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● *Original Contribution*

A NEW ULTRASONOGRAPHIC "FLUTTERING SIGN" FOR HEPATIC HEMANGIOMA

Natsuko Kobayashi,[*,†] Hiroko Iijima,[†,‡] Toshifumi Tada,[§] Yoko Shibata,[†] Takashi Nishimura,[†,‡] Takashi Kumada,[¶] Mariko Hashimoto,[†] Akiko Higashiura,[†] Masahiro Yoshida,[†] Junko Nishimura,[†] Nobuhiro Aizawa,[‡] Naoto Ikeda,[‡] Tomoyuki Takashima,[‡] Ryo Takata,[‡] Hiroki Nishikawa,[‡] Yoshinori Iwata,[‡] Hirayuki Enomoto,[‡] Seiichi Hirota,[‖] and Etsuro Hatano[#]

* Department of Internal Medicine, Kenwakai Hospital, Iida, Nagano, Japan; † Ultrasound Imaging Center, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan; ‡ Division of Gastroenterology and Hepatology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan; § Department of Internal Medicine, Himeji Red Cross Hospital, Himeji, Hyogo, Japan; ¶ Faculty of Nursing, Gifu Kyoritsu University, Ogaki, Gifu, Japan; ‖ Department of Surgical Pathology, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan; and # Division of Hepatobiliary and Pancreatic Disease, Department of Surgery, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan

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Abstract—The aim of the study described here was to clarify the diagnostic value of the fluttering sign, a new sign that characterizes hepatic hemangiomas in gray-scale ultrasonography (US). It refers to a phenomenon in which the speckled echogenicity inside the hemangioma changes continuously and seems to be moving. A total of 172 hemangiomas diagnosed with contrast-enhanced US were evaluated. The fluttering sign was found in 123 of 172 hemangiomas (71.5%). Its prevalence was significantly higher than that of the marginal strong echo (89/172, 51.7%, $p < 0.001$), posterior acoustic enhancement (103/172, 59.9%, $p = 0.031$) and chameleon sign (100/172, 58.1%, $p = 0.013$). In addition, the fluttering sign was observed significantly more frequently in mixed or hypo-echoic tumors than in hyper-echoic tumors ($p < 0.001$), relatively large tumors ($p < 0.001$) and tumors that were less than 5 cm from the body surface ($p = 0.015$). The fluttering sign in gray-scale US has great potential to be a new complementary sign for the diagnosis of hemangioma. (E-mail: hiroko-i@hyo-med.ac)

Key Words: **Hepatic hemangioma, Fluttering sign, Ultrasound, Speckle, Echogenicity.**

INTRODUCTION

Hepatic hemangioma is the most common benign tumor of the liver, with a prevalence of up to 20% in autopsy cases (Karhunen 1986). It is a benign non-epithelial tumor consisting of multiple blood-filled cavities of various sizes. It has a spongy appearance on cut sections. The cavities are covered by a single layer of endothelial cells (Bajenaru et al. 2015), and separated by fibrous septa of various thicknesses (Bioulac-Sage et al. 2008). Since most hemangiomas are asymptomatic (Gandolfi et al. 1991), they are often found incidentally on ultrasound examinations of the liver. Most are less than 3 cm in diameter. They are usually solitary, but approximately 20% of patients have more than one hemangioma (Bruneton et al. 1983; Gandolfi et al. 1991).

Since small asymptomatic hemangiomas do not require treatment (Gandolfi et al. 1991; Etemadi et al. 2011), it is necessary to make a definitive diagnosis with a minimally invasive examination. Gray-scale ultrasonography (US) is convenient, inexpensive and relatively non-invasive compared with other imaging tests. Therefore, US is often performed as a screening test.

Typically, hemangiomas appear on gray-scale US as well-defined, homogeneous and hyperechoic tumors with posterior acoustic enhancement (Nelson and Chezmar 1990). Approximately 70% of hemangiomas are hyperechoic and the remaining 30% are hypoechoic or have mixed echogenicity (Nelson and Chezmar 1990; Vassiliades et al. 1992). In addition, posterior acoustic enhancement is reported to be present in approximately 75% of hyperechoic hemangiomas (Taboury et al.

Address correspondence to: Hiroko Iijima, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo, Japan, 663-8501. E-mail: hiroko-i@hyo-med.ac

1983), and an echoic border (a strong echo signal at the margin) has been reported to be useful for the diagnosis of hemangioma with atypical findings (Moody and Wilson 1993). In addition, the echogenicity of hemangiomas changes with postural changes or compression (Choji et al. 1988; Okano et al. 2001).

On the other hands, contrast-enhanced ultrasonography (CEUS) is considered the gold standard for diagnosis of hepatic hemangioma because of its good diagnostic ability (Kim et al. 2000a, 2000b; Bioulac-Sage et al. 2008). The findings of hepatic hemangioma in CEUS indicated that peripheral, globular or rim-like patterns of enhancement with progressive centripetal fill-in are characteristic of hemangioma; these patterns are seen in almost all hemangiomas but are never observed in malignant tumors (Kim et al. 2000a, 2000b).

Around 1995, we discovered a phenomenon in which the speckled echogenicity of hemangioma changes continuously so that there seems to be movement inside the hemangioma in real time during gray-scale US examination. We named this phenomenon the *fluttering sign*. Because this sign can be confirmed by magnifying the tumor and observing it for 5−10 s, it has great potential to be a new complementary sign for the diagnosis of hemangioma. However, there had not been sufficient investigations regarding to the utility of this fluttering sign in the gray-scale US for diagnosis of hepatic hemangioma.

Few reports describe hepatic hemangiomas with changes in echogenicity during gray-scale US examination. Therefore, in this study, we investigated the value of the fluttering sign on gray-scale US for diagnosing hepatic hemangioma.

METHODS

Patients

A total of 171 patients with 214 tumors were diagnosed with liver hemangioma based on CEUS at the Hyogo College of Medicine between January 2007 and December 2014. Of these, 31 patients with 42 tumors were excluded because of insufficient imaging quality for evaluation of US findings. Consequently, 140 patients with 172 tumors were included in this retrospective study. The patients comprised 69 females and 71 males with a median age of 56.0 y (interquartile range [IQR]: 46.0−66.0 y). The median tumor size was 18.0 mm (IQR: 12.0−28.3 mm). Each hepatic hemangioma was routinely evaluated with gray-scale US and CEUS.

This retrospective study was in compliance with the Helsinki Declaration and was approved by the institutional review board (No. 2762) of the Hyogo College of Medicine. Before the start of the study, written informed consent was obtained from all patients for the use of clinical data, including US imaging.

Gray-scale US and CEUS

Gray-scale US and CEUS images were obtained using an Aplio XG/500/300/MX scanner (Canon Medical Systems, Tokyo, Japan), a LOGIQ E9/S8 scanner (GE Healthcare, Wauwatosa, WI, USA) or an iU22 scanner (Philips Ultrasound, Bothell, WA, USA) with a 3- to 5-MHz transducer, 6- to 8-MHz convex transducer or 8- to 12-MHz linear transducer.

Gray-scale US was performed as a screening test. When a suspicious lesion was identified, we evaluated its characteristics. The focal point was just under the bottom of the lesion. The frame rate was 15−20 frames/s. The distance from the body surface to the upper edge of the tumor was measured.

Next, CEUS was carried out at a low mechanical index of 0.2−0.33, frame rate of 15 frames/s and dynamic range of 40 dB. The focal point was just under the bottom of the lesion. Perflubutane (Sonazoid, Daiichi Sankyo Co., Ltd., Tokyo, Japan) was used as the US contrast agent. One-half of the recommended clinical dose for imaging liver lesions (0.0075 mL of encapsulated gas/kg of weight (Maruyama el al. 2009a, 2009b) was administered as an intravenous slow push and flushed with 2−3 mL of saline through a 22-gauge cannula in the median cubital vein.

CEUS images were divided into two phases: vascular and post-vascular. The vascular phase lasted up to 120 s after the injection of contrast agent; during this time, the contrast agent remained in blood vessels during CEUS. The post-vascular phase started approximately 10 min after injection; during this phase, the intravascular concentration of the contrast agent had decreased sufficiently so that it no longer provided contrast (Terminology and Diagnostic Criteria Committee 2014). The vascular phase was further divided into the arterial phase (up to 30 s after contrast agent injection) and the portal venous phase (after the arterial phase) (Terminology and Diagnostic Criteria Committee 2014). After administration of the contrast agent, moving images were taken for approximately 1 min to observe the flow of contrast agent into the tumor. Subsequently, moving images 5−10 s in duration were captured every min until 5 min.

Patients were instructed to hold their breath during tumor evaluation. One sonologist (US technician) from our institution (Y.S., who has 20 y of experience in sonography and 10 y of experience in CEUS of the liver, as of 2014) performed the gray-scale US and CEUS examinations. She was blinded to the patient's clinical data.

Diagnosis of hepatic hemangioma using gray-scale US and CEUS

In this study, diagnosis of hepatic hemangioma was confirmed by CEUS.

Differentiation of hepatic tumors based on gray-scale US and CEUS findings was performed according

to the ultrasound diagnostic criteria for hepatic tumors (Terminology and Diagnostic Criteria Committee 2014). Diagnosis with gray-scale US is based on the tumor's shape, borders and internal echo characteristics. Findings characteristic of hepatic hemangioma include a round or roundish shape, as well as a well-defined and slightly rough border. Sometimes hepatic hemangiomas have an echoic border (marginal strong echo) and posterior acoustic enhancement. We classified hepatic hemangiomas into three types: hyperechoic, mixed and hypo-echoic. Another finding associated with hepatic hemangioma, reported by Ohtake et al. (1991), is the chameleon sign, which refers to changes in tumor echogenicity caused by postural changes during the examination.

CEUS findings for differentiating hepatic hemangioma during each phase are as follows. In the arterial phase, hemangiomas are enhanced from the periphery to the center, and there is dot-like or patchy enhancement in the periphery. In the portal phase, hemangiomas are further enhanced toward the center but the center itself often remains unenhanced. In the post-vascular phase, hemangiomas are iso-enhanced relative to liver parenchyma but sometimes some parts are not enhanced.

Diagnosis of hepatic hemangioma based on CEUS and assessment of gray-scale US findings were performed by two hepatologists specializing in abdominal US (T.N. and H.I., who have 16 and 36 y of experience as of 2014, respectively). Both were unaware of the patients' clinical data and reviewed video images recorded on digital disks. In cases of discrepancy, they discussed the case until a consensus was reached. Cases were excluded from subsequent statistical analysis when they had only findings of poor quality and made precise evaluation difficult; for example, the lesions were difficult to observe in detail because of attenuation of echoes in deep parts of liver or in fatty liver. In our institution, a sonologist (Y.S.) performed ultrasonography (gray-scale US and CEUS). Based on the findings of gray-scale US and CEUS, physicians (T.N. and H.I.) determined each finding of hepatic hemangiomas.

Assessment of "fluttering sign"

We assessed the fluttering sign for diagnosing hepatic hemangioma using gray-scale US findings at a frame rate of 15−20 frames/s. The focal point was just under the bottom of the lesion.

Fluttering inside the hemangioma relative to the surrounding normal liver parenchyma was considered to be positive for what we named the fluttering sign. The sonographic features of the fluttering sign are continuous changes in speckled echogenicity of the hemangioma in real time during the examination and moving or wriggling inside the tumor on gray-scale US (Supplementary Video S1, online only). Because the change in echogenicity is seen to be quite small, it is necessary to magnify it so that the change in echogenicity of the speckle can be seen. We magnify the tumor in gray-scale US so that it is approximately 30 mm on the screen. The phenomenon is observed in the entire tumor or a part of the tumor for approximately 5−10 s during breathholding. The presence of fluttering was confirmed by two hepatologists as described above.

Statistical analysis

Continuous variables are expressed as the median (interquartile range). The Mann−Whitney *U*-test was used for continuous variables. The χ^2-test or Fisher's exact test was used for categorical variables.

Statistical significance was defined at a p value <0.05. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria) (Kanda 2013). More precisely, we used a modified version of the R Commander designed to add statistical functions frequently used in biostatistics.

RESULTS

Hemangioma findings

Table 1 summarizes the hemangioma characteristics. The 172 hemangiomas assessed consisted of 51 hyperechoic (29.7%), 58 mixed-type (33.7%) and 63 hypo-echoic (36.6%) tumors. The median diameters of the hyperechoic, mixed and hypo-echoic tumors were 13.0, 21.5 and 18.0 mm, respectively (Table 2).

Marginal strong echo (sometimes hepatic hemangiomas have an echoic border), posterior acoustic enhancement and chameleon sign were observed in 89, 103 and 100 tumors, respectively. On the other hand, the fluttering sign was observed in 123 tumors (71.5%). The prevalence of the fluttering sign was significantly higher than the prevalence of marginal strong echo (89/172, 51.7%, $p < 0.001$), posterior acoustic enhancement

Table 1. Liver hemangioma characteristics (n = 172)

Tumor size, maximum diameter (mm)*	18.0 (12.0−28.3)
Number of tumors (single/multiple)	113/27
Tumor location (segment 1/2/3/4/5/6/7/8)	(0/14/19/16/22/39/29/33)
Distance from body surface to tumor (mm)*	34.0 (20.0−50.0)
Internal echo type (hyperechoic/mixed/hypo-echoic)	51/58/63
Marginal strong echo (present/absent)	89/83†
Posterior acoustic enhancement (present/absent)	103/69†
Chameleon sign (present/absent)	100/72†
Fluttering sign (present/absent)	123/49

* Median (interquartile range).
† The prevalence of the fluttering sign differed significantly across categories.

Table 2. Analysis based on internal echo type

	Internal echo type			*p* Value
	Hyperechoic (n = 51)	Mixed (n = 58)	Hypo-echoic (n = 63)	
Tumor size (mm)*	13.0 (10.0−18.5)	21.5 (17.0−36.3)	18.0 (12.0−30.0)	<0.001
Chameleon sign	31 (60.8%)	41 (70.7%)	28 (44.4%)	0.013
Fluttering sign	20 (39.2%)	50 (86.2%)	53 (84.1%)	<0.001

* Median (interquartile range).

(103/172, 59.9%, $p = 0.031$) and chameleon sign (100/172, 58.1%, $p = 0.013$).

There were no cases of discrepancy in the US findings between the two reviewers.

Comparison of tumor size in tumors with versus without the chameleon or fluttering sign

The median diameter of tumors with the chameleon sign was 18.0 mm (IQR: 13.0−31.5 mm) mm, whereas the median diameter of tumors without the chameleon sign was 16.0 mm (IQR: 10.0−23.5 mm) ($p = 0.036$). The median diameter of tumors with the fluttering sign was 20.0 mm (IQR: 14.0−33.0 mm), whereas the median diameter of tumors without the fluttering sign was 12.0 mm (IQR: 9.0−18.0 mm) ($p < 0.001$).

Prevalence of chameleon and fluttering signs by internal echo type

The prevalence of the chameleon sign was 60.8% (31/51) for hyperechoic tumors, 70.7% (41/58) for mixed tumors and 44.4% (28/63) for hypo-echoic tumors (Table 2). For the fluttering sign, the prevalence was 39.2% (20/51) for hyperechoic tumors, 86.2% (50/58) for mixed tumors and 84.1% (53/63) for hypo-echoic tumors (Table 2). The prevalence of the fluttering sign was significantly higher for mixed or hypo-echoic tumors than for hyperechoic tumors ($p < 0.001$).

The chameleon sign was more common in hyperechoic tumors ($p = 0.047$) (Fig. 1a). In addition, the prevalence of the chameleon or fluttering sign was similar in mixed tumors (Fig. 1b). By contrast, the fluttering sign was more common in hypo-echoic tumors ($p < 0.001$) (Fig. 1c).

Comparison of distance to body surface for tumors with versus without chameleon or fluttering sign

We divided tumors into two groups based on the distance from the body surface to the tumor: <5 cm (n = 124) and ≥5 cm (n = 47). The prevalence of the chameleon sign was similar in the two groups ($p = 1.000$). By contrast, the prevalence of the fluttering sign was significantly higher when the distance was <5 cm ($p = 0.015$) (Table 3).

DISCUSSION

We have discovered a new sign in gray-scale US that characterizes hepatic hemangiomas, which we named the fluttering sign. This is a phenomenon in which

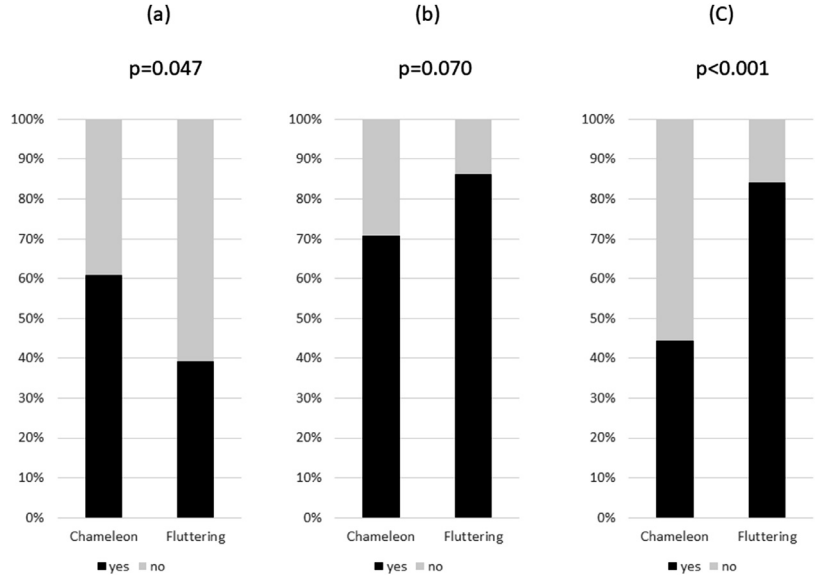

Fig. 1. Prevalence of the chameleon and fluttering signs by internal echo type. (a) Hyperechoic type. (b) Mixed type. (c) Hypo-echoic type. The fluttering sign was more common in hypo-echoic type tumors ($p < 0.001$).

Table 3. Distance from body surface to tumors with versus without chameleon or fluttering sign

	Distance from body surface to tumor		*p* Value
	<5 cm (n = 124)	≥5 cm (n = 47)	
Chameleon sign	73 (58.9%)	27 (57.4%)	1.000
Fluttering sign	96 (77.4%)	27 (57.4%)	0.015

the speckled echogenicity of the hemangioma changes continuously and seems to be moving in real time inside the hemangioma during the examination. This sign can be confirmed by magnifying the tumor and observing it for 5−10 s with gray-scale US.

In our study, the 172 hemangiomas assessed comprised 51 hyperechoic tumors, 58 mixed tumors and 63 hypo-echoic tumors. The fluttering sign was observed in 123 tumors (71.5%); this percentage was significantly higher than that of marginal strong echo ($p < 0.001$), posterior acoustic enhancement ($p = 0.031$) and the chameleon sign ($p = 0.013$). In addition, the fluttering sign was observed significantly more frequently in mixed and hypo-echoic tumors than in hyperechoic tumors ($p < 0.001$). Tumors with the fluttering sign had a relatively larger diameter than those in which the sign was not observed ($p < 0.001$). Furthermore, the prevalence of the fluttering sign was significantly higher when the distance from the tumor to the body surface was <5 cm ($p = 0.015$). Therefore, the sign we discovered is useful for diagnosing relatively large hemangiomas of the mixed or hypo-echoic type that are close to the body surface.

Some previous studies have reported changes in echogenicity observed in hemangiomas using gray-scale US.

Okano et al. (2001) reported the variable echo sign in which the echogenicity of the tumor varies with postural change from the supine position to the standing position or with compression over the abdominal wall for at least 30 min. They observed this sign in 26 cases (41%) of hemangiomas and presumed that it might be associated with changes in the distribution of blood flow in the tumor.

In addition, Ohtake et al. (1991) named the phenomenon in which the echogenicity of a hemangioma changes in response to postural changes as the chameleon sign. It was seen in 14 cases (82%) of hemangiomas and not seen in 10 cases (100%) of hepatic tumors, including hepatocellular carcinoma. Since being reported in Japanese in 1991, the chameleon sign has been recognized in Japan as an important sign for diagnosing hemangiomas.

The fluttering sign we discovered, however is a phenomenon different from both the variable echo sign and the chameleon sign. Although the latter two signs exhibit changes in internal echo pattern, for example, from hyperechoic to hypo-echoic, the fluttering sign exhibits much finer changes in which the speckled echogenicity inside the tumor changes as if it were moving or wriggling. The fluttering sign has the advantage of not requiring postural changes and being observable in a short time, 5−10 s.

The fluttering phenomenon in hemangiomas is considered to occur through the following mechanism. Scatterers such as red blood cells in the cavernous tissue structure are moved by acoustic streaming from ultrasound, which is observed as a change in the speckled echogenicity. The cavities of relatively smaller vessels in the hemangioma are likely to cause multiple reflections inside the tumor, resulting in a hyperechoic image (Gibney et al. 1987; Bajenaru et al. 2015) that is a typical US finding in hemangioma. In hyperechoic tumors, observation of the fluttering sign might be difficult because the small vessel space and narrow interval between the septa make it difficult for scatterers to move. On the other hand, relatively larger vessel cavities lead to a hypo-echoic image, which is a more atypical US finding. In larger hemangiomas, mixed or hypo-echoic internal echo patterns are frequently seen (Gibney et al. 1987; Gandolfi et al. 1991). Hypo-echoic tumors, in which the vessel space is enlarged, might have a large stagnant blood volume and high fluidity, which makes it easier to observe the movement of scatterers as the fluttering sign. Technological advances in US devices have increased tissue contrast in B-mode, which might be a factor leading to observation of the fluttering phenomenon.

The prevalence of the fluttering sign was lower when the distance from the tumor to the body surface was ≥5 cm. This might be explained by the low occurrence of acoustic flow deep in the liver.

CEUS is considered the gold standard for diagnosis of hepatic hemangioma because of its high sensitivity and specificity (Kim et al. 2000a, 2000b; Bioulac-Sage et al. 2008). Kim et al. (2000a, 2000b) reported that peripheral, globular or rim-like patterns of enhancement with progressive centripetal fill-in are characteristic of hemangioma; these patterns are seen in 95% of hemangiomas but never observed in malignant lesions. In another report, the sensitivity of CEUS for histologically proven hepatic hemangioma was reported to be 98% (Dietrich et al. 2007).

On the other hand, the sensitivity of gray-scale US for the diagnosis of hemangioma ranges from 60%−70%, and the specificity ranges from 60%−80% (Trotter and Everson 2001). Among patients in a low-risk group for liver malignancy, such as chronic hepatitis, cirrhosis and any other malignancy, it is quite probable that hyperechoic nodules are hemangiomas (Gandolfi et al. 1991). However, patients at high risk for liver malignancy often have hyperechoic hepatocellular carcinoma (Caturelli et al. 2001; Hashemi et al. 2008) that is

difficult to differentiate from hemangioma. The fluttering sign will be especially useful in these patients. In addition, large hemangiomas, which generally tend to have mixed or hypo-echoic echo images, are difficult to differentiate from other malignant hepatic tumors. As the fluttering sign is frequently observed in mixed or hypo-echoic hemangiomas, it may be especially useful in differentiating hemangiomas from malignant hepatic tumors of these echo types.

Our study has limitations. Only hepatic hemangiomas were investigated, and comparisons with other kinds of liver tumors were not performed. Therefore, we could not calculate the sensitivity, specificity, positive predictive value, negative predictive value and correct diagnosis rate of this fluttering sign for diagnosis of hepatic hemangioma. In addition, the relationship between these imaging findings and pathologic findings is not well established. Third, it was possible that there was a bias for reviewing the US and CEUS findings because of the difference in levels of experience between the two physicians.

In conclusion, the fluttering sign in gray-scale US has great potential to be a new complementary sign for the diagnosis of hemangioma. Further studies have to be done to evaluate the presence of this sign not only in other populations, but also in other tumors, particularly hepatocellular carcinoma.

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Conflict of interest disclosure—The authors have no conflicts of interest to declare.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ultrasmedbio.2020.12.004.

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