Ultrasound in Med. & Biol., Vol. ■■, No. ■■, pp. ■■–■■, 2018

0301-5629/$ - see front matter

ELSEVIER

https://doi.org/10.1016/j.ultrasmedbio.2018.03.030

● *Clinical Note*

USE OF CONTRAST-ENHANCED ULTRASOUND IN THE ASSESSMENT OF UTERINE FIBROIDS: A FEASIBILITY STUDY

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(*Received* 24 *October* 2017; *revised* 23 *February* 2018; *in final form* 29 *March* 2018)

Abstract—Contrast-enhanced ultrasound (CEUS) is an innovative ultrasound technique capable of visualizing both the macro- and microvasculature of tissues. In this prospective pilot study, we evaluated the feasibility of using CEUS to visualize the microvasculature of uterine fibroids and compared CEUS with conventional ultrasound. Four women with fibroids underwent gray-scale ultrasound, sonoelastography and power/color Doppler scans followed by CEUS examination. Analysis of CEUS images revealed initial perfusion of the peripheral rim, that is, a pseudo-capsule, followed by enhancement of the entire lesion through vessels traveling from the exterior to the interior of the fibroid. The pseudo-capsules exhibited slight hyper-enhancement, making a clear delineation of the fibroids possible. The centers of three fibroids exhibited areas lacking vascularization, information not obtainable with the other imaging techniques. CEUS is a feasible technique for imaging and quantifying the microvasculature of fibroids. In comparison with conventional ultrasound imaging modalities, CEUS can provide additional diagnostic information based on the microvasculature. (E-mail: ljm.juffermans@vumc.nl) © 2018 World Federation for Ultrasound in Medicine & Biology. All rights reserved.

Key Words: **Uterine fibroids, Microvasculature, Contrast-enhanced ultrasound, Ultrasound imaging, Ultrasound contrast agents, Microbubbles.**

INTRODUCTION

Uterine fibroids are benign monoclonal tumors arising from a single smooth muscle cell of the myometrium. The reported prevalence of symptomatic fibroids ranges from 25% to 46% (Stewart 2001; Wegienka et al. 2013). Pathologic examination suggests that the prevalence is even higher, up to 70% to 80% by the age of 50 (Baird et al. 2003). The presence of fibroids often goes unnoticed; however, possible symptoms vary from excessive bleeding and anemia, to pelvic pain, bowel and bladder dysfunction, miscarriages and subfertility dependent on their location and deformation of the uterine cavity (Brölmann and Huirne 2007; Pritts et al. 2009). Furthermore, fibroids are the most common indication for hysterectomies worldwide (Farquhar and Steiner 2002) and accounted for 45% of all hysterectomies in the United States in 2010 (Wright et al. 2013).

It is thought that fibroids affect angiogenesis and the vascular structure in the adjacent myometrium, leading to increased vessel number and size (Stewart 2001; Stewart and Nowak 1996). Fibroids typically have a peripheral rim of vascularization, the *pseudo-capsule,* from which vessels penetrate the center of the fibroid (Fleischer 2003). Malignant lesions, such as sarcomas, may have a distinct vascular pattern and increased vessel diameter compared with normal tissue and benign lesions (Abramowicz 2005; Exacoustos et al. 2007; Van den Bosch et al. 2015). A clear depiction of the vasculature is therefore of importance for accurate discrimination between fibroids and sarcomas and is in fact crucial for choosing the appropriate treatment of fibroids.

To get an impression of the microvasculature, Doppler imaging can be used. Contrast-enhanced ultrasound (CEUS) is an innovative imaging technique capable of visualizing both the macro- and microvasculature (Testa et al.

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2005). Currently used contrast agents are gas-filled microbubbles stabilized by a shell. Microbubbles (2–5 μm) are injected intravenously and are capable of passing through the smallest capillaries (Smeenge et al. 2011). Microbubbles oscillate particularly at frequencies used for diagnostic imaging (1–10 MHz), reflecting a unique non-linear echo (Blomley et al. 2001). Although the use of CEUS is already quite established in the assessment of liver lesions (Brannigan et al. 2004), renal carcinoma (Dong et al. 2009) and cardiac imaging (Porter et al. 2014), the use of this novel technique is still limited in the field of gynecology (Testa et al. 2005; Zhang et al. 2010).

The objective of the current feasibility study was to visualize fibroid microvasculature with CEUS and to compare fibroid characteristics with gray-scale ultrasound, sono-elastography, power/color Doppler results, to explore the added clinical value of CEUS in imaging fibroids.

METHODS

Patients

Patients enrolled in this prospective observational feasibility study were women with uterine fibroids who visited the outpatient clinic of the Vrije Universiteit Medical Center (VUmc) between June and August 2014. This study was performed at both VUmc and the Academic Medical Center (AMC), both in Amsterdam, The Netherlands. The study was approved by the institutional review board. All patients with fibroids on conventional ultrasound were asked to participate in the study.

Patients gave written informed consent before inclusion. Exclusion criteria were post-menopausal, pregnant or lactating status; known allergy to Sonovue; history of any clinically unstable cardiac condition; severe cardiac rhythm disorders 7 d before CEUS; severe pulmonary or systemic hypertension; and respiratory distress syndrome.

Equipment and conventional ultrasound

All sonographic examinations were performed using a Philips iU22 scanner equipped with a C10-3 v transvaginal probe (Philips, Bothell, WA, USA) at the AMC. Conventional ultrasound examinations were performed in a standardized manner before CEUS and consisted of 2-D gray-scale ultrasound, sonoelastography, color Doppler and 3-D power Doppler. Two-dimensional gray-scale ultrasound was performed using the following settings: resolution R1 (optimized settings for maximum image quality), general mid-range frequencies, dynamic range 56, gain at 71% and 15-Hz frame rate.

Sonoelastography is an ultrasound technique used to estimate strain and discriminate soft from stiff tissue. Sonoelastography images were obtained according to a standardized method described by Stoelinga et al. (2014), with the following settings: resolution R1, high persistence level and a 15-Hz frame rate.

The Doppler ultrasound had a frequency of 5–8 MHz. The settings used for color Doppler were as follows: resolution RP(optimized settings for color sensitivity), wall filter 47 Hz at low color persistence, pulse repetition frequency (PRF) of 500 Hz, gain fixed at 60% and a frame rate of 15 Hz. After completion of 2-D gray-scale and color Doppler analysis, 3-D power Doppler was activated at the 700-Hz PRF, resolution RP, a 49-Hz wall filter, fixed gain of 62% and 15-Hz frame rate. All Doppler scans were performed with the same settings.

Subjective assessments of blood flow (low, average, high) in the pseudo-capsule and the center of the fibroid were made on color and power Doppler. The cardiac phase was not included in the analysis of color and power Doppler images. All images were transferred to an external hard disk in the digital imaging and communications in medicine (DICOM) format.

Contrast-enhanced ultrasound procedure

During gray-scale ultrasound, the fibroid of interest was identified in a sagittal plane, and machine settings were converted to contrast mode at 3.5-MHz power modulation, resolution RS (optimized settings to improve speed), fixed gain at 68%, low mechanical index of 0.06 and 10-Hz frame rate. These settings were fixed for all four patients. A bolus of 1.2 mL contrast agent, that is, SonoVue (Bracco, Geneva, Switzerland), was administered through a periphery-placed intravenous cannula and followed by a flush of saline (5.0 mL) to push the agent into the central venous stream. The target lesion was continuously monitored for 2 min from the start of contrast injection ($t = 0$ s). This procedure was repeated by injection of a second 1.2-mL bolus to obtain contrast-enhanced images of the myometrium without fibroid tissue. The entire procedure was recorded and transferred to an external hard disk connected to the ultrasound machine. The CEUS examinations were performed by a single gynecologist (J.A.H.) with more than 15 y of experience in ultrasonography.

Contrast-enhanced ultrasound images were analyzed offline using VueBox (Bracco Suisse, SA, Trial Version 5.0.1.50339). The complete clip was reviewed to describe the contrast-enhancement characteristics of fibroid and normal uterine tissue. Next, time–intensity curves were obtained from manually selected regions of interest: entire fibroid, pseudo-capsule, center of fibroid, myometrium adjacent to fibroid, myometrium distant from fibroid and endometrium. Three parameters were calculated from these time–intensity curves: *peak enhancement* (maximal level of enhancement, associated with relative blood volume); *rise time* (time from baseline to peak enhancement, related to blood flow velocity) and *wash-in rate* (peak enhancement/rise time).