and T1-weighted imaging before and after intravenous administration of a gadolinium-based contrast agent (Gadovist, Bayer Schering Pharma, Berlin, Germany; 0.1 mmol/kg). Additionally, MR angiography (MRA) with double-dose contrast agent was performed (TR 4.7 ms; TE 1.2 ms; flip angle 40° ; matrix 256×128 ; FOV 430×430 ; slice thickness 15.0 mm; NSA 1) to assess blood supply toward the fibroid.

MRA resulted in a detailed map of the uterine arteries and feeding segmental branches of the fibroid. A three-dimensional reconstruction of the MRA images was made and projected on T2-weighted screening images in three orthogonal planes. Vessels were projected in color to facilitate visualization (Fig. 1). Location of the supplying blood vessels and possibilities for safe, targeted vessel ablation were evaluated. Imaging processing was performed by MeVisLab software (MeVis Medical Solutions, Bremen, DE).

Treatment was performed with the Sonalleve MR-HIFU system (Philips Healthcare, Helsinki, Finland) integrated with a 1.5 T MRI scanner. The Sonalleve MR-HIFU system uses volumetric ablation with automated feedback for real-time tissue temperature mapping in multiple planes, steering of the focal point via real-time feedback, and temperature control delivering an optimal dose to the target

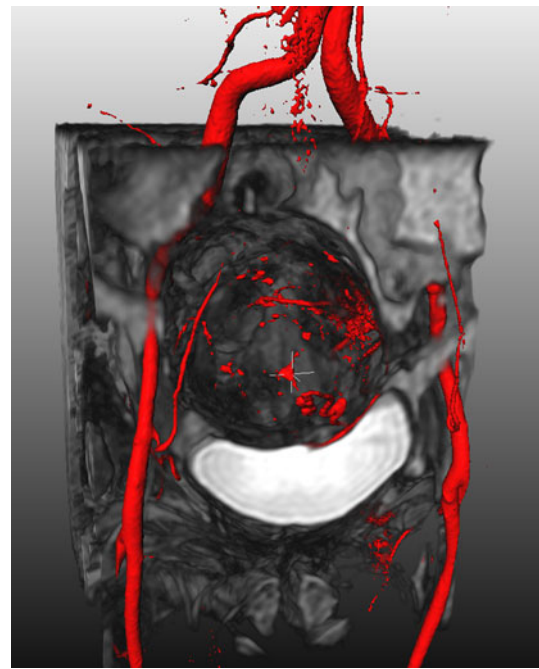


Fig. 1 Reconstruction of T2-weighted MR image fused with MR angiography images, showing the blood vessels

location [17]. Patients were consciously sedated during treatment. Treatment was focused primarily on the area where vessels entered the fibroid. Treatment cells with a diameter of 8 or 12 mm were centrally placed overlapping in and around this area. The initial power level was 120 W, adjusted to a higher level when insufficient buildup of heat was visualized on the temperature map. Apart from the targeted vessel ablation, we also performed MR-HIFU ablation of the fibroid tissue with respect for the treatment safety margins.

Directly after treatment, contrast-enhanced (CE) MRI was performed to visualize the treatment result. We used these images to calculate the fibroid volume, NPV, and the applied predicted thermal dose volume. The NPV is defined as the nonenhancing area within the fibroid on CE T1-weighted images, corresponding to the devascularized area. Fibroid volumes and NPVs were calculated by a sum-of-slice method. Regions of interest were outlined in each sequential slice with a MR workstation (ViewForum R5.1V1L2 SP3, Philips Medical Systems, The Netherlands), and the volume of each segment was calculated and summed for all slices. The NPV was also calculated as a percentage of the fibroid volume to indicate the ablated fibroid percentage. The predicted thermal dose volume (PTV) applied was calculated by the MR-HIFU system and defined as the volume receiving a thermal dose of 240 equivalent minutes at 43°C (threshold value for thermal ablation) [18]. This is the actual treated volume as planned during the MR-HIFU treatment. Dividing of the NPV by the PTV resulted in the ratio between these two values.

Table 1 Baseline symptom and health-related quality-of-life scores

Characteristic	Patient 1 (age 37 years)	Patient 2 (age 48 years)	
		Fibroid A	Fibroid B
Fibroid volume (ml)			
Baseline	232	135	222
3 months after treatment (volume change)	173 (−25%)	85 (−37%)	132 (−41%)
6 months after treatment (volume change)	161 (−31%)	56 (−59%)	115 (−48%)
Transformed Symptom Severity Score ^a			
Baseline	31.3	53.1	
3 months after treatment	9.4	34.4	
6 months after treatment	9.4	12.5	
Health-related quality-of-life score ^b			
Baseline	88.8	58.6	
3 months after treatment	93.1	84.5	
6 months after treatment	100.0	98.3	

^a Transformed Symptom Severity Score, range 0–100 points, higher score indicating more symptoms

^b Health-related quality-of-life score, range 0–100 points, higher score indicating better quality of life



Fig. 2 Patient 1. **A** Pretreatment sagittal T2-weighted image showing the fibroid selected for treatment. **B** Pretreatment CE T1-weighted image showing vascularization of all fibroids. **C** Posttreatment CE

T1-weighted image showing almost complete devascularization of the large fibroid. **D** CE T1-weighted image acquired 6 months after treatment

Patients were followed for 6 months. One, 3 and 6 months after treatment, patients received questionnaires. Follow-up CE MRI was performed 3 and 6 months after treatment.

Treatment effect was quantified by fibroid shrinkage 3 and 6 months after treatment and improvement in symptoms and quality of life. Symptom and quality-of-life scores were assessed at baseline, and 1, 3, and 6 months

after treatment with the Uterine Fibroid Symptom and Quality of Life questionnaire [19].

Results

Two patients were treated, aged 37 and 48 years. Presenting symptoms included menorrhagia, bloating, pelvic pain, and frequent urination. Table 1 lists baseline symptom and health-related quality-of-life scores. Treatment in patient 1 was aimed on the dominant fibroid (Fig. 2A, B) with a volume of 232 ml ($7.8 \times 8.1 \times 6.6$ cm). Patient 2 had two large intramural fibroids (designated A and B) with volumes of 135 ml ($6.4 \times 6.0 \times 6.4$ cm) and 222 ml ($5.8 \times 7.1 \times 8.3$ cm).

In patient 1, targeted vessel ablation was performed using three 12-mm (dimensions $12 \times 30 \times 30$ mm) and two 8-mm (dimensions $8 \times 20 \times 20$ mm) treatment cells (Fig. 3). The required ultrasound power to achieve sufficient heating in this area was higher than in other areas of the fibroid (150–180 W instead of 120 W). The PTV calculated by the MR-HIFU system was 45 ml; however, the NPV in the target fibroid was 195 ml (Fig. 2C)—4.3 times larger than expected based on the PTV. The NPV as a percentage of the fibroid volume was 84% ($195/232$ ml). Additionally, four small fibroids, which were also present, were also completely devascularized, although they were not sonicated.

In patient 2, targeted vessel ablation was performed with two 8-mm treatment cells (power 100–120 W). The PTVs were 40 ml (fibroid A) and 82 ml (fibroid B). The NPVs in the targeted fibroids were 92 ml (fibroid A) and 190 ml (fibroid B); 2.3 ($92/40$ ml), respectively, which was 2.3 ($190/82$ ml) larger than expected. The NPVs as percentage of fibroid volume were 68% ($92/135$ ml) and 86% ($190/222$ ml).

Total treatment time (from first to last sonication) for these patients was 132 and 213 min. Total time in the MR room was approximately 60 min longer. Sonication time (actual time that sonications were executed) was 22 and 37 min.

Both patients experienced mild to severe abdominal pain the first days after treatment, which resolved with over-the-counter pain medication. No skin burns or serious adverse events occurred. Three and 6 months after treatment, follow-up MRI was performed (Fig. 2D). The volume of the treated fibroids did shrink during follow-up, and both patients experienced a reduction in symptoms and an increase in quality of life over the 6-month follow-up period (Table 1).

Discussion

We presented a novel method for targeted vessel ablation during MR-HIFU treatment of uterine fibroids, resulting in

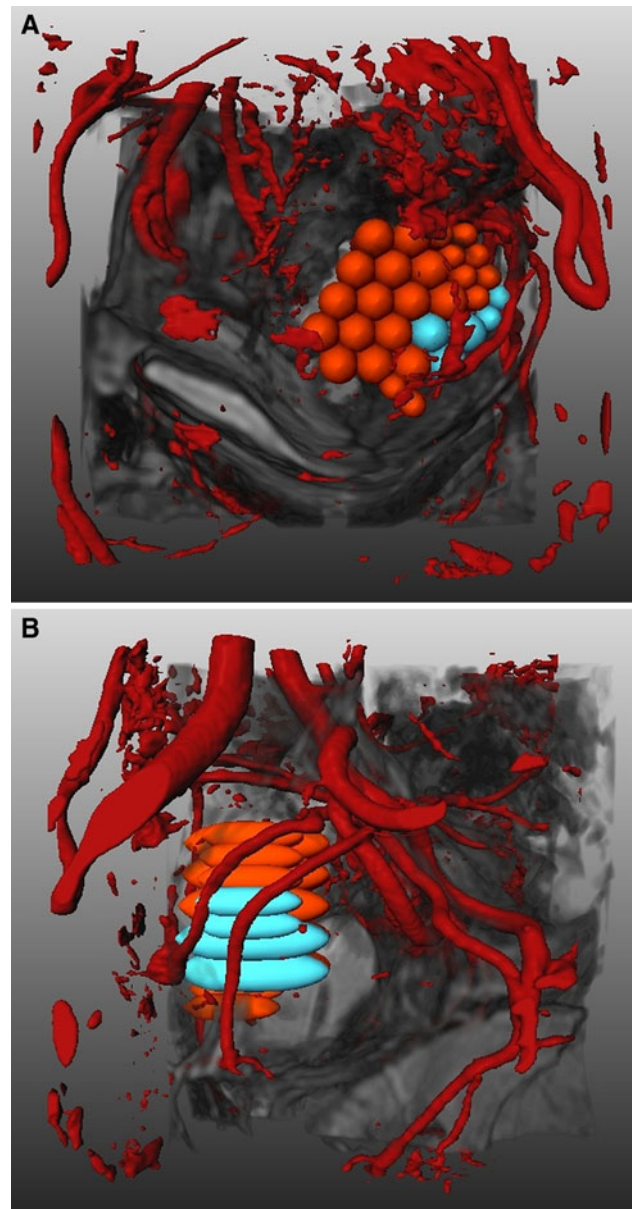


Fig. 3 Patient 2. Posttreatment sagittal (A) and coronal (B) reconstruction of sonicated treatment cells on T2-weighted images fused with MR angiography. Orange cells were easy to heat; blue cells did not heat very well. The blue cells were located on a large supplying vessel (Color figure online)

nearly complete fibroid necrosis in two patients. The percentage of devascularized tissue was, respectively, 4.3, 2.3, and 2.3 times larger than expected based on predicted thermal dose volumes. Postprocessing of the sonicated treatment cells with MRA images confirmed ablation of segmental branches of the uterine arteries. Both women reported a clinically relevant improvement in symptoms 3 and 6 months after treatment.

The hypothesis of targeted vessel ablation was developed after observations that the NPV on posttreatment CE

T1-weighted MR images was larger than expected based on the actual ablated volume [20, 21]. For the MR-HIFU system used in this study, we found a ratio of 1.4 ± 0.6 during conventional fibroid treatments [4]. De Melo et al. [22] demonstrated a similar case of complete fibroid necrosis after limited MR-HIFU treatment, resulting in 98% volume decrease 12 months after treatment.

The exact pathophysiologic mechanism that occurs during vessel ablation is still unclear. Several theories have been proposed. Hynynen et al. [23] proved that noninvasive vessel occlusion could be achieved using MR-HIFU. Wu et al. [24] showed that MR-HIFU can induce tumor vessel necrosis in solid malignancies, which may be a promising strategy for future treatments. The possible mechanism is that the thermal stimulus causes vessel constriction, resulting in decreased cooling by blood and thus increased temperature, inducing thermal coagulation of the vessel wall. Detailed visualization of fibroid-supplying blood vessels is necessary to perform targeted vessel ablation. We used contrast-enhanced MR angiography; however, this requires the usage of a contrast agent. Contrast cannot be administered immediately before MR-HIFU treatment because the possible side effects of heating of gadolinium-based contrast are unclear. Therefore, we planned targeted vessel ablation on screening contrast-enhanced MR angiography images acquired several weeks before treatment. A limitation of this approach is that patient position on the treatment day is not equal with screening. A solution would be to use a noncontrast-based method to visualize the supplying blood vessels so it can be used before treatment. Integration of image processing for treatment planning of targeted vessel ablation in the workflow is essential to plan vessel ablation on the treatment day, instead of using screening images. The next step for research is investigating how to do this and implementing it into the workflow. Unfortunately, targeted vessel ablation is not possible in all candidates. Treatment must be safe, and generally used safety margins to sensitive structures have to be taken into account. Moreover, areas containing vessels might be difficult to heat because of the heat sink effect, and thus do not receive a sufficient dose for necrosis [25].

Ablated fibroid volume correlates linearly with relief of clinical symptoms after MR-HIFU [7, 8, 12]. For uterine fibroid embolization, which is another minimal invasive treatment option for uterine fibroids, these results are quite similar. Kroencke et al. [26] studied the effect of partial versus complete infarction after uterine artery embolization on fibroid-related symptoms and the rate of additional interventions. They found that women with >90% fibroid infarction showed significantly better symptom control and fewer additional treatments than women with a lower infarction rate. This study emphasizes the relevance of focusing on treating as much fibroid tissue as possible with MR-HIFU.

We conclude that targeted vessel ablation is a promising new method to enhance treatment results, and MR-HIFU ablation of uterine fibroids is efficacious in clinical practice.

Conflict of interest The authors declare that they have no conflict of interest.

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