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Contrast-enhanced harmonic ultrasonography with Sonazoid in pancreatic diseases

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Background

Contrast-enhanced ultrasonography by means of Levovist®, a galactose-based ultrasound contrast agent that is infused intravenously has allowed the observation of the vasculature of the abdominal organs. Particularly, contrast harmonic imaging, which is the specific imaging mode for Levovist®, can depict signals from microbubbles in very slow flow without Doppler-related artifacts and is used to characterize tumor vascularity in liver, pancreas, gallbladder, and gastrointestinal tract during transabdominal ultrasonography. The diagnosis of pancreatic diseases has sometimes been difficult even when combination of various imaging modalities such as ultrasonography, magnetic resonance imaging, endoscopic retrograde cholangiopancreatography (ERCP), endosonography (EUS) and contrast-enhanced computed tomography (CT) were employed. Among those imaging technologies, EUS has been widely used to diagnose pancreatic diseases, because it is superior to any other modality with respect to spatial resolution. Until recently, there was no contrast harmonic imaging technique available for EUS examination, because the transducer for current echoendoscopes is of a limited band frequency and too small to produce enough acoustic power for contrast harmonic imaging using Levovist®. Second generation ultrasound contrast agents like Sonazoid produce harmonic signals at a low acoustic power, and are therefore suitable for EUS of low acoustic power. We have recently developed an echoendoscope with a wide-band transducer and a specific imaging mode for contrast-enhanced harmonic EUS. The echoendoscope has a wide-band transducer that can produce and detect harmonic signals from second generation contrast agents. In this lecture, usefulness of contrast-enhanced harmonic EUS (CEH-EUS) for depiction and differentiation of the pancreatic diseases are discussed.

Materials and methods

A prototype echoendoscope developed for CEH-EUS was used. The radius of curvature, the center of scanning frequency, and the scanning range of its transducer were 5 mm, 7.5 MHz, and 180°, respectively. Image analysis was performed using ExPHD mode, which is specific for contrast-enhanced harmonic ultrasonography. The ExPHD mode combines receiving frequencies of filtered fundamental and second harmonic components with a transmitting frequency of 4.29 MHz. The mechanical index was set as 0.3. Sonazoid (15 µl/kg) was used as the ultrasound contrast agent. A total of 145 consecutive patients suspected of having pancreatic diseases underwent EUS followed by contrast-enhanced EUS with a contrast agent, Sonazoid at Kinki University School of Medicine. The pancreas in those patients was observed in a real-time fashion. For comparison, the patients enrolled in this study underwent multidetector computed tomography (MDCT). Between EUS, CEH-EUS and MDCT, the depiction rate and the diagnostic ability of pancreatic carcinomas were compared.

Results

The normal pancreatic tissue presented several vessels distributed homogeneously on the vessel image and a homogeneous stain on the perfusion image. The echo intensity reached the maximum level about 30 seconds after the infusion of Sonazoid, and the
pancreatic parenchymal perfusion images lasted for more than 180 seconds. The pancreatic duct and the common bile duct were more easily recognized because of sharp contrast with the parenchyma than fundamental B mode EUS. Histological examinations of resected tissue or samples obtained by EUS guided fine needle biopsy revealed pancreatic carcinomas in 34 of 145 patients. When pancreatic carcinomas were defined as the lesions with slight heterogeneous enhancement in the hypovascular area, values for sensitivity, specificity and accuracy in diagnosing pancreatic ductal carcinomas on CEH-EUS were 94%, 85% and 91%, respectively. MDCT failed to depict one of 3 endocrine tumors and 2 of 4 mural nodules of intraductal papillary mucinous neoplasias, all of which CEH-EUS depicted as hypervascular lesions. It was difficult to depict 3 pseudocysts caused by chronic pancreatitis due to the inclusion of similar echogenicity to the surrounding pancreatic tissue. CEH-EUS revealed the pseudocysts as avascular area with the sharp contrast with the surrounding tissue.

Discussion

Power or color Doppler mode has been employed up until now for contrast-enhanced EUS\textsuperscript{6-8}. However, artifacts such as blooming and overpainting are inevitable. Furthermore, the Doppler mode is of limited value in producing parenchymal perfusion images when contrast agents are used. The prototype echoendoscope with a broad-band transducer and Sonazoid permit CEH imaging using lower acoustic powers. The CEH-EUS showed diffuse pancreatic perfusion images without any artifacts. The pancreatic duct, the common bile duct and the cystic lesion were more easily recognized because of sharp contrast with the parenchyma than fundamental EUS, indicating that perfusion imaging by CEH-EUS depicts avascular regions which are not depicted by the fundamental B mode EUS. In addition, the diagnostic ability of CEH-EUS is equal or superior to MDCT. Particularly, CEH-EUS is useful for the depiction of small lesions such as mural nodules of IPMN.

Conclusion

CEH-EUS successfully visualized parenchymal perfusion and microvasculature in the pancreas, and may play an important role in the depiction and the differential diagnosis of pancreatic diseases.

References

Utility of contrast-enhanced endoscopic ultrasonography (CE-EUS) in the diagnosis of pancreato-biliary diseases using Sonazoid

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[Purpose]
The purpose of this study was to investigate the utility of CE-EUS in the diagnosis of pancreato-biliary diseases using new contrast agent Sonazoid.

[Methods]
Subjects consisted of 133 patients with pancreatic diseases and 15 patients with gallbladder cancer. The details are as follows: 23 with pancreatic ductal carcinoma, 75 with intraductal papillary mucinous neoplasm (IPMN: including 9 cases invasive carcinoma derived from IPMN), 6 with endocrine tumor, 18 with chronic pancreatitis and 11 with various types of diseases. After observing the target lesions in B-mode, harmonic imaging method was used for CE-EUS. The change of echo intensity was observed after peripheral injection of Sonazoid. We performed following two settings:
(S-1) Endoscopy and ultrasound machine used were EG-3670URK, 3870UTK (Pentax) and HV-900 (Hitachi).
(S-2) Endoscopy and ultrasound machine used were Olympus EUS and SSD α-10 (Aloka).
The dosage and the injection procedure of Sonazoid obeyed an attached document.
Observation condition in (S-1) was WPI (wide-band pulse inversion) for harmonic imaging method, and MI value was from 0.16 to 0.58. The observation condition in (S-2) was fixed MI value to 0.25 in EXPHD (extended pure harmonic detection) for harmonic imaging method. We observed one minute after infusion continually, and observed by 30 seconds after infusion 3 minutes and 5 minutes later.
The evaluated items were as follows:
1) The change of echo intensity (on the basis of subjective image change).
2) The quantitative echo intensity change (TIC: time intensity curve).
3) Estimation of vascular distribution (SD (standard deviation) in histogram was used to estimate the vascular distribution.

[Results]
1. The contrast enhanced effect by Sonazoid lasted for five minutes.
2. Pancreatic ductal carcinoma: Echo intensity of the tumor increased to the degree as for the pancreatic parenchyma and immediately echo intensity of the tumor decreased for less than 1 minute, and the state continued for five minutes (21/23).

IPMN: The lesion that papillary growth was denied without mural nodules being contrasted in CE-EUS could leave serial observations (28 cases), operated cases with the enhancement in their papillary growth were at least adenomas.
In addition, there were 6 cases of microinvasive carcinoma and 1 CIS (carcinoma in situ). Invasive carcinoma derived from IPMN showed the similar enhanced pattern, that was, coexistence of hypervascular papillary growth parts and hypovascular invasive area. These findings were regarded as a pattern to be specific for this invasive carcinoma, and a
preoperative diagnosis was possible.

Endocrine tumor: The echo intensity of the tumor increased beyond the pancreatic parenchyma just after injection of Sonazoid, and decreased three minutes later.

Chronic pancreatitis: Comparatively uniform contrast enhanced effect was seen just after injection of Sonazoid and vascular distribution became heterogeneous with a time course, and became sparse (Rise of SD value and left shift of intensity histogram).

[Conclusion]

CE-EUS using Sonazoid may add the new vascular information and be useful in the diagnosis of pancreato-biliary diseases.
Contrast ultrasound of gastrointestinal tract

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Background and Aim
Sonazoid has been introduced into clinical practice since 2007. The liver is most commonly observed by contrast ultrasound with Sonazoid, partly because this contrast agent has been approved by the ministry only for the diagnosis of liver tumors. In this study we have used Sonazoid for the contrast ultrasound of gastrointestinal tract to investigate the usefulness in clinical practice.

Patients and Methods
A total of 115 patients with various gastrointestinal diseases underwent contrast ultrasound. Sonazoid (NC100100; Nycomed Amersham, Oslo, Norway) was injected intravenously as a bolus in dose of 0.015 ml/Kg. Harmonic imaging with a low acoustic power (mechanical index: 0.2 - 0.4) was employed and the observation time was two minutes. The ultrasound equipment employed was SSA-770A (Toshiba, Japan) with 3 MHz convex probe and 6 - 7 MHz linear probes. Patients with gastric tumors (n=7) were examined after the ingestion of tea (approximately 200 ml), while no other special preparations such as injection of antispasmodic agents, was executed. This study was approved by the institutional review board at Kawasaki Medical School and informed consent was obtained from every patient.

Results
We could obtain the perfusion images of the gastrointestinal lesions in all patients. The visualization of vascular structure helped us in the differential diagnosis and the evaluation of therapeutic effects for neoplastic diseases. In the differentiation between simple bowel obstruction and strangulation, contrast ultrasound was found to be very effective. Although it seemed promising, further research with large number of patients was thought to be required to clarify the usefulness of contrast ultrasound in the evaluation of disease activities in the inflammatory bowel diseases.

Conclusion
Contrast ultrasound with Sonazoid is useful in the evaluation of blood flow in a variety of gastrointestinal diseases.
S8-4 A novel intraoperative ultrasonographic technique by Sonazoid for hepatectomy for liver tumors

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Background:
Intraoperative ultrasonographic (US) guidance has been useful for hepatectomy for liver tumors. While recent advances on Sonazoid-enhanced US are remarkable, it has not been evaluated for the utility of intraoperative US for hepatectomy.

Materials and Methods:
We analyzed 15 patients who received surgical operation for liver tumors from July to October, 2007, including 12 cases of hepatocellular carcinoma (HCC), 2 cases of liver metastasis from colorectal cancer, and 1 case of cholangiocarcinoma. Preoperative and postoperative US examinations were performed using images of Kupffer phase and vascular phase. Histopathological diagnoses were assessed to identify the relationship between Sonazoid US images and tumor characteristics.

Results:
Intraoperative Sonazoid US images provided clearer images than preoperative ones in many cases. For example, the tumor border was observed partially unclear only by intraoperative images, resulting in extra-capsular infiltration of the HCC cells pathologically. At present, we could not determine relative merits to detect multiple HCCs by Sonazoid US compared to angiography-CT. In addition, various vascular patterns in the tumors were identified by intraoperative Sonazoid US: broadly enhanced by thin branches, some branches growing into center, or poorly enhanced. In the cases after transcatheter arterial embolization (TAE) for HCC, we found specific images of spiral or straight vascular patterns in tumor only by intraoperative US, indicating the rest of viable tumor cells pathologically. Histopathological diagnosis was obtained in 10 HCC cases: 7 cases of moderately differentiated HCC, 1 case of moderately to poorly differentiated, and 2 cases of poorly differentiated HCC. The association between the vascular patterns and HCC differentiation are now analyzing in detail.

Conclusion:
Intraoperative Sonazoid US is a promising technique to evaluate characteristics of liver tumors as well as to perform appropriate hepatectomy. Further studies should be required to establish the contribution to the surgical operation.
ULTRASOUND CONTRAST IMAGING OF BREAST TUMORS

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Objective:

The purpose of this study was to investigate the value of contrast medium-enhanced ultrasound using Sonazoid™ as contrast agent for assessment of the vascularization of breast tumors and lymph nodes.

Subjects and Methods

We conducted a prospective study of 17 breast tumors and 5 lymph nodes. Mammography in eight patients showed suspicious malignant findings, six mammographic findings were indeterminate. Tumors ranged from 1.5 to 3.0 cm (mean size, 2.0 ± 0.5 cm). Histological findings were obtained in all cases by ultrasound-guided fine needle aspiration and/or 14 gauge core needle biopsy or 10 gauge vacuum assisted biopsy. We conducted all examinations the operation day using a LOGIQ 7 (GE Yokogawa Medical Systems, Ltd.) with a 6-12 MHz linear transducer. With B-mode sonography, the tumor was first located and imaged. Then imaging with color-coded duplex sonography was performed on a representative section of the tumor. Both the tumor itself and the surrounding tissue were included. We were careful not to exert any pressure on the transducer because small tumor vessels can be easily compressed.

After the initial examination, Sonazoid™ was diluted to 2 ml by a standard saline solution and injected intravenously as a bolus of 0.015mL/kg into a 21 gauge peripheral indwelling cannula followed by a flushing injection of 5 ml of standard saline. A low reduced mechanical index (MI) of less than 0.28 was chosen to avoid early gas bubble destruction.

The ethic committee of our institution approved this study. An informed consent was signed by each patient for the ultrasound examination and before administering for the contrast medium.

Results:

Of the 14 histopathologically proven primary breast cancers, 11 were invasive ductal carcinoma and 2, invasive ductal carcinoma with predominant intraductal component, and two mucinous carcinoma. Of the 7 recurrent breast cancers, 7 were lymph nodes and 2 were chest walls. Only one case was intraductal papilloma. After the application of Sonazoid™, vascularization was shown in all tumors. There were no complications after injection of the ultrasound contrast medium. There were no allergic reactions.

Conclusion:

Sonazoid™ has advantages for real-time visualization and was effective for detection of fine tumor vessels.
S8-6  Myocardial Opacification Using by Sonazoid from Animal Studies

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Recently, Sonazoid could be commercially available for an abdominal field in Japan. It could be available for cardiac field in near feature. However, there were little informations about right condition settings to have good opacification using Sonazoid. In this symposium, we will present suitable conditions to get good perfusion images using dog & rat models.

Methods: In dog and rat models, we use a basic mode, a second harmonic, a power Doppler mode for intermittent mode and a pulse subtraction mode and so on for real-time mode. We measured video intensity of myocardium in several settings of mechanical index and pulse interval using SONOS 5500 (Philips) with 1.8/3.6 MHz probe and a high frequency transducer (s12 probe: 5-12MHz), Power Vision 6000 (Toshiba) with 1.875/3.75 MHz probe, Sequoia 512 (SEMENS) with a 1.75/3.5 MHz probe during infusion of Sonazoid. In dog models, the dose of Sonazoid is 0.03 µL MB/kg and we inject 20-40% diluted NC100100 in rat models. In a rat model, we also establish the methodology of intravenous MCE to assess the ischemic area by the ligation of left coronary artery.

Results: Sufficient myocardial opacification was obtained in dog and rat models in both intermittent and real-time mode. Myocardial opacification in high MI, long pulse interval and a harmonic mode is better than that in low MI, short interval and a basic mode. However, the effect of MI in dog models is not so significant compared with that in rat models. In ischemic rat models, the ischemic area is well concordant with the perfusion defect by MCE. In real-time mode, the adjustment of acoustic power is very important to obtain good myocardial opacification in each equipment or mode.

Conclusion: Intravenous MCE using Sonazoid is feasible to evaluate the myocardial perfusion in dogs and rats by using appropriate setting of the ultrasonic equipment.