Contrast Advanced Dynamic Flow Imaging and Contrast Pulse Subtraction Imaging: Preliminary Results in Hepatic Tumors

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Abstract

Purpose: To investigate the usefulness of contrast advanced dynamic flow imaging and contrast pulse subtraction imaging in the intranodular hemodynamics of hepatic tumors.

Materials and Methods: Ten patients underwent contrast advanced dynamic flow imaging and contrast pulse subtraction imaging using Levovist®, a microbubble contrast agent. Fourteen hepatic tumor nodules were studied: 9 were hepatocellular carcinoma, 1 metastasis, 1 hemangioma, 1 adenomatous hyperplasia, and 2 metastatic lymph nodes of hepatocellular carcinoma. Real-time scanning of contrast advanced dynamic flow imaging and intermittent interval-delay scanning of contrast pulse subtraction imaging were carried out in the early arterial phase, the late vascular phase, and the postvascular phase. The results obtained from contrast advanced dynamic flow imaging and contrast pulse subtraction imaging were compared with those obtained by precontrast power Doppler imaging and three-phase dynamic CT, respectively.

Results: The rate of detection of intranodular vascularity by contrast advanced dynamic flow imaging (93%) or contrast pulse subtraction imaging (93%) was significantly higher than that of precontrast power Doppler imaging (29%) and was as high as that of dynamic CT. Characteristic intranodular hemodynamics were detected in hepatocellular carcinoma, metastasis, hemangioma, and adenomatous hyperplasia with typical appearance of an intranodular blood vessel image in the early arterial phase, a parenchymal stain image in the late vascular phase, and a perfusion defect image in the post-vascular phase.

Conclusion: Contrast advanced dynamic flow imaging and contrast pulse subtraction imaging clearly show the intranodular hemodynamics in hepatic tumors.

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Keywords

contrast media, liver neoplasm, pulse inversion harmonic imaging, ultrasound, wide band harmonic imaging

1. Introduction

With the advancement of microbubble contrast agents, ultrasonographic imaging technologies are facing a major challenge in detecting echoes from microbubbles with high sensitivity and high resolution[1)-5)]. As previous studies have pointed out, although conventional color Doppler imaging and power Doppler imaging have greatly improved the depiction of blood-flow signals through their use of microbubble contrast agents[6)-8)], they nevertheless have intrinsic drawbacks such as blooming and noise artifacts, which limit their usefulness in the clinical setting[9)].

New ultrasound technologies have improved our ability to detect blood-flow signals by receiving the harmonic components from the nonlinear movement of the microbubbles, the signals from which are a multiple or submultiple of the emitted ultrasound frequency[10)-18)]. Thorough study of the depiction of characteristic hemodynamics of hepatic tumors using second harmonic imaging and pulse/phase inversion harmonic imaging in particular has resulted in great

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progress in the differential diagnosis of hepatic tumors[10)-18)].

Advanced dynamic flow imaging (ADF, Toshiba Medical Systems, Toshiba Company, Tokyo, Japan) is a new technology which, based on the improvement of conventional dynamic flow imaging, uses digital imaging optimization filtering technology. The high sensitivity to the signals produced by microbubbles and the resulting high resolution of advanced dynamic flow imaging is obtained by making transmission and reception conditions similar to those used for B-mode imaging, and eliminating motion artifacts by digital imaging optimization filtering. Advanced dynamic flow imaging can thus recognize Doppler as well as B-mode signals with good accuracy and at a high frame rate.

Pulse subtraction imaging is another new microbubble-specific technology that combines pulse/phase inversion harmonic imaging with subtraction technology. Multiple reversions, 90- or 270-degree phase inversion, for example, are used in combination, efficiently canceling fundamental signals and boosting harmonic signals, resulting in optimized imaging. Theoretically, high detectability of enhanced blood-flow signals is obtained on pulse subtraction imaging when used with a microbubble contrast agent.

We used contrast advanced dynamic flow imaging and contrast pulse subtraction imaging with Levovist®, a microbubble contrast agent, to investigate the usefulness of these methods in depicting intranodular hemodynamics of hepatic tumors.

2. Materials and Methods

2.1 Patients

From August to September 2001, 10 patients (7 men, 3 women) were studied with contrast advanced dynamic flow imaging and contrast pulse subtraction imaging. The patients were aged 37 to 77 years (mean, 60 years). Six patients had 9 hepatocellular carcinoma nodules: 7 had not yet been treated, and 2 had received percutaneous radio-frequency ablation. The remaining 4 patients had 1 liver metastasis, 1 hemangioma, 1 adenomatous hyperplasia, and 2 metastatic lymph nodes of hepatocellular carcinoma. Thus, 14 nodules were studied. The diagnoses were based on laboratory tests, α-fetoprotein and prothrombin-induced vitamin K absence (PIVKA-II), and typical finding on dynamic CT, dynamic MRI, or hepatic angiography.

Size and number of nodules were ascertained from the ultrasound findings. The nodules ranged from 1 to 6.1 cm (mean $\pm$ SD, 2.55 $\pm$ 1.38 cm) in diameter. Depth and location, defined as the distance between the deepest edge of the nodule and a point on the surface of the body, ranged from 2 to 10 cm (mean, 5.7 cm). Of the nine hepatocellular carcinomas, two were hypoechoic; four were mosaic-echoic, and three were hyperechoic in the B-mode image. The metastasis was mixed echoic with cystic change in a hypoechoic lesion. The hemangioma was hyperechoic, while the adenomatous hyperplasia and the two lymph nodes were hypoechoic in the B-mode image.

2.2 Contrast medium

The contrast agent used in this study was Levovist® (Schering Company, Berlin, Germany). Levovist® is an intravenous microbubble agent that contains 99.9 percent D-galactose and 0.1 percent palmitic acid. Vigorously mixing 7 ml of sterile water with 2.5 grams of Levovist® microparticles yielded a total of 8.5 ml of suspension at a concentration of 300 mg/ml. This suspension was injected as a bolus through a 20 gauge cannula placed in the antecubital vein at a rate of 1 ml/s and soon flushed with 10 ml of normal saline. Levovist® was injected once for each nodule. However, each injection of Levovist® was separated by an interval of not less than 10 minutes.

2.3 Imaging

A Toshiba Aplio (Toshiba Medical Systems, Toshiba Company, Tokyo, Japan) ultrasound unit with a wide-band convex-array transducer was used in all ultrasound studies. Fundamental B-mode imaging was used before the contrast agent was injected, to find a plane that clearly showed both the nodule and the surrounding liver parenchyma. Power Doppler imaging at 3.0 MHz was used to evaluate intranodular vascularity. In contrast ultrasound imaging, when the first enhanced signal appeared in the liver parenchyma about 10 seconds after administration of Levovist®, the patient was asked to hold his/her breath to minimize motion artifacts and avoid losing the target nodule. Contrast ultrasound imaging took place during the early arterial phase (10 to 40 seconds), the late vascular phase (1 to 3 minutes), and the postvascular phase (5 to 7 minutes).

A frequency of 2.0 to 2.5 MHz was used in the contrast advanced dynamic flow imaging study. Pulse repetition frequency was 3.9 KHz. A single focus point was set at the nodule's deepest margin. A low mechanical index (0.2 to 0.3) was set for B-mode imaging, and a relatively high mechanical index (1.3) was used for advanced dynamic flow imaging mode. Contrast advanced dynamic flow imaging continued for 10 to 30 seconds in each phase while the scanning plane was varied slightly to enable us to study the entire nodule. Sweep scanning was used in the postvascular phase. Different frame rates were set by changing the scanning area in advanced dynamic flow imaging: five frames per second in the early arterial phase; two frames per second in the late vascular and the postvascular phase.

Contrast pulse subtraction imaging was performed at 3.2 MHz. A single focus point was set on the deepest margin of each lesion. The acoustic power had

a mechanical index of 1.2. Intermittent interval-delay scanning of contrast pulse subtraction imaging was carried out with an additional real-time B-mode display at a low mechanical index of 0.2 to 0.3 in dual display mode. A 0.2 to 0.5-second interval was used in the early arterial phase; and 1.0 second was used in the late vascular and postvascular phases.

All ultrasound data were recorded on videotape from the beginning of B-mode imaging. Still pictures were stored on the hard disk of the ultrasound unit by reviewing the cine-loops.

All but one patient, who had hemangioma, underwent three-phase dynamic CT 1 week before or after the contrast ultrasound study. A helical CT system (Toshiba X-vigor, Toshiba Medical Systems, Tokyo, Japan) was used. A total of 100 ml of iopamiron (Iopamidol, Nihon Schering Company, Osaka, Japan), with an iodine concentration of 370 mg/ml, was injected into an antecubital vein.

2.4 Data Analysis

The intranodular hemodynamics of the nodules on ultrasound imaging were evaluated by two certified sonographers who had no knowledge of the results obtained by dynamic CT or other imaging methods. Compared with the surrounding liver parenchyma, the tumors were assessed as hypervascular, isovascular, or hypovascular in the early arterial and the late vascular phases. In the postvascular phase, the object was to determine whether or not the perfusion defect was visualized. Three-phase dynamic CT was interpreted by three other hepatologists or radiologists who had no knowledge of the results of contrast ultrasound. High, iso, and low attenuation of the nodules were defined as hypervascular, isovascular, and hypovascular, respectively, when compared with the surrounding liver parenchyma. Different assessments in intranodular vascularity among the reviewers were resolved using reevaluation and discussion to reach a consensus.

The rates at which intranodular vascularity was detected by contrast advanced dynamic flow imaging and contrast pulse subtraction imaging were compared to those obtained using precontrast power Doppler imaging and dynamic CT, respectively. The Chi-square test was used to evaluate the difference. A p value less than 0.05 was considered to be a significant difference.

The same protocol was used in studying all patients and had been approved by the Institutional Ethics Board of the Kinki University School of Medicine.

3. Results

Precontrast power Doppler imaging depicted blood-flow signals in only 4 (29%) of the 14 hepatocellular carcinoma nodules. After Levovist® was administered, both advanced dynamic flow imaging and pulse subtraction imaging depicted intranodular vascularity in 13 of the 14 nodules (93%), the exception being the nodule proved by dynamic CT to be completely necrotic after radio-frequency ablation. The difference between precontrast power Doppler imaging and contrast advanced dynamic flow imaging or contrast pulse subtraction imaging was statistically significant ($p<0.05$).

In the early arterial phase, intranodular blood vessel images were detected because of the high frame rate of contrast advanced dynamic flow imaging and the short interval of contrast pulse subtraction imaging. In the late vascular phase, the parenchymal stain image resulted from the pooling of microbubbles in the nodules during the long interval. Perfusion defect images in the postvascular phase resulted from the microbubbles having been washed out.

Similar appearance of the intranodular hemodynamics of the lesions was obtained by contrast advanced dynamic flow imaging and contrast pulse subtraction imaging. In the early arterial phase, intratumoral blood vessels were depicted in eight of the nine hepatocellular carcinomas (**Fig. 1**). Tumor blood vessels were detected first at the periphery of the tumors and were then seen to flow gradually to the center of the tumor. Homogeneous or heterogeneous tumor parenchymal stain appeared in all eight hepatocellular carcinomas in the late vascular phase. In the postvascular phase, the perfusion defect was detected in these tumors as a result of the rapid washout of Levovist® from the tumor. This hemodynamic appearance of hepatocellular carcinoma corresponded closely with that observed on dynamic CT: high attenuation in the arterial phase and low attenuation in the portal and delayed phase. In the remaining hepatocellular carcinoma nodule, which had been shown to respond positively to radio-frequency ablation, contrast advanced dynamic flow imaging detected no blood-flow signal in the early arterial phase, the late vascular phase, or the postvascular phase. In contrast, liver metastasis was indicated by a few linear blood vessels in the marginal area in the early arterial phase, rim enhancement in the late vascular phase, and perfusion defect in the postvascular phase (**Fig. 2**). This was similar to findings from three-phase dynamic CT. The typical spotty pooling pattern or cotton-wool appearance, which lasted throughout the postvascular phase, was detected in the hemangioma (**Fig. 3**). The adenomatous hyperplasia that was proved by ultrasound-guided biopsy and three-phase dynamic CT showed findings typical of harmonic imaging: early arterial hypovascularity with portal perfusion in the vascular phase presumed by interval-delay scanning. In the two metastatic lymph nodes from hepatocellular carcinoma, intranodular vascularity appeared to be the same as that in the hepatocellular carcinoma nodule previously

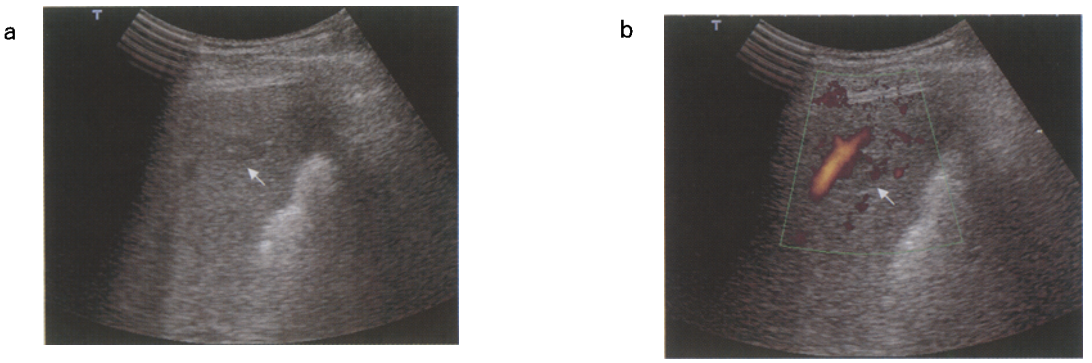
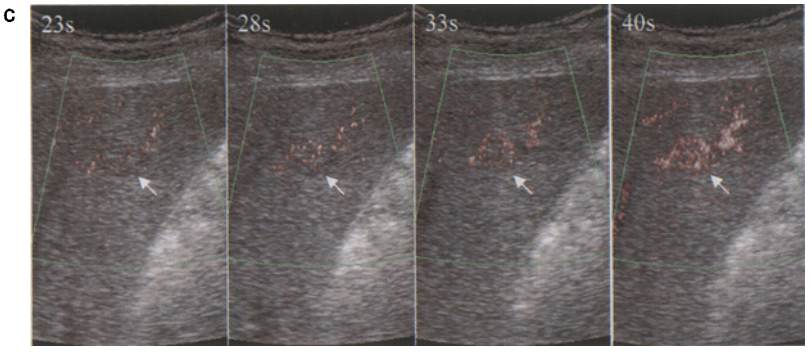
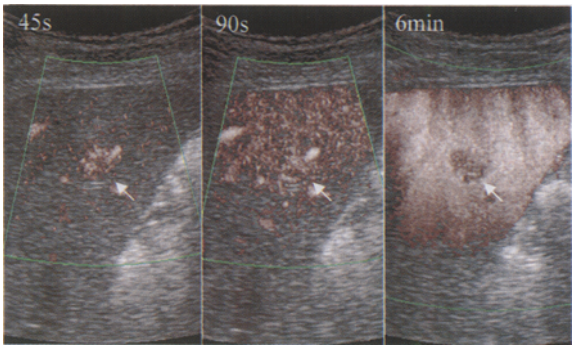
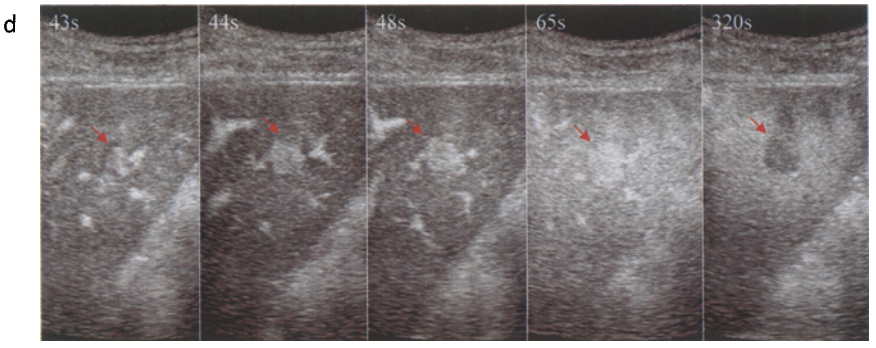


Fig. 1 A 1.2 cm hepatocellular carcinoma in a 66-year-old man. (a) B-mode imaging detected a hypoechoic lesion (white arrow). (b) Precontrast power Doppler imaging showed a dotlike blood-flow signal within the lesion (white arrow).



(c) Contrast advanced dynamic flow imaging clearly showed characteristic intratumoral hemodynamics: blood vessels supplying the tumor from the periphery and gradually encroaching upon the center (23 to 40 seconds) and fast tumor parenchymal stain (45 seconds) in the early arterial phase (white arrow): tumor parenchymal stain within the tumor in the late vascular phase (90 seconds) with 1-second interval-delay scanning (white arrow), and washout in the postvascular phase appearing as a defect area (6 minutes) (white arrow).





(d) Contrast pulse subtraction imaging, showed intratumoral blood vessels (43 seconds, 44 seconds) (red arrow) gradually entering the tumor, accompanied by dense tumor parenchymal stain (48 seconds, 65 seconds) (red arrow). Perfusion defect (red arrow) was clearly shown in the postvascular phase as a result of fast washout of the Levovist® from the tumor (320 seconds). These findings appear to be the typical intratumoral hemodynamics of hepatocellular carcinoma.

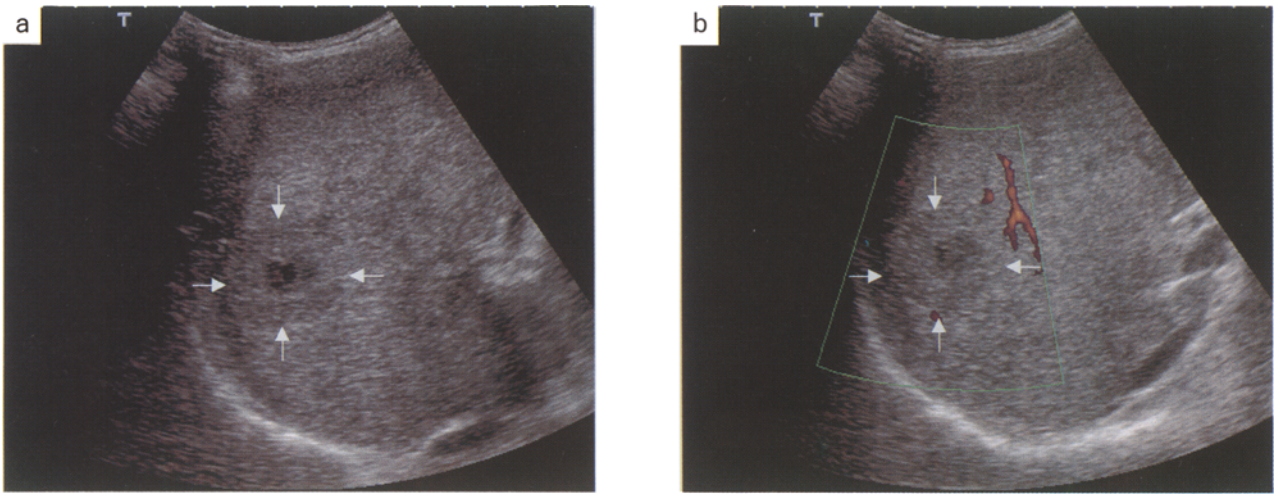
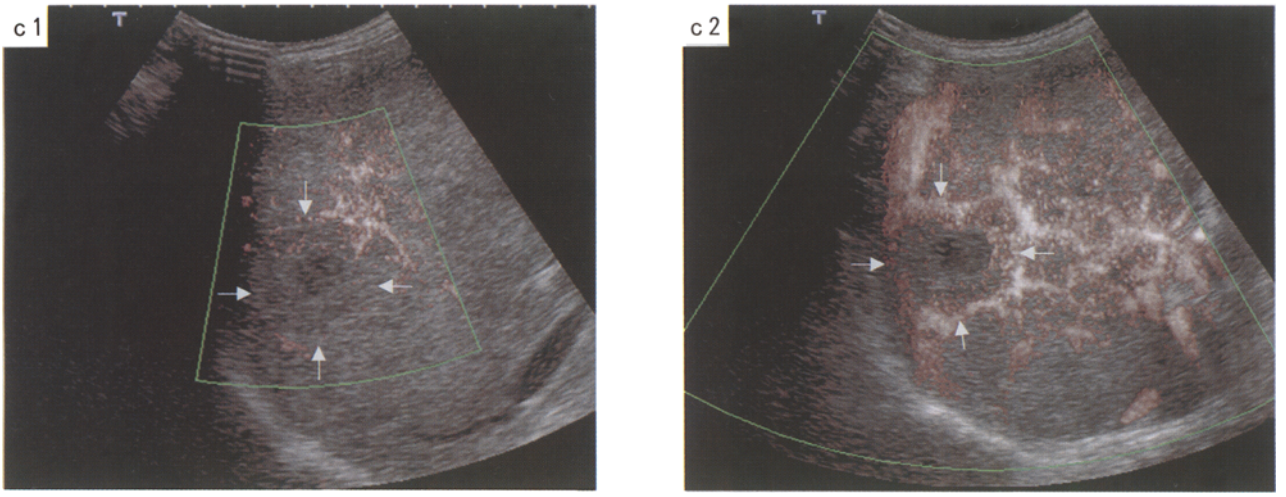
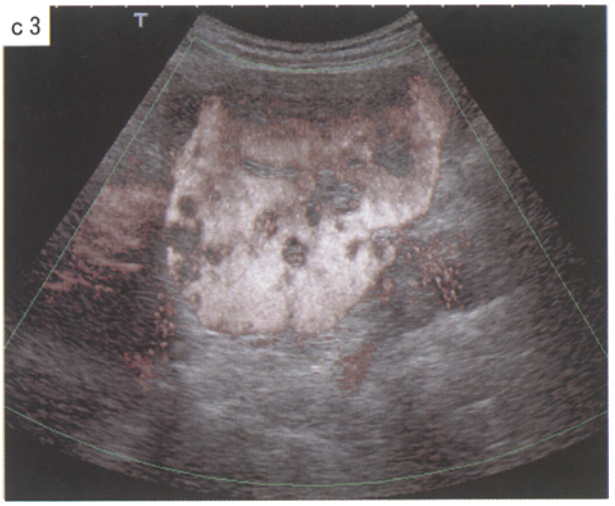


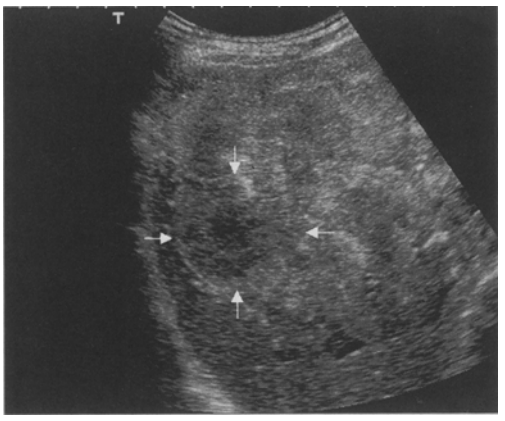
Fig. 2 Metastases in a 67-year-old man with carcinoma of stomach. (a) B-mode image showed a mixed hypoechoic lesion with cystic change in the center (white arrows). (b) Power Doppler imaging detected no blood-flow signal in the tumor (white arrows).



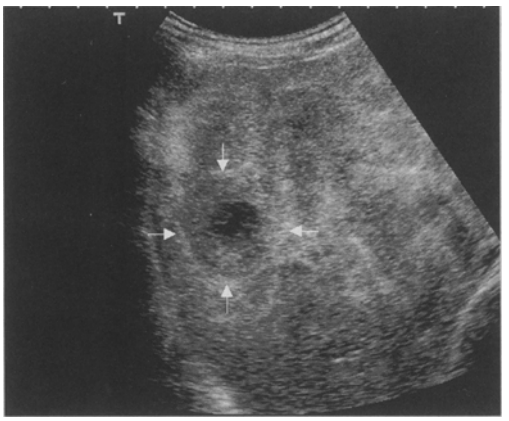


(c) Contrast advanced dynamic flow imaging showed short, linear blood vessels (c, 1) and tumor parenchymal stain. (c, 2) in the marginal area of the tumor (white arrows). Sweep scanning in the postvascular phase showed multiple metastases as a defect area in the left lobe of the liver (c, 3).

d 1



d 2



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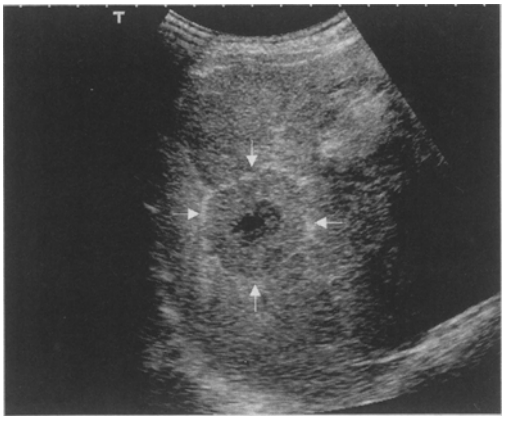
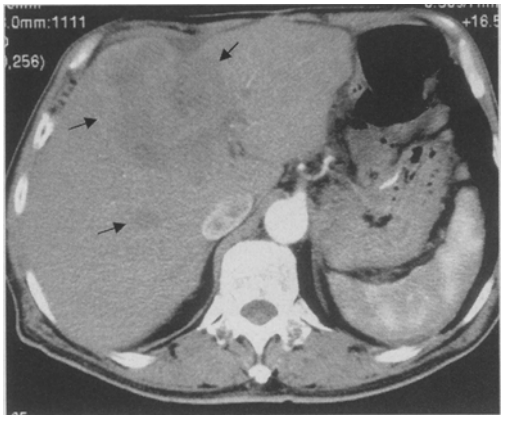


(d) On contrast pulse subtraction imaging, linear blood vessels (d, 1), rim enhancement (d, 2), and defect area (d, 3) were shown in the early, late, and postvascular phase, respectively (white arrows).

e 1



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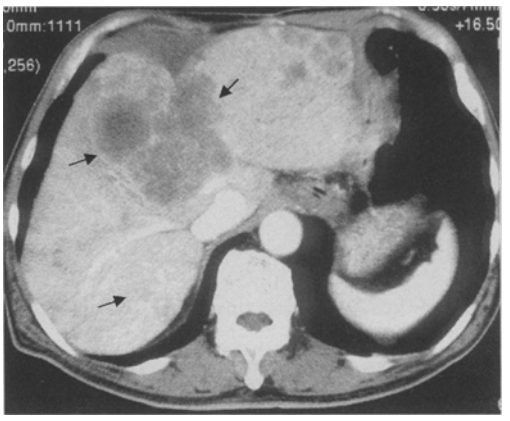

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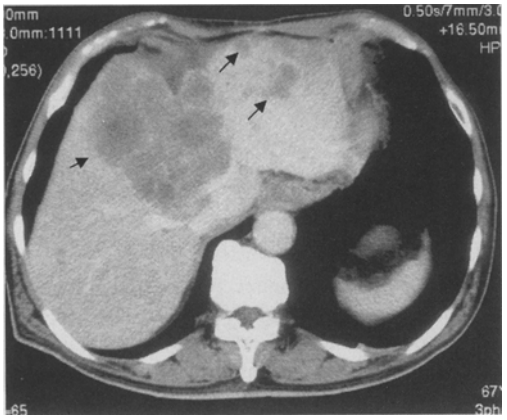


(e) Three-phase dynamic CT (e, 1; e, 2; and e, 3) showed multiple intrahepatic metastases (arrows) as rim enhancement in the arterial (e, 1) and portal (e, 2) phases, and defect in the delayed phase (e, 3).

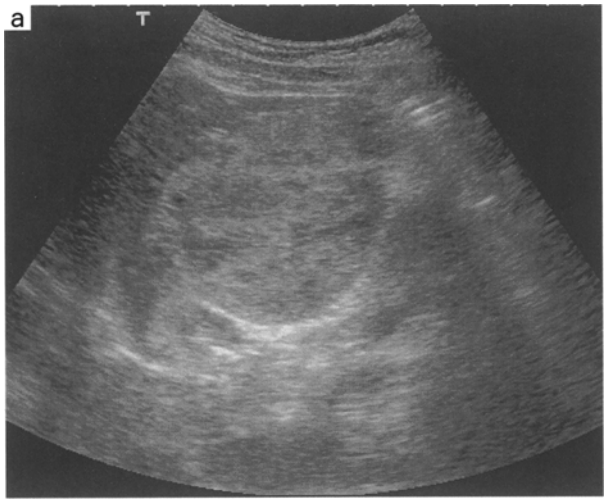
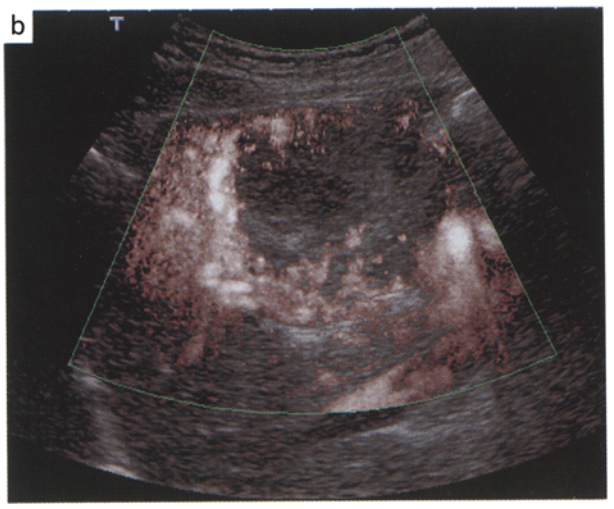
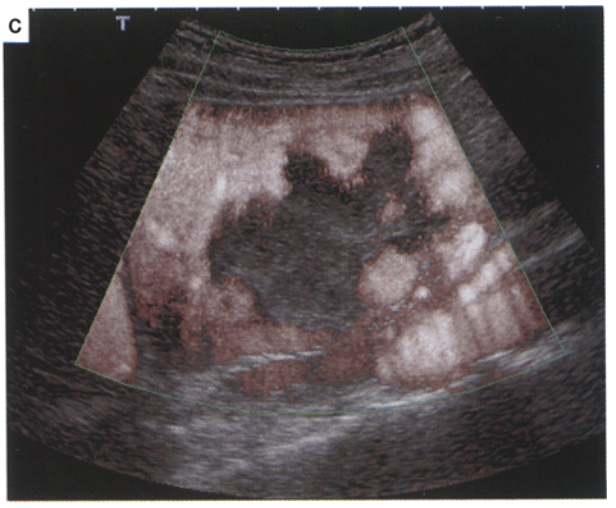
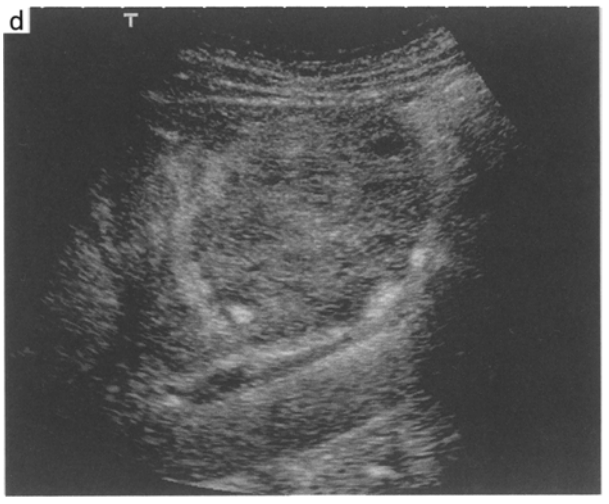


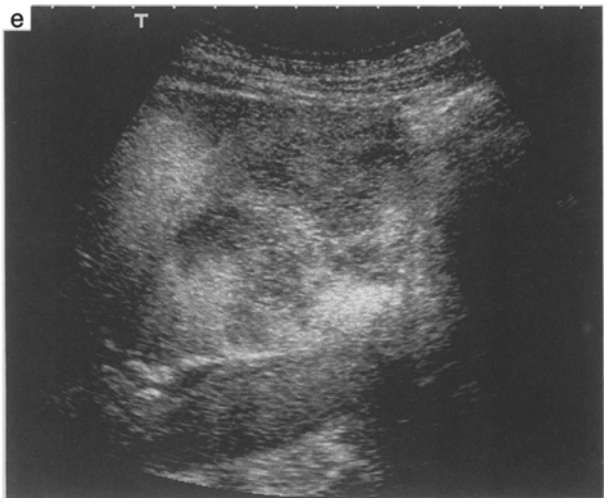
Fig. 3 A typical hepatic hemangioma in a 37-year-old woman. (a) B-mode imaging detected a heterogeneously hyperechoic lesion in the left lobe of the liver.





(b) Spotty-pooling blood vessels were detected by contrast-enhanced advanced dynamic flow imaging in the early arterial phase. (c) In the late vascular phase, advanced dynamic flow imaging depicted the tumor with cotton-wool tumor parenchymal stain, which lasted more than 8 minutes.





(d and e) Contrast-enhanced pulse subtraction imaging showed spotty-pooling blood vessels (d) and cotton-wool tumor parenchymal pooling (e). This is the typical picture of the hemodynamics of hepatic hemangioma.

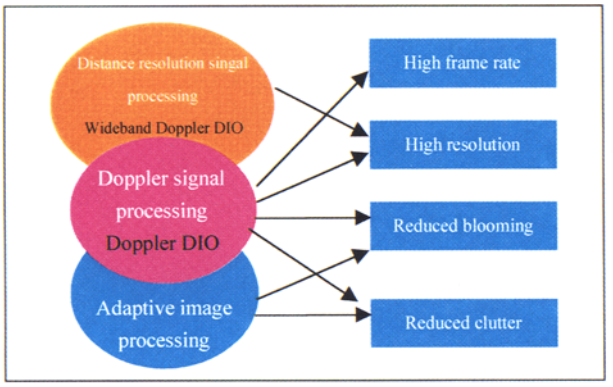


Fig. 4 Technology of advanced dynamic flow (Reprinted with permission from the Toshiba Corporation, Japan).

described.

The detectability of contrast advanced dynamic flow imaging and contrast pulse subtraction imaging of intranodular vascularity of hepatic tumors was the same in the 13 nodules examined by dynamic CT, (12/13, 92%). When compared with results obtained using dynamic CT, diagnostic sensitivity, specificity, and accuracy were 100% (12/12, 1/1, and 13/13, respectively).

4. Discussion

Ultrasound is one of the most commonly used imaging methods for diagnosing hepatic tumors. However, conventional color Doppler imaging and power Doppler imaging are not sensitive enough to adequately depict the intranodular blood flow signals, especially when blood velocity is low[19)20)]. Contrast agents are widely used in conjunction with CT, MRI, and other imaging methods; however, some workers have also attempted to use them to diagnose hepatic tumors. CO_2-enhanced ultrasound angiography clearly depicts the characteristic intranodular blood vessels and stain in hepatic tumors[21)-23)]. However, CO_2-enhanced ultrasound angiography is invasive and requires complex catheterization in the hepatic artery.

Intravenous ultrasound contrast agents have undergone remarkable improvement in recent years. Various gases, with or without shell, have been used to obtain strong and stable enhancement in the detection of blood flow[1)-3)]. Of these, Levovist® is the most widely studied microbubble contrast agent. Its small microbubbles (1-8 μm; mean, 1.3 μm) can pass through the pulmonary capillaries and reach the abdominal organs when it is injected into a peripheral vein. Furthermore, the small quantity of palmitic acid contained in Levovist® forms a thin membrane on the surface of the microbubbles, increasing their stability and thus prolonging the duration of enhancement.

As noted in previous studies, the behavior of Levovist® microbubbles in the blood is complex[1)-5)24)25)]. The microbubbles resonate with a specific frequency that is determined by their diameters when they are insonated by ultrasound beam of weak acoustic power. On the other hand, when the microbubbles are destroyed under exposure to an ultrasound field of high acoustic power, their nonlinear movement produces harmonic signals that are multiples or submultiples of the fundamental frequency. Although the intensity of these harmonic signals is low, it is strong enough to be of diagnostic value, because the tissue harmonic signal is extremely weak compared to the bubble-producing harmonic signal[1)-5)]. When the ultrasound beam is transmitted intermittently, a momentary high-intensity echo (flash echo) from the microbubbles appears in the first frame. This flash echo results from sudden expansion followed by collapse of the microbubbles pooled in the capillary bed during the interval[24)25)].

As previously described, however, conventional color Doppler and power Doppler imaging are not up to the challenge presented by contrast agents, although their sensitivity to blood-flow signals has been improved. The blooming, color noise artifacts, and other intrinsic drawbacks of color Doppler and power Doppler imaging sometimes influence the detection of blood-flow signals and result in misdiagnosis, limiting their use in clinical settings[6)-9)].

An impressive array of ultrasound technologies has grown out of the basic principle underlying the usefulness of microbubble contrast agents. Second harmonic imaging and pulse/phase inversion harmonic imaging are two of the more commonly used methods. Second harmonic imaging ignores some of the backscattered signals and has been shown to produce less-enhanced signals that do not last as long as those obtained using fundamental Doppler imaging[10)]. Some workers reported that pulse/phase inversion harmonic imaging showed improved sensitivity and resolution to the signals produced by microbubbles because it transmits two ultrasound waves with 180-degree phase inversion and receives the sum of the echoes back from both. Pulse/phase inversion harmonic imaging has been shown to be superior to conventional or second harmonic imaging[14)-17)]. Nonetheless, when pulse/phase inversion harmonic imaging is used in the intermittent mode, however, the targeted lesion may sometimes be easily lost for lack of real-time capability.

Advanced dynamic flow imaging and pulse subtraction imaging are two new ultrasound technologies. Advanced dynamic flow imaging is a wide-band Doppler imaging method that can eliminate motion artifacts using digital imaging optimization filtering technology. Moreover, advanced dynamic flow imaging uses a low

mechanical index in B-mode imaging that will not destroy the microbubbles, whereas use of a high mechanical index in advanced dynamic flow imaging causes the microbubbles to collapse, producing strong enhancement. On the other hand, the transmission and reception conditions of advanced dynamic flow imaging are similar to those used for B-mode imaging. Consequently, advanced dynamic flow imaging uses a high frame rate and achieves high sensitivity to and resolution of the signals returned by the microbubbles.

Pulse subtraction imaging is yet another microbubble-specific technology. This method combines pulse/phase inversion harmonic imaging and subtraction technology, which cancels the fundamental signal and boosts the harmonic signals produced by the microbubbles. The resulting, pulse subtraction imaging is highly sensitive and specific to the contrast-enhanced signals. Furthermore, even when intermittent transmission of pulse subtraction imaging is used, because of its low mechanical index a dual-display mode is available with a real-time B-mode monitor, making it possible to avoid losing the targeted nodules without destroying the microbubbles[11].

Contrast advanced dynamic flow imaging at a high frame rate continuously depicted intranodular blood vessels in the early arterial phase. Parenchymal stain was visible in the late vascular phase in real-time scanning at a relatively low frame rate that gave time for the microbubbles to flash into the nodule and made it possible to detect the flash echo image while slightly changing the scanning plane. Contrast advanced dynamic flow imaging was further able to show whether the perfusion defect appeared in the postvascular phase resulting from washout of Levovist®, which has been reported to be important in the differential diagnosis of hepatic tumors[13)16)17)21)].

Contrast pulse subtraction imaging was carried out using intermittent scanning. The intranodular blood vessel was detected in the early arterial phase with short time interval-delay scanning while the parenchymal stain image appeared in the late vascular phase with long interval-delay flash echo imaging. The washout of Levovist® was also demonstrated with and without perfusion defect in the postvascular phase.

This preliminary study detected different intranodular hemodynamics in different hepatic tumors. The characteristic hemodynamics are generally considered important for differentiating hepatic tumors[21)-23)]. Here, the typical intratumoral hemodynamics were depicted by contrast advanced dynamic flow imaging and contrast pulse subtraction imaging in hepatocellular carcinoma, metastasis, hemangioma, and adenomatous hyperplasia. They were similar to those of three-phase dynamic CT and facilitated an accurate diagnosis. Our results corresponded closely to those reported by other workers[13)-16)23)].

These two different microbubble-specific ultrasound technologies are provided in a new ultrasound system. This preliminary study showed that these two contrast ultrasound imaging methods have a similar power of detection, which is as high as that of dynamic CT.

We conclude that real-time contrast advanced dynamic flow imaging and intermittent contrast pulse subtraction imaging are significantly superior to precontrast power Doppler imaging in depicting intranodular blood vessels, parenchymal stain, and perfusion defects in hepatic tumors. The results obtained using contrast advanced dynamic flow imaging and contrast pulse subtraction imaging corresponded closely to those of three-phase dynamic CT. Confirmation of our preliminary observations may require further studies of large populations.

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