B-Flow Contrast US with Levovist in Hepatic Tumors:
Preliminary Results

NAOFUMI ONO, HIROYASU IJUIN*, HIDEYA SUGA, YOSHINOBU OKABE, KAZUAKI YAKUSHIJI, MICHITOSHI HASHIGUCHI, TOSHIHIKO KUROHIJI**, NOBUHIKO KOGA**, RYUKICHI KUMASHIRO AND MICHIO SATA

Department of Medicine, Kurume University School of Medicine, Kurume 830-0011, Tenyoukai Central Hospital, Kagoshima 892-0822 and Sinkoga Hospital, kurume 830-0033, Japan

Summary: Usefulness of Levovist contrast ultrasonography by the B-Flow method was evaluated in cases of hepatic tumor. Subjects included 14 patients with moderately differentiated hepatocellular carcinoma and 4 patients with hepatic hemangioma. Each patients had a single tumor mass. Images showed strong staining in 11 of the 14 nodes in the hepatocellular carcinomas and all 4 hemangiomas. Staining was seen only in lesions located within 4 cm of the probe. Thus B-Flow ultrasonography using Levovist was proved useful for evaluating vascularity of superficially located.

Key words B-Flow, Levovist, contrast agents, hepatocellular carcinoma, hemangioma of liver

INTRODUCTION

Contrast ultrasonography is known to be very useful for evaluation of vascularity in hepatocellular carcinoma [1,2]. Unfortunately, this method invasive administration of ultrasonographic contrast media such as injection of CO2 microbubbles from the hepatic artery. The recent clinical availability of Levovist (Schering AG, Berlin, Germany) together with improvements in ultrasonographic apparatus, now permit performance of contrast ultrasonography not only by the Color Doppler method [3-5] but also by the harmonic echo method. Contrast ultrasonography by the Color Doppler method involves such problems such as motion and blooming artifacts [6-8] while the harmonic echo method has other drawbacks such as poor contrast resolution, near the body surface [9,10].

Recently, as ultrasonographic apparatus underwent further improvement, the B-Flow method has been established for evaluation of vascularity [11]. This method indicates real-time vascularity by the B-mode without using the Doppler effect, but dose not readily permit visualization of vessels and stainings in hepatocellular carcinoma unless Levovist is used. We performed B-Flow contrast ultrasonography with Levovist in cases of hepatic tumor to evaluate the clinical usefulness of these images.

MATERIALS AND METHODS

Subjects

Subjects were 18 patients with the 18 liver masses who underwent Levovist contrast ultrasonography by the B-Flow method between January and October 2000. The 18 tumors consisted of 14 moderately differentiated hepatocellular carcinomas and 4 hepatic hemangiomas; these were diagnosed by various other imaging methods or by histologic examination. Mean tumor diameter was 15 mm (range, 12 to 40). Patients consisted of 12 men and 6 women. Mean age was 65.2 years (range, 42 to 80).

Methods

Contrast ultrasonography
Apparatus used for ultrasonography was of the LOGIQ 700MR EXPERT Series using a probe was 739L (linear; transmit frequency, 7 MHz). Focus was positioned within the mass, and ultrasonography was performed at an acoustic output of 100%. The B-Flow method includes a "background on" mode, in which flow information and B-mode images are indicated in a single image, and a "background off" mode, in which flow information alone is displayed.

As contrast medium for ultrasonography, 2.5 g of Levovist was prepared at a concentration of 300 mg/ml and injected manually into the cubital vein over a period of about 10 sec.

The region of the tumor first was observed by continuous transmission using the "background on" mode. Beginning at about 10 sec after Levovist injection, when blood flow into the tumor was detected, the tumor region was observed using the "background off" mode with breath holding during transmission at intervals of 2 to 4 sec, over 20 to 30 sec.

Evaluation methods
We determined whether tumor blood vessels were imaged by continuous transmission, as well as whether the tumors were imaged by intermittent transmission. The depth of the lesion, which determined the distance between the lesion and probe, was considered with respect to effect on visualization of tumor vessels and stain. Images recorded on video tape were evaluated by two ultrasonographers.

RESULTS
Imaging of hepatocellular carcinoma

In 11 of the 14 hepatocellular carcinomas, peripheral blood vessels and tumor blood vessels were imaged by continuous transmission in the early imaging stage. In 8 of these 11 masses, the entire lesion was strongly stained, in contrast to the hepatic parenchyma with intermittent transmission (Fig. 1). In the remaining 3 masses, staining was observed at the focal depth alone, and the region stained moved

![Fig. 1. Hepatocellular carcinoma (S3, 12×12 mm) at a depth of about 3 cm from the probe.](image)
A. B-Flow image (background on) before contrast. Arteries in the periphery of the tumor and the surrounding veins are seen, but imaging of blood flow within the tumor is insufficient. B. Image obtained 6 sec after Levovist injection. An increase in peripheral blood flow and flow of Levovist into the tumor are seen. C. Image obtained 10 sec after Levovist injection. D. The entire tumor is stained by transmission at intervals of 2 sec (background off).
**Fig. 2.** Hepatocellular carcinoma, 40×50 mm.
A. A tumor of low echogenicity was observed in the B-mode. B-D. With the B-Flow imaging after injection of Levovist. With changes in the position of the focus point, a different region shows staining. Staining is seen around the focus point (arrow).

**Fig. 3.** Hepatocellular carcinoma (S2, 3, 25 mm) at a depth of 5 cm from the body surface.
A. B-mode image. B. No blood flow is seen in the tumor or its periphery on the B-Flow image before contrast administration, although blood flow in the portal umbilical region is shown. C. An artery in S3 is seen but blood flow within the tumor is not seen on an image obtained 15 sec after Levovist injection. D. No staining of the tumor is visualized by intermittent transmission.
as the focal region was changed (Fig. 2). In the other 3 hepatocellular carcinomas, neither tumor blood vessels nor staining of the tumor were observed by continuous transmission in the early imaging stage or by intermittent transmission (Fig. 3).

**Imaging of hepatic hemangioma**

In all 4 hepatic hemangiomas, staining of the peripheral zone of the lesion was observed by continuous transmission, while staining of the entire lesion occurred with was observed by intermittent transmission (Fig. 4).

**Effect of mass location**

The 15 masses with vascular staining all were within 4 cm of the probe. The 3 unstained lesions all were deeper than 4 cm. Levovist was imaged by B-Flow ultrasonography as hyperechoic foci extending in a direction perpendicular to the probe.

**DISCUSSION**

B-Flow ultrasonography is a greatly improved method of visualizing vascularity by the B-mode without using Doppler methods or contrast media [11,12]. Unlike the Color Doppler method, the B-Flow method clearly shows blood vessels and vascularity in detail, which should make the latter technique clinically valuable. For imaging of vascularity, Coded Excitation techniques are used for efficient amplification of signals. In the amplified signals, changing and constant signal components may be distinguished. Because the latter components are derived mainly from tissues rather than flowing blood, vascularity is studied by suppressing constant components. The contrast medium Levovist takes the
form of small bubbles with a mean diameter of 1.3 μm, that are undetectable by conventional B-mode imaging. In the B-Flow method, clear contrast images can be obtained using Levovist because blood flow is selectively amplified and imaged. When we examined hepatic tumors using Levovist contrast ultrasonography by the B-Flow method, staining of relatively superficial hepatocellular carcinomas and their blood vessels could be seen. With hepatic hemangiomas, staining of the periphery first occurred, followed by the entire lesion.

Our study identified several problems with this imaging technique. First, Levovist was shown as extending in a direction perpendicular to the body surface in B-Flow images. This artifact resulted from ultrasound-induced disintegration of the Levovist bubbles together with effects of Coded Excitation techniques. However, these artifacts were distinguishable from other artifacts and were useful as a sign of Levovist inflow. A second problem was imaging depth. Tumors in regions deeper than 4 cm could not be imaged, probably because ultrasound sufficientic waves for depicting Levovist did not reach these deeper regions at the primary probe frequency 7 MHz. This problem should be solved by developing a low-frequency probe for B-Flow imaging. Finally, only a small region around the area of focus could be imaged by the B-Flow method. The imaging apparatus must be improved.

New imaging methods using Levovist have been developed, but adequate images have not been obtained with Levovist contrast ultrasonography by harmonic imaging methods with the probe at the body surface. Because the contrast B-Flow method used in this study was highly sensitive to Levovist in shallow regions within 4 cm of the surface, Levovist contrast ultrasonography by the B-Flow method is considered to be the most informative way to examine relatively superficial regions and to evaluate vascularity of lesions during surgery.

REFERENCES