Evaluation of the Hemodynamic Status of Focal Hepatic Lesions 20 mm or Less in Diameter by Contrast-Enhanced Ultrasonography Using Sonazoid

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Key Words

Contrast-enhanced ultrasonography • Dynamic computed tomography • Focal hepatic lesions, hemodynamics • Hepatic lesions ≤ 20 mm, hemodynamic status • Hepatocellular carcinoma • Kupffer imaging • Sonazoid • Time intensity curve • Ultrasonography

Abstract

Objective: To clarify the validity of the evaluation of the hemodynamics of hepatic lesions ≤ 20 mm in diameter using contrast-enhanced ultrasonography (CE-US) with Sonazoid.

Methods: Sixty-two hepatic lesions in 55 patients with chronic hepatitis or cirrhosis due to hepatitis C virus were studied. We evaluated by quantitative analysis the time intensity curve (TIC) on hepatic lesion and parenchyma in the early vascular phase and Kupffer imaging in the post-vascular phase. **Results:** TIC patterns were classified into those with a maximum slope (Max slope) steeper in the hepatic lesion than in the parenchyma (Pattern I), those with a Max slope similar in the hepatic lesion and parenchyma (Pattern II), and those with a Max slope gentler in the hepatic lesion than in the parenchyma (Pattern III). The blood flow was considered to be higher, the blood flow velocity to be faster, and the contrast agent to reach the lesion more rapidly in Pattern I lesions than in the hepatic parenchyma. Pattern III lesions

showed that the velocity of arterial blood influx was slow.

Conclusion: Our study suggested the possibility that the TIC allows a detailed evaluation of the hemodynamics of hepatic lesions.

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Introduction

Sonazoid (Daiichi Sankyo, Tokyo, Japan), a second-generation ultrasound microbubble agent, was approved in January 2007 for clinical use in Japan. It is more stable and resistant to ultrasound exposure and radiates sufficient harmonic signals by low mechanical index (MI) transmission power to allow continuous real-time imaging, but unlike Levovist (Schering, Berlin, Germany), which is too sensitive for the ultrasound pulse, the non-real-time imaging method has to be used. Moreover, since the microbubbles of Sonazoid are markedly taken up by Kupffer cells, which are hepatic macrophages, it is stable for up to at least 3 h after injection and tolerable for multiple scanning, and can be obtained in the low-power acoustic field [1–7]. Because of these characteristics, Sonazoid is expected to be useful for the detection, characterization and hemodynamic evaluation of hepatic lesions and assessment of function of Kupffer cells.

Fig. 1. **a** B-mode US revealing the hypoechoic lesion (arrow). **b** CE-US reveals tumor staining in the early phase. When obtaining TIC, ROI is placed on the whole lesion (red) and the surrounding parenchyma (green) at the same depth as the lesion, excluding large blood vessels.

Hepatocellular carcinoma (HCC) is often a multistep pathway in cirrhosis [8, 9], and lesions ≤ 20 mm in diameter can be classified into dysplastic nodules (DN) or early HCC (e-HCC) according to their arterial and portal hemodynamics as well as histopathological findings. However, these two lesions are often difficult to differentiate by imaging modalities such as ultrasonography (US) and dynamic computed tomography (dCT). Close evaluation of the hemodynamics of hepatic lesions is considered to promote the understanding of the progression along the multistep pathway of HCC, i.e. the diagnosis of the characterization. There has been no detailed study on the hemodynamics of hepatic lesions using contrast-enhanced US (CE-US) with Sonazoid.

In this study, we performed CE-US using Sonazoid in hepatic lesions ≤ 20 mm and prepared time intensity curves (TIC) of hepatic lesions and surrounding parenchyma. We compared the TIC in the early vascular and Kupffer imaging in the post-vascular phase with dCT findings and clarified the validity of the evaluation of the hemodynamics and diagnosis of hepatic lesions using the quantified TIC.

Materials and Methods

Sixty-two hepatic lesions (maximum mean diameter 13.7 ± 4.1 mm) in 55 consecutive patients (38 men and 17 women, mean age 67 ± 9.3 years) with chronic hepatitis and liver cirrhosis due to hepatitis C virus who underwent B-mode US between April 2007 and September 2008 were found to be ≤ 20 mm in diameter in the liver. Thereafter, the patients underwent CE-US using Sonazoid. Hepatic lesions clearly diagnosed to be hemangioma, focal

nodular hyperplasia, cholangiocellular carcinoma or metastatic liver tumor on the basis of the clinical course or findings on B-mode US or other imaging modalities were excluded. Examination of US was performed using an Aplio XG (Toshiba, Tokyo, Japan) and a convex probe (PVT-375 BT, 3.75 MHz; Toshiba). The acoustic power of CE-US was set at a MI of 0.2; the dynamic range was fixed at 60–65 dB. A single focus point was set at the lower margin of the lesion, and a bolus intravenous injection of Sonazoid (0.015 ml/kg b.w.) was performed via the left elbow venous line followed by 10 ml of normal saline flush. After injection of Sonazoid, the patients were requested to hold their breaths. The images of the ideal scanning plane were displayed in real-time mode for all phases. The vascular findings on pulse subtraction harmonic imaging US were shown as lesion vessel flow in the early vascular phase (about 15–40 s after the injection of Sonazoid). Parenchymal findings were obtained as Kupffer imaging in the post-vascular phase at least 15 min after the intravenous injection of Sonazoid. Images and videoclips were stored on a hard disk for offline analysis. Prototype software dedicated to the Aplio XG was used to calculate TIC for the hepatic lesion and surrounding parenchyma. Regions of interest (ROI – a circular region of 8–15 mm in diameter) were set corresponding to the whole lesion and a part of the surrounding parenchyma at the same depth as the lesion, excluding large blood vessels (fig. 1).

In the TIC (fig. 2), the steepest slope in the rising phase of echo intensity was defined as the maximum slope (Max slope). The Max slope was compared between the hepatic lesion and parenchyma. In the post-vascular phase, staining of the hepatic lesion was examined according to the presence or absence of a defect. dCT was also performed in all subjects almost simultaneously with CE-US. dCT was performed by 16 multidetector CT scanner (Aquilion 16, Toshiba), and images were obtained cephalocaudal with section thickness of 5 mm and pitch 0.94, with intravenous bolus injection of non-ionic contrast material (90 ml of 300 mgI/dl, Iopamiron; Bayer Schering Pharma, Osaka, Japan) at 3 ml/s. The lesions were classified according to their images in the early (30–40 s) and late (120–150 s) phases into Groups A (high- and low-density areas, respectively), B (iso- and low-density areas, re-

Table 1. Comparison of TIC in the early vascular and post-vascular phase (Kupffer imaging) with dynamic CT

CE-US ^a	Dynamic CT ^b			
	A (high-low)	B (iso-low)	C (low-low)	D (iso-iso)
I	26/5 ^c	3/1	1/1	1/2
II	0	1/2	0/2	1/6
III	0	0/1	2/2	0/5

^a CE-US: contrast-enhanced ultrasonography using Sonazoid.

^b Dynamic CT findings (early phase-late phase); high, iso, low: high-, iso-, low-density.

^c Number of lesions: defect yes/no in the post-vascular phase (Kupffer imaging).

Fig. 2. Schematic representation of the measurement of parameters on the TIC.

Fig. 3. TIC on ROI on hepatic lesion (red) and hepatic parenchyma (green). TIC patterns were classified into those with a maximum slope (Max slope) steeper in the hepatic lesion than in the hepatic parenchyma (Pattern I, **a**), those with a Max slope similar in the hepatic lesion and hepatic parenchyma (Pattern II, **b**), and those with a Max slope gentler in the hepatic lesion than in the hepatic parenchyma (Pattern III, **c**).

Fig. 4. Correlation between SI (Max slope of lesion/Max slope of parenchyma) values obtained with TIC and the maximum lesion diameter.

spectively), C (low-density areas in both phases), and D (iso-density areas in both phases, i.e., not visualized in either phase on dCT). The Max slope and presence or absence of a defect in each lesion was compared with dCT findings. The TIC was prepared without the knowledge of dCT findings.

In the TIC, the Max slope was determined in the hepatic lesion and parenchyma. The ratio of the Max slope between the hepatic lesion and parenchyma [slope index (SI) = Max slope in the hepatic lesion/Max slope in the hepatic parenchyma] was calculated and compared with the maximum lesion diameter.

In the TIC, the relationships of (a) the difference between the time of the beginning of the ascent of the hepatic lesion curve (lesion arrival time) and that of the hepatic parenchymal curve (parenchyma arrival time) (AT), (b) difference between the echo intensity at the peak of the hepatic lesion curve (lesion peak dB) and that of the hepatic parenchyma curve (parenchyma peak dB) (PdB), and (c) time until one-half of the peak of hepatic lesion echo intensity (1/2dB time; 1/2dBT) with the Max slope were evaluated.

The SI and lesion diameter were compared using Pearson's correlation coefficient. The AT, PdB, and 1/2dBT were compared with the TIC pattern defined according to the Max slope using the Kruskal-Wallis test. The level of significance of the tests was $p < 0.05$.

This study was approved by the Ethical Review Board of Toho University Medical Center, Omori Hospital.

Results

According to the TIC, the lesions were classified into those with a Max slope steeper in the hepatic lesion than in the hepatic parenchyma (Pattern I), those with a Max

slope similar in the hepatic lesion and hepatic parenchyma (Pattern II), and those with a Max slope gentler in the hepatic lesion than in the hepatic parenchyma (Pattern III) (fig. 3). Forty lesions showed Pattern I, of which 31 belonged to Group A, but 3 lesions in Group D not imaged by dCT also showed this pattern. 12 lesions showed Pattern II, and 10 showed Pattern III. Although there was no characteristic distribution of patterns in these groups, no group A lesion showed these patterns. In the post-vascular phase of CE-US, no defect was noted in 5 lesions of Group A, which exhibited typical characteristics of HCC on dCT. Forty-seven lesions were imaged as low-density areas in the late phase, i.e. they were classified as Groups A, B, or C, and 33 of them showed a defect in the post-vascular phase of CE-US. Defects were also observed in 2 of the 12 lesions that showed Pattern II (table 1).

No significant correlation was noted between the SI and lesion diameter in all 62 lesions ($r = 0.079$, $p = 0.543$) (fig. 4). Also, no significant correlation was noted in the 35 lesions that showed defects in the post-vascular phase of CE-US ($r = -0.211$, $p = 0.229$) or the 40 lesions showing Pattern I TIC ($r = -0.176$, $p = 0.284$).

The median AT was -0.56 s (range -7.78 to 0.72 s) in Pattern I, -0.11 s (range -1.67 to 0.62 s) in Pattern II, and 2.46 s (range 0 to 7.67 s) in Pattern III, with significant differences between Patterns I and III ($p < 0.001$) and between Patterns II and III ($p < 0.05$). While no significant difference was noted between Patterns I and II, the ascent of the hepatic lesion curve tended to begin earlier in Pattern I (fig. 5).

The median PdB was 5.43 dB (range -1.16 to 28.98 dB) in Pattern I, 0.66 dB (range -4.54 to 8.25 dB) in Pattern II, and 0.31 dB (range -8.32 to 7.43 dB) in Pattern III, with significant differences between Patterns I and II ($p < 0.05$) and between Patterns I and III ($p < 0.01$) (fig. 6).

The median 1/2dBT was 2.64 s (range 0.889 to 5.224 s) in Pattern I, 2.20 s (range 1.445 to 3.279 s) in Pattern II, and 4.34 s (range 2.001 to 6.891 s) in Pattern III, with significant differences between Patterns I and III ($p < 0.05$) and between Patterns II and III ($p < 0.05$) (fig. 7).

Discussion

There have been a few reports on the hemodynamic examination of hepatic lesions by CE-US using Levovist, SonoVue (Bracco, Milan, Italy), and CO_2 angiography [10–14]. However, microbubbles of Levovist easily collapse upon US emission because of their fragile property. Therefore, CE-US using Levovist images are basically ob-

Fig. 5. Comparison of TIC pattern and AT (the difference between the time of the beginning of the ascent of the hepatic lesion curve and that of the hepatic parenchymal curve).

Fig. 6. Comparison of TIC pattern and PdB (the difference between the echo intensity at the peak of the hepatic lesion curve and that of the hepatic parenchyma curve).

tained intermittently, real-time images are obtained within a short period of time at an early vascular phase [3, 15]. Also, SonoVue is a second-generation microbubble agent of ultrasound, as is Sonazoid, and produces stable non-linear oscillations in the low MI, and supplies very good details of the second harmonic signals in real-time. Therefore, it is useful for blood flow assessment, but the evaluation of Kupffer cell function is difficult because it is not easily phagocytosed by Kupffer cells [3, 16]. Furthermore, CE-US using CO₂ angiography [14] is highly invasive, and it has been rarely employed recently due to the development of microbubble agent of ultrasound. Compared with these methods, Sonazoid consists of microbubbles of perfluorobutane gas stabilized by phospholipid monolayer shells with a median volume diameter of 2–3 μ m; it is more stable and resistant to ultrasound exposure, and it radiates sufficient harmonic signals by low MI transmission power to allow continuous real-time imaging. Also, it is taken up by Kupffer cells immediately after intravenous injection and exists as microbubbles for 3 h within Kupffer cells; the hepatic parenchyma-specific contrast by Sonazoid is due to the distribution of the microbubbles in Kupffer cells [1–7]. It is therefore considered to be useful for the hemodynamic evaluation of hepatic tumors, diagnosis of their presence, and assessment of Kupffer cell function. There have been few reports on the hemodynamic evaluation of hepatic lesions using CE-

Fig. 7. Comparison of TIC pattern and 1/2dBT (the time until one-half of the peak of hepatic lesion echo intensity).

US by Sonazoid, and regarding lesions ≤ 20 mm in diameter, which are classified as DN to e-HCC in particular, no evaluation has been made.

In chronic hepatitis or liver cirrhosis, hepatic lesions that do not markedly and grossly destroy the background

liver architecture but stand out from the surrounding tissues as lesions are frequently observed. Portal components and pseudo-interlobular connective tissues are noted in many of such lesions, which are usually ≤ 20 mm in diameter. These lesions may be classified into DN or e-HCC according to their arterial and portal hemodynamics as well as histopathological findings. Forner et al. [17] reported that hepatic lesions ≤ 20 mm in diameter and showing the imaging finding of arterial hypervascularization on CE-US using SonoVue were diagnosed as HCC, with a specificity of 86% and a positive predictive value of 92%. Hatanaka et al. [6] also reported that in HCC (mean diameter 22.6 ± 16.3 mm) the presence of intratumoral vessels supplied from the periphery and fast washout by CE-US using Sonazoid were the most typical HCC, with a sensitivity of 96.6% and specificity of 94.4%, but the differentiation of the two hepatic lesions (DN and e-HCC) by imaging is difficult if they are hypovascular lesions, and so this often requires histopathological examination. However, the biopsy of small nodular lesions in cirrhosis is not entirely reliable. In fact, needle placement may be difficult and a sampling error may occur. Moreover, it is very difficult to distinguish well-differentiated HCC from DN on small biopsy specimens, as there is not a clear-cut dividing line between DN and well-differentiated HCC [18]. Moreover, there have been reports on needle tract seeding after the fine-needle biopsy (FNB) of hypervascular lesions [19]. We therefore prepared TIC of hepatic lesions ≤ 20 mm in diameter by CE-US using Sonazoid in patients with chronic liver diseases, who have a risk of developing HCC, and evaluated whether the TIC is useful for the hemodynamic evaluation of hepatic lesions or the diagnosis of HCC.

The TIC is a curve indicating changes in echo intensity. Its slope is considered to change with the inflow volume of the contrast agent, i.e. the blood flow. When a fixed amount of Sonazoid is injected intravenously in bolus, the TIC shows an initial rise with increases in the concentration of the contrast agent flowing into the ROI. In the phase in which the concentration of the contrast agent is stabilized, the amount of the contrast agent flowing into the ROI is fixed, and the TIC becomes linear until it reaches a peak. Near the peak, the amount of contrast agent flowing into the ROI is saturated, and the TIC deviates again. Therefore, we thought that it is best to analyze the blood flow in the phase in which changes in echo intensity per unit time are fixed. The change in echo intensity per unit time in the phase of linear TIC corresponds to the level of influx of the contrast agent per unit time, i.e. the blood flow, and we designated it the Max

slope. In patients with chronic liver disease, the hepatic parenchymal flow is known to change with the progression of the disease stage, showing arterialization [20, 21], and the Max slope in the lesion alone is inadequate to assess the hemodynamics of the lesion. We therefore compared the Max slopes in the lesion and surrounding parenchymal regions. We also considered it necessary to evaluate the ratio of the Max slope between the lesion and surrounding parenchymal regions for quantitative analysis. For these reasons, we defined the SI and used it for the quantitative comparison of the blood flow in individual lesions.

As observed above, the TIC could be classified into 3 patterns. Of the 40 lesions that showed Pattern I, 31 belonged to Group A on dCT, and no lesion in Group A was observed in Pattern II or III. Since all lesions that belonged to Group A on dCT showed Pattern I, this pattern was suggested to indicate a hypervascular lesion. Also, 4 lesions in Group B, 2 in Group C, and 3 in Group D showed Pattern I among the lesions that were hypovascular or were not visualized on dCT. In addition, 1 lesion in Group D was diagnosed to be well-differentiated HCC on FNB (fig. 8). This suggested the possibility that changes in the blood flow can be evaluated more sensitively by CE-US using Sonazoid than by dCT. Some hypervascular lesions may be imaged as hypovascular by dCT due to the effects of various factors including the timing of imaging, cardiac output, and portal hemodynamics. However, CE-US using Sonazoid, which facilitates the evaluation of the hemodynamics from immediately after the administration of the contrast agent, shows good temporal resolution and is able to present serial changes in the blood flow. Recently, modalities such as perfusion CT have begun to be used, but CE-US using Sonazoid is considered to be useful for the early hemodynamic evaluation in consideration of problems such as exposure to radiation and iodine allergy. Furthermore, we determined 3 parameters, i.e. AT, PdB and $1/2\text{dBT}$, from TIC curves quantitatively to evaluate 3 patterns of Max slope visually provided from TIC, and we pushed forward the examination about the TIC.

HCC is known to show progression along the multi-step pathway [8, 9], and a close correlation is observed between the arterial and portal hemodynamics in the lesion and the histopathological degree of differentiation [22]. Therefore, information concerning the hemodynamics in hepatic lesions is extremely important for their diagnosis. In the process of dedifferentiation from benign low-grade DN (LGDN), through the stages of high-grade DN (HGDN) and e-HCC, to classical HCC, the ar-

Fig. 8. The patient was an 80-year-old woman with hepatitis C cirrhosis. On dCT, no lesion was visualized in any phase (Group D). **a** On B-mode US, a hypoechoic lesion of 13 mm in diameter was delineated in S6 (arrow). **b** The TIC prepared by CE-US using Sonazoid showed Pattern I. **c** A diagnosis of well-differentiated HCC was made by FNB. HE. $\times 200$.

terial and portal blood flows change [23]. With the progression of the degree of differentiation, the arterial blood flow decreases temporarily in an early stage of multi-step process (LGDN to e-HCC), but increases again by development of new arterial vessels, termed unpaired arteries, which become the dominant blood supply in overt HCC lesions, showing a biphasic pattern. On the other hand, the portal blood flow is known to show a monophasic pattern, i.e. it decreases gradually with the progression of the degree of differentiation from the stage of HGDN, and almost disappears before the stage of advanced HCC [23–25].

Hirota et al. [10], in their evaluation of the hemodynamics in the hepatic parenchyma by CE-US using Levovist, reported that the time lag between the arrival of the contrast agent at the hepatic artery and its arrival at the portal vein was about 5 s in the normal liver, chronic hepatitis, and liver cirrhosis. This time is considered to be the phase in which there is only the arterial blood flow, i.e., pure arterial phase. On the basis of these results, the quantitative data on Pattern III may include the portal blood flow, and, thus, may not be an evaluation of the pure arterial blood flow, but the evaluation of the Max slope, AT, PdB, and 1/2dBT of the TIC is considered at least equivalent to the evaluation of the arterial blood flow.

The AT showed significant differences between Patterns I and III and between Patterns II and III, and the

arrival of the contrast agent at lesions that show Pattern III was found to be delayed compared with its arrival at the hepatic parenchyma. Also, while there was no significant difference in Pattern I or II, the contrast agent tended to arrive at the lesion earlier than at the hepatic parenchyma in Pattern I. The 1/2dBT was considered to represent the time of increase in echo intensity in the phase with a stable blood flow and to reflect changes in echo intensity, i.e. blood flow velocity of the lesion. Pattern III showed significant differences compared with Patterns I and II, and the blood flow velocity may be slow in lesions that show Pattern III. The 1/2dBT revealed no significant difference between Patterns I and II, but the blood flow velocity tended to be faster in lesions that showed Pattern I. The PdB in lesions showing Pattern I differed significantly compared with those in lesions showing Patterns II and III, the blood flow was considered to be higher in lesions showing Pattern I, and this difference was indicated as changes in echo intensity. Thus, in this study, changes in the blood flow in lesions could be detected as changes in echo intensity without being affected by the echogenicity of the lesions themselves. In consideration of these results, the blood flow is considered to be higher, the blood flow velocity to be faster, and the contrast agent to reach the lesion more rapidly in lesions showing Pattern I than in the hepatic parenchyma. Therefore, Pattern I is considered to indicate

Fig. 9. The patient was a 67-year-old man with hepatitis C cirrhosis. **a** The hepatic lesion was imaged as a hypoechoic lesion 16 mm in diameter in S6 on B-mode US and as iso- and low-density areas in the early and late phases, respectively, of dCT (Group B). **b** The TIC of this lesion showed Pattern II. This patient was periodically followed up by US and dCT. No change was noted on dCT. **c** The TIC pattern changed to Pattern I after 12 months. A diagnosis of well-differentiated HCC was made by FNB.

e-HCC or classical HCC with development of tumorous arteries, but no significant difference was noted in the AT or 1/2dBT between Patterns I and II, suggesting that tumorous arteries may not be developed in lesions ≤ 20 mm in diameter even if they are HCCs, and that the differentiation between normal and tumorous artery is difficult. Evaluation of a greater number of patients may disclose a significant difference between Patterns I and II even in lesions ≤ 20 mm in diameter. Pattern III was considered to represent HGDN to e-HCC, in which the velocity of arterial blood influx is slow, and normal arteries are few or absent. In this study, comparisons with histopathological findings were not performed, and no significant difference was noted between Patterns I and II, but, as for the arterial blood flow, the TIC pattern is considered to change from II $\rightarrow$ III $\rightarrow$ I with the progression of the degree of differentiation in the progression along the multistep pathway of HCC (fig. 9).

In this study, there was no significant correlation between the SI and maximum lesion diameter. In particular, no correlation was noted between the SI and maximum lesion diameter in the 35 lesions that showed defects in the post-vascular phase or 40 lesions that showed Pattern I on TIC, which are generally diagnosed as HCC. In the progression along the multistep pathway of HCC,

the intratumoral blood flow does not change uniformly, and the hemodynamics vary widely. Therefore, the TIC is considered to be useful to assess the blood flow of the entire lesion, but may not reflect slight changes in hemodynamics within the lesion. In this study too, lesions ≤ 20 mm in diameter, in which evaluation of the hemodynamics is extremely difficult, were examined. This is considered to explain the absence of a correlation between the SI and maximum lesion diameter.

A major characteristic of Sonazoid is that Kupffer imaging, which is extremely stable and tolerable for multiple scanning at least up to 3 h in the post-vascular phase, is feasible, and a defect in the post-vascular phase is reportedly useful for the diagnosis of the presence of HCC [2–4]. In this study, however, no defect was observed in the post-vascular phase in 5 of the lesions usually diagnosed to be typical HCC, i.e. those classified in Group A by dCT, and 1 each of the 4 lesions of Group B and 2 lesions of Group C that showed Pattern I. While the post-vascular phase is set at 15 min after injection, defects are often obscure in this phase even in typical HCC, and occasionally become clear after this phase. Also when the echo intensity of the tissue is high, as in advanced fatty liver, sufficient contrast enhancement of the deep area may not be possible, or the distinction between a faint delineation

or a defect may be difficult to make in high echoic lesions. Furthermore, in well-differentiated HCC, the density of Kupffer cells may be equal or increased compared with the surrounding parenchyma [26], and the absence of a defect in the post-vascular phase does not exclude the possibility of the presence of HCC. A definitive diagnosis of HCC is considered to be possible by the examination of both the hemodynamics in the vascular phase and, with sufficient knowledge of the above problems, the presence or absence of a defect in the post-vascular phase.

The hemodynamics-based diagnosis of hepatic lesions using CT during arterial portography has been reported sporadically [22–25]. However, as the portal blood flow in the lesion may increase temporarily in the progression along the multistep pathway of HCC [27], a decrease in the portal blood flow is not a reliable index for the diagnosis of HCC, and CT during arterial portography is not necessarily a gold standard. On the other hand, contrast enhancement in the early vascular phase and a defect in the post-vascular phase on CE-US using Sonazoid guarantee a diagnosis of HCC [6], but clear lesion images may be difficult to obtain depending on the stage of the disease in the hepatic parenchyma [20, 21], and the judgment of whether the contrast is enhanced is occasionally difficult to make even in hypervascular lesions. This study, in which the hemodynamics in the early vascular phase

were quantitatively evaluated using the TIC, suggested that the diagnostic ability of CE-US using Sonazoid can be further improved. In this study, however, the number of subjects was small, and they may have included regenerative nodules and focal fat sparings other than e-HCC and DN, because a histopathological examination was not performed. Also, as mentioned above, even if FNB had been performed for every lesion, a sample obtained by FNB alone is insufficient for the histopathological evaluation of the entire lesion. Comparison of the TIC with surgically resected specimens and findings by other modalities including Gd-EOB-DTPA magnetic resonance image (EOB-MRI) in a larger number of patients is expected to clarify the validity of the hemodynamic assessment of hepatic lesions and their diagnosis using the TIC.

In conclusion, the hemodynamics of hepatic lesions ≤ 20 mm in diameter were evaluated using the TIC prepared by CE-US using Sonazoid. Although the number of subjects was small, the results suggest the possibility that the TIC allows a more detailed evaluation of the hemodynamics of hepatic lesions than dCT. Also, the TIC pattern was found to show specific tendencies, and its evaluation along with the presence or absence of a defect in the post-vascular phase is considered to improve the sensitivity of the diagnosis of HCC.

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