

New Advances in Contrast-enhanced Ultrasonography for Pancreatic Disease-usefulness of the New Generation Contrast Agent and Contrast-enhanced Ultrasonographic Imaging method-

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ABSTRACT

The aim of our study is to evaluate whether Sonazoid[®] and new sonography technique will be able to be applied in pancreatic diseases, and to investigate comparatively CE-US with Levovist[®]. The subjects were 50 patients with pancreatic diseases. With Sonazoid[®], the hemodynamics of a lesion area and its periphery were observed by new sonography technique; with Levovist[®], they were observed by conventional methods. The contrast pattern and level of visualization of the microvasculature were evaluated for both agents. Both Sonazoid[®] and Levovist[®] produced almost the same contrast pattern in all the patients, however, more detailed contrast images, the structures of the microvasculature in the mass lesion, were obtained with Sonazoid[®] than Levovist[®]. The irregular rolling sign was characteristic in malignant mass lesion and useful in differentiating between benign and malignancy. Compared to Levovist[®], use of Sonazoid[®] improved visualization of the hemodynamics by 10% and diagnosis by 9%. The performance of CE-US with Sonazoid[®] in pancreatic diseases improved the diagnostic capacity better than when Levovist[®] was used, and was useful in the differential diagnosis.

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Key words: Contrast-enhanced ultrasonography; Levovist; Sonazoid; Pancreatic disease; Irregular rolling sign

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INTRODUCTION

Advancements in the various image diagnostic procedures and their spread have led to dramatic improvements in the visualization and diagnostic capacity of biliopancreatic diseases^[1-7]. In ultrasonography in particular, the arrival of the Power Doppler technique, Tissue Harmonic Imaging (THI), and the 2-3 μ m microbubble that can pass through capillaries, that is, the intravenous contrast agent, Levovist[®], that does not leak in the extravascular interstitium, have been developed around 1995. The appearance of this low invasive contrast-enhanced ultrasonography (CE-US) made it possible to evaluate not only the richness of arteries but also the hemodynamics of organs or lesions, which is reflected with hemodynamics of arteries-capillaries-veins, i.e., perfusion of organs or lesions. This procedure has come to play an important role in improving the diagnosis of lesions from simply their existence to a qualitative diagnosis^[8,23].

To date, we have reported that CE-US coupled with hemodynamics is useful in the diagnosis of pancreatic diseases^[16,17,23]. It is the differentiation between pancreatic mass and cystic lesions, particularly, pancreatic cancer (PC) and mass-forming pancreatitis (MFP) in mass lesions, and evaluation of the level of cancer progression. However, the limitations and problems of CE-US when the high mechanical index (MI) contrast agent, Levovist[®] is used have also become evident. In the evaluation of the hemodynamics that reflect the tissue conditions, use of high MI contrast agent has limitations and the precise evaluation was difficult. Thus, the development of the second generation of low MI contrast agent and new ultrasound devices that will enable more precise visualization and evaluation were awaited.

OBJECT

Sonazoid® was the first second generation low MI contrast agent that was launched in Japan on January 10, 2007 and since then it has been approved and launched for the first time in various countries world wide. Furthermore, a new sonography technique using Sonazoid® was developed^[24,25]. This new sonography technique was developed in the field of hepatic diseases. The aim of our study is to evaluate whether this new sonography technique will be able to be applied in pancreatic diseases, and to investigate comparatively CE-US that uses the conventional contrast agent, Levovist®.

MATERIALS AND METHODS

Materials

The subjects were 50 patients with pancreatic diseases from whom informed consent was obtained at this department and for whom CE-US with both Sonazoid® and Levovist® were used. All the patients had obtained a histologically confirmed diagnosis by surgical excision or biopsy. The breakdown of the patients are: 30 with pancreatic cancer, 3 with Solid-pseudopapillary neoplasm (SPN), 3 with metastatic pancreatic tumor (MPT) (renal and lung cancer), 3 with pancreatic neuroendocrine tumor (PNET), 4 with pancreatic cystic neoplasm (PCN), 7 with mass-forming pancreatitis (MFP).

The contrast agent

The second low MI ultrasound contrast agent, Sonazoid®, is a lyophilized powder made up of microbubbles of fluorocarbon gas (perflubutane) enclosed in a lipid shell (hydrogenated egg yoke phosphatidylserine sodium) (Figure1). It is reconstituted in 2 mL of distilled water and has a particle diameter of 2-3 µm. The recommended volume of administration of Sonazoid® is 0.015 mL/kg bodyweight (for an adult weighing 60 kg, 0.9 mL should be administered). If tissue harmonic imaging with good sensitivity is used, good imaging results can be obtained with half that quantity. The quantity used is 0.5 mL regardless of body weight in our institution. Four injections can be administered from one vial. As to acoustic pressure, pancreatic diseases are examined at an acoustic MI range of 0.16-0.26 at our hospital.

Levovist® (2.5 g) was prepared at a dose of 300 mg/mL, and a bolus of 7 mL was injected through the median cubital vein at a speed of 1 mL/s.

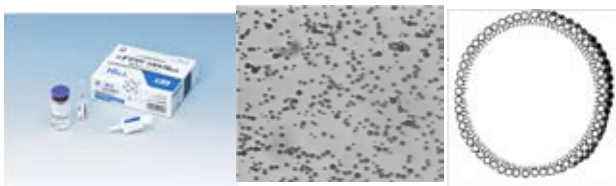


Figure 1 The second generation contrast agent of low MI, Sonazoid.

Ultrasound device and imaging procedure

The ultrasound device used was Aplio XG (Toshiba Medical Systems) (Figure 2). In addition to the imaging methods to date, new imaging methods that uses the second generation ultrasound contrast agent Sonazoid® and produces more detailed images of the microvascular structure and better observation of hemodynamics has been developed.

Dynamic imaging (DI): After intravenous injection of Sonazoid®, changes in the hemodynamics in lesion and non-lesion areas are observed in real time. Normally, contrast images of the arterial phase can be obtained in 15-20 s.

Flash replenishment imaging (FRI) and micro flow imaging (MFI): When the contrast agent fills the parenchyma and 10-30 frame scanning (burst scan) is performed at a high acoustic transmission with an MI value of ≥ 1.0 , the bubbles in the scan volume are swept away. Then, when the observation is repeated using the low acoustic harmonic method, reperfusion of blood flow containing new bubbles in the scan volume can be visualized under low acoustics. Imaging of this reperfusion is called flash replenishment imaging (FRI) (Figure 3A). Furthermore, when visualizing the reperfusion after the bubbles have disappeared by the maximum intensity holding procedure that maintains the peak brightness at each pixel, good and continuous visualization of microvasculature becomes possible. This method is micro flow imaging (MFI) (Figure 3B). FRI and MFI can be performed repeatedly.

As to Levovist®, after a detailed observation of the lesion in B-mode, a vascular image was depicted for 60 s after injection of contrast agent at the speed of 5 frames/s (fps) with holding breath, focusing on the blood flow dynamics in the lesion and surrounding pancreatic tissue. Thereafter, perfusion images were depicted for 180 seconds after injection with an intermittent transmissions for periods of 2-10 s to observe the enhancement of the lesion.



Figure 2 Ultrasound device; Aplio XG (Toshiba Medical Systems).

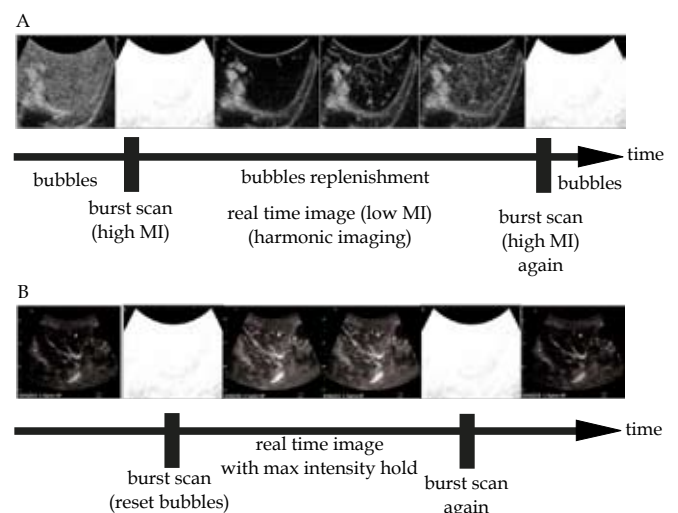


Figure 3 Imaging procedure; A: Flash replenishment imaging (FRI); B: Micro flow imaging (MFI).

Outcome

With Sonazoid®, the hemodynamics of a lesion area and its periphery were observed by DI and MFI; with Levovist®, they were observed by conventional methods. The contrast pattern and level of visualization of the microvasculature as well as the accuracy of

Table 1 The visualization of enhancement patterns and microvasculature in Levovist and Sonazoid.

	Numbers of cases	Excellent		Fair		Poor		Diag. rate of concordance	Rate of Improvement of diag. preclslon (S/L)
		S*	L#	S	L	S	L		
Total	50	43 (82%)	32 (62%)	7 (18%)	14 (28%)	0 (0%)	5 (10%)	43/50 (86%)	49/46 (8%)
PC	30	25 (83%)	21 (70%)	5 (17%)	6 (20%)	0 (0%)	2 (7%)	26/30 (87%)	30/27 (10%)
MFP	7	6 (86%)	4 (57%)	1 (14%)	2 (29%)	0 (0%)	1 (1%)	5/7 (71%)	7/5 (29%)
SPN	3	3 (100%)	0 (0%)	0 (0%)	3 (100%)	0 (0%)	0 (0%)	2/3 (67%)	3/2 (33%)
MPT	3	3 (100%)	2 (86%)	0 (0%)	1 (7%)	0 (0%)	0 (0%)	3/3 (100%)	3/3 (0%)
PNET	3	2 (67%)	2 (86%)	1 (33%)	1 (7%)	0 (0%)	0 (0%)	3/3 (100%)	3/3 (0%)
PCN	4	4 (100%)	3 (75%)	0 (0%)	1 (25%)	0 (0%)	0 (0%)	4/4 (100%)	4/4 (0%)

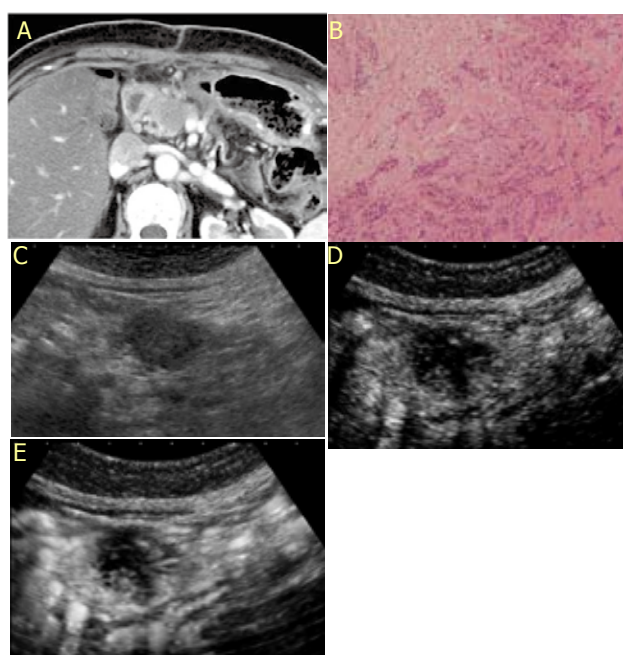


Figure 4 CE-US imaging using Sonazoid of malignant mass. A: CT; B: Pathological finding; adenocarcinoma; C: B-mode US; D: DI; This imaging showed hypovascularity and the irregular rolling blood flow signal of microbubble in the mass (irregular rolling sign); E: MFI; This imaging showed hypovascularity and the microbubbles attempted to enter the mass, however, images showing their inability to enter the center and images of blood flow showing their irregular rolling blood flow (irregular rolling sign) in the periphery by contrast could be observed in real-time.

diagnosis were evaluated for both agents. For all the patients, the images were recorded, and three doctors experienced in CE-US judged the reactions of the contrast agents using the same image. This study was approved by the Ethics Committee of this medical institution.

RESULTS

The results of the 50 patients with pancreatic diseases showed that on the whole, Sonazoid[®] produced superior resolution compared to Levovist[®] (Table 1). Both Sonazoid[®] and Levovist[®] produced almost the same contrast pattern in all the patients, however, more detailed contrast images were obtained with Sonazoid[®] than Levovist[®]. Moreover, contrast evaluation with unprecedented precision was possible. In addition, when MFI with Sonazoid[®] was used, the structures of the microvasculature in the mass lesion could be observed in real-time compared to Levovist[®]. Detailed movements of microbubbles in the capillaries that were difficult to visualize with Levovist[®] could be visualized repeatedly in real-time with Sonazoid[®]. With malignant mass lesion in particular, the microbubbles rolled irregularly but in phase with the microvasculature in the mass area. The irregular rolling sign (Figure 4A~E) was characteristic in

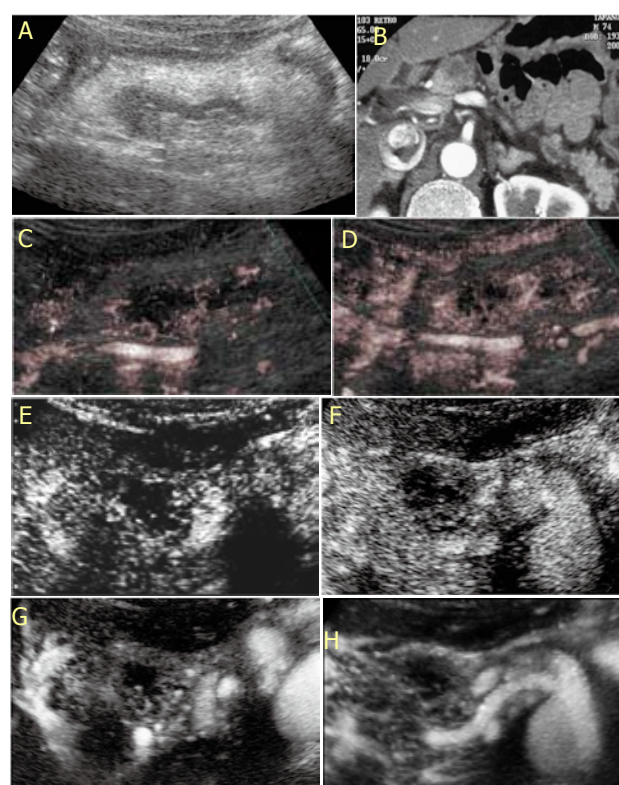


Figure 5 CE-US imaging of PC. A: B-mode US; B: CT; C: CE-US with Levovist (vascular imaging); D: CE-US with Levovist (perfusion imaging). This imaging of Levovist showed hypovascularity, but the degree of enhancement was weak and was hard to discriminate; E, F: CE-US with Sonazoid (DI); G, H: CE-US with Sonazoid (MFI). The dynamics of Sonazoid could be visualized in real-time. The imaging of Sonazoid showed more detailed contrast images compared with Levovist. The irregular rolling blood flow signal of microbubble in the mass (irregular rolling sign).

malignant mass lesion and useful in differentiating between benign and malignancy.

In the results of these investigations, eventually, the rate of concordance of both agents regarding diagnosis was 87%. Compared to Levovist[®], use of Sonazoid[®] improved visualization of the hemodynamics by 10% and diagnosis by 9%. This method has now enabled better imaging of the microvasculature and more detailed observation of the hemodynamics in the lesion areas compared to before.

Next, the contrast capacity of Sonazoid[®] was compared to that of Levovist[®] to evaluate its usefulness in pancreatic diseases.

Pancreatic cancer (PC): As with Levovist[®], the enhancement pattern obtained with Sonazoid[®] was primarily hypovascularity. Even with Levovist[®], weak punctiform or fine dendritic blood flow signals were observed (Figure 5A~D). However, with Sonazoid[®], rather than

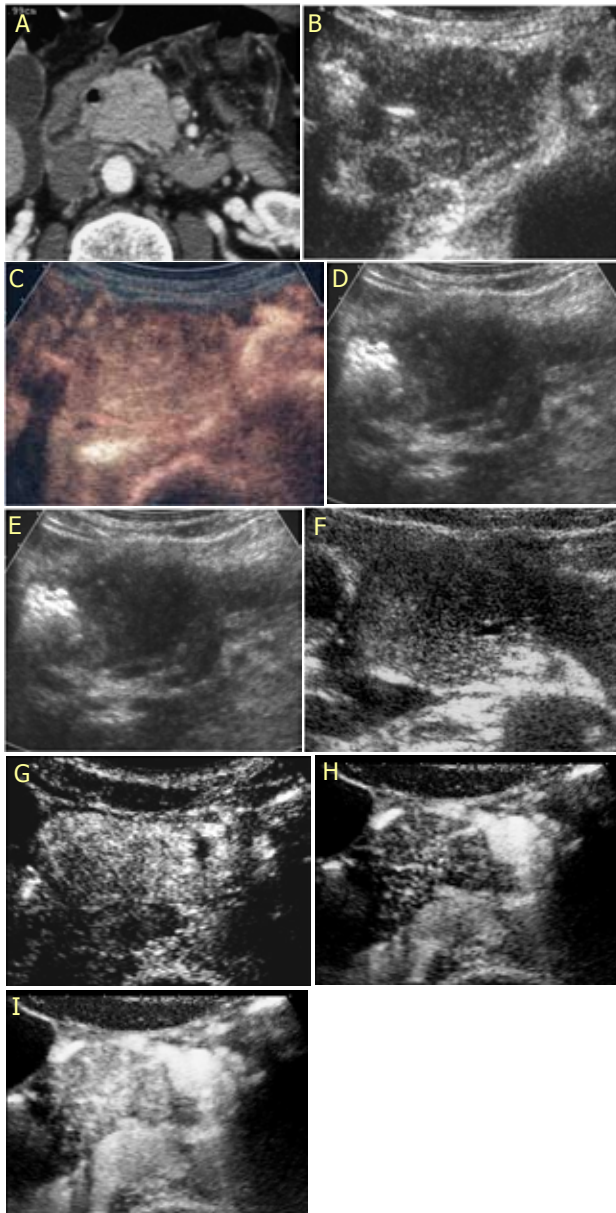


Figure 6 CE-US imaging of MFP. A, B, C: This case was difficult to diagnose using Levovist. 35mm diffuse homogeneous isovascularity mass lesions was scanned by Levovist. EUS-FNA was performed 2 times, but the results were inflammatory change; D, E: But after 5 months, this CE-US imaging of Levovist showed hypovascularity, and the peripheral margin was isovascularity. EUS-FNA showed adenocarcinoma; F: B-mode US; G~I: DI (g) and MFI(H,I) imaging with the use of Sonazoid in MFP showed that the entry of microvasculature into the tumor that could not be visualized with Levovist, could now be visualized and the irregular rolling sign indicative of malignancy was not seen. Moreover, the contrast spread homogeneously in the mass showing isovascularity.

the presence or absence of a single blood flow signal in the mass, the dynamics of the microbubble could be visualized in real-time. The irregular rolling blood flow signal of microbubble in the mass, that is, irregular rolling sign was characteristic in PC (Figure 5E, F). In MFI, the microbubbles attempted to enter the mass, however, images showing their inability to enter the center and images of blood flow showing their irregular rolling blood flow (irregular rolling sign) in the periphery by contrast could be observed in real-time (Figure 5G, H).

Mass-forming pancreatitis (MFP): With Levovist®, diffuse homogeneous isoperfusion pattern was characteristic of MFP, and

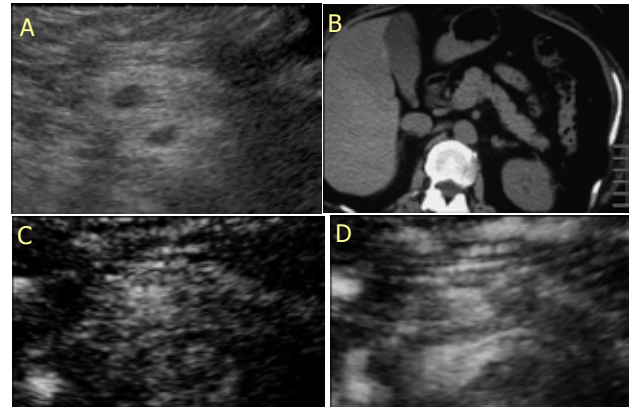


Figure 7 CE-US imaging of PNET. A: B-mode US; B: plain CT (the case in which contrast agent for CT couldn't be given); C, D: DI(c) and MFI(d): Typical PNET showed the contrast spread homogeneously showing a hypervascular pattern with no irregular rolling sign.

inhomogeneous isoperfusion pattern was shown for PC. However, there were 4 cases diffuse homogeneous isoperfusion cases in PC (Figure 6A~E). On the other hand, with the use of Sonazoid® in DI and MFI contrast methods, the entry of microvasculature into the tumor that could not be visualized with Levovist®, could now be visualized and the irregular rolling sign indicative of malignancy was not seen. Moreover, the contrast spread homogeneously in the mass showing isovascularity (Figure 6F~I).

Pancreatic neuroendocrine tumor (PNET): In typical PNET, the margin was clear and commonly showed hypervascular enhancement pattern. However, PNET and papillary adenocarcinoma had the same inhomogeneous hypervascularity pattern. The irregular rolling sign indicative of malignancy was not seen with the use of Sonazoid® in PNET cases. In 3 benign patients in whom Sonazoid® was used, the contrast spread homogeneously showing a hypervascular pattern with no irregular rolling sign (Figure 7A~D).

Solid-pseudopapillary neoplasm (SPN): Small solid type of 3 SPNs found in this institution, with DI, showed a slight delay in the bubbles entering the mass compared to the surrounding normal pancreas, however, they were contrasted to almost the same extent after that. No irregular rolling sign indicating malignancy was seen. With MFI, irregular vascular image that is indicative of malignancy was not seen, and the mass was contrasted to almost the same degree as the surrounding normal pancreas though there was a slight delay (Figure 8A~G).

Metastatic pancreatic tumor (MPT): The dynamics of contrast imaging that varied according to the tissue of the primary lesion were captured. The difference in contrast was more clear with Sonazoid® than Levovist®. Moreover, in metastasis of renal cancer, MFI revealed that the contrast dynamics of the mass was cotton-wool like and could be visualized in real-time (Figure 9A~D).

Intraductal papillary-mucinous neoplasm (IPMN): In patients that had a nodular area internally, the septum and internal nodular components were contrasted, and the enhancement pattern showed iso-hypervascularity (Figure 10A~D). It is possible to differentiate the elevation of tumor and mucus lump. With Levovist®, it was difficult to differentiate between adenoma and adenocarcinoma. However, there was the irregular rolling sign that allowed differentiation in adenocarcinoma patients in whom Sonazoid® was used.

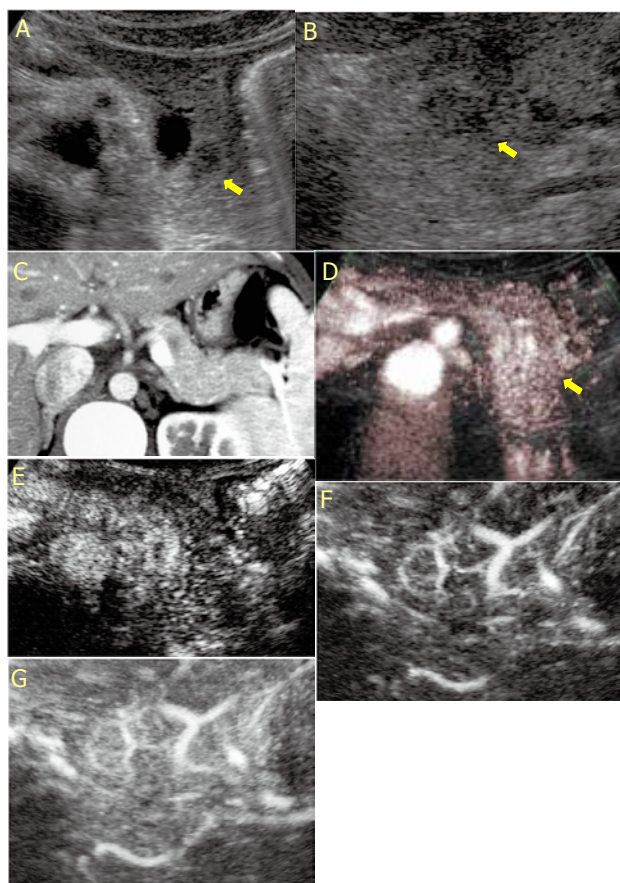


Figure 8 CE-US imaging of SPN. A, B: B-mode US; B-mode US showed hypo echoic mass (13mm) in pancreas body; C: CT; D: CE-US imaging with Levovist; The mass was enhanced homogeneously, but the fine vessel signal in mass could not be obtained; E~G: CE-US imaging with Sonazoid; Irregular vascular image (irregular rolling sign) that is indicative of malignancy was not seen, and the mass was contrasted to almost the same degree as the surrounding normal pancreas though there was a slight delay.

Serous cystic neoplasm (SCN): The septum of the internal microcysts could be contrasted by CE-US providing clear visualization of the internal structure of the tumor. Thus, the procedure was useful in differentiation. The structure of the septum was distinctly more clear when Sonazoid[®] than Levovist[®] was used (Figure 11A, B).

Mucinous Cystic Neoplasm (MCN): With CE-US, the structure of the lumen was clear, showing effective contrasting of the nodular lesion.

DISCUSSION

The results of the 50 patients with pancreatic diseases in whom Sonazoid[®] was used showed that on the whole, more detailed contrast images were obtained with Sonazoid[®] compared to Levovist[®]. Moreover, contrast evaluation that was more precise compared to the past methods was possible. In addition, detailed movements of microbubbles in the capillaries that were difficult to visualize with Levovist[®] could be visualized repeatedly in real-time with Sonazoid[®]. Thus, the diagnostic and differentiation capacities can be expected to improve than before.

These second generation ultrasound contrast agents that are represented by Sonazoid[®], are generally low MI contrast agents, which compared to the conventional high MI contrast agent, Levovist[®], undergo less granular disintegration by the ultrasound waves, and high-resolution images can be obtained in real-time.

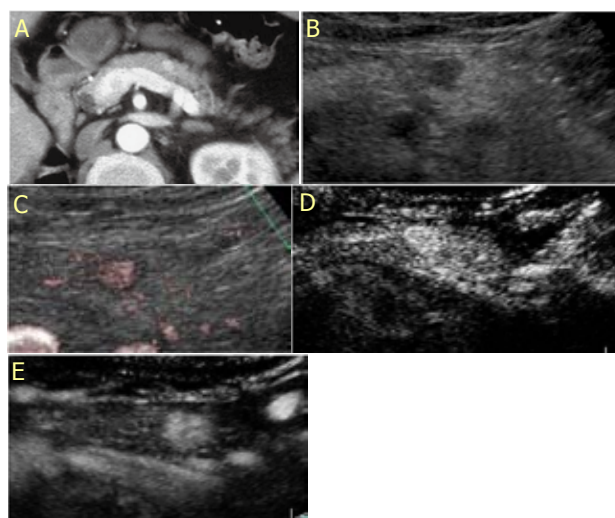


Figure 9 CE-US imaging of MPT (renal cancer). A: CT; CT showed high density mass in pancreas body; B: B-mode US; B-mode US showed hypo echoic mass (10mm) in pancreas body; C: CE-US imaging with Levovist; D(DI), E(MFI): The difference in contrast was more clear with Sonazoid than Levovist. MFI revealed that the contrast dynamics of the mass was cotton-wool like and could be visualized in real-time.

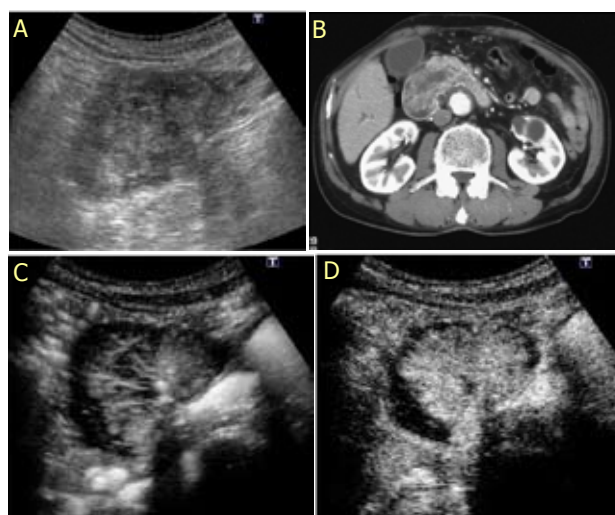


Figure 10 CE-US imaging of IPMN. A: B-mode US; The mass was recognized in pancreas head, but the mass could not be identified if the mass was IPMN or not; B: CT; CT imaging showed cystic lesion with mass inside in pancreas head and the dilatation of main pancreatic duct; C, D: CE-US imaging with Sonazoid; The septum and internal nodular components were contrasted, and the enhancement pattern showed isohypervascularity. Moreover, there was the irregular rolling sign in internal nodule indicated malignancy.

In the case of Levovist[®], the high acoustic transmission caused the bubbles to disintegrate, therefore, the evaluation needed to be done in a short time, and one had to wait for the air bubble to flow back into the parenchyma by the intermittent transmission to evaluate the parenchymal contrast. On the other hand, with Sonazoid[®], the acoustics of the transmitted ultrasound wave is low, the air bubbles resonate without disintegrating and a continuous and long signal is generated, therefore, parenchymal contrast can be obtained in real-time.

The evaluation of the hemodynamics used contrast agent reflects the tissue conditions. The typical enhancement pattern of PC is hypovascularity pattern, and that of chronic pancreatitis including MFP is diffuse homogenous isovascularity pattern^[16]. If an atypical contrast pattern (particularly an isovascularity enhancement pattern) suspicious of PC is shown, it needs to be carefully differentiated

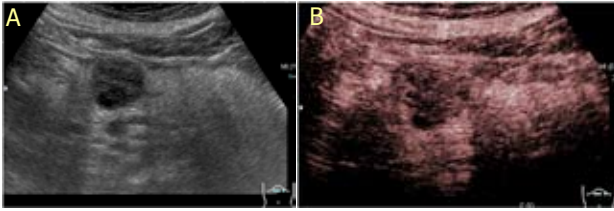


Figure 11 CE-US imaging of SCN. A: B-mode US; B: CE-US imaging with Sonazoid; The septum of the internal microcysts could be contrasted by CE-US providing clear visualization of the internal structure of the tumor. The structure of the septum was distinctly more clear than Levovist.

from MFP. In addition, chronic pancreatitis causes atrophy of the entire pancreas and if there is intense fibrosis, the degree of contrast weakens creating unevenness and the evaluation maybe difficult. In the evaluation of the hemodynamics that reflect the tissue conditions, use of high acoustic contrast agents has limitations and so precise evaluation was difficult. The reason why such differentiation is difficult is because differences in contrast reactions are involved. Inflammatory changes as well as form of growth and grade of histological differentiation of tumor contribute to those differences. In addition, fibrous hyperplasia, amount of interstitial connective tissue, blood vessel occlusion due to invasion of the tumor, degree of vascular opening, and vascular density are also involved. Therefore, it was difficult that the high acoustic contrast agent like Levovist[®], reflected precisely such tissue conditions in the evaluation of the hemodynamics. On the contrary, the second generation of low acoustic contrast agent like Sonazoid[®] and ultrasound devices enabled more precise visualization and evaluation.

In our comparative investigation of the conventional Levovist[®] and the second generation low acoustic contrast agent, Sonazoid[®] in a new contrast method, eventually, the rate of concordance of both agents regarding diagnosis was 87%. Compared to Levovist[®], use of Sonazoid[®] improved visualization of the hemodynamics by 10% and diagnosis by 9%. Now, lesions can be clearly observed with less degradation of the image than before, observations can be repeated several times, the microvascular structure and hemodynamics in the mass can be observed in detail, and all these will assist in the differentiation between benign and malignancy. Use of Sonazoid[®] with the new contrast method to perform CE-US was useful in evaluating the degree of progression of lesions. Thus, it can be concluded that CE-US with Sonazoid[®] is more useful for diagnosis and differentiation compared to Levovist[®]. In malignant tumor in particular, the microbubbles rolled irregularly but in phase with the microvasculature in the mass. The irregular rolling blood flow signal of microbubble, so-called, irregular rolling sign was characteristic and useful in differentiating between benign and malignancy and is positioned as an important finding.

The enhancement pattern of PC showed typically hypovascularity pattern with Levovist[®] and Sonazoid[®]. The dynamics of the microbubble with Sonazoid[®] could be visualized in real-time. The irregular rolling blood flow signal of microbubble (irregular rolling sign) in the mass was characteristic in PC. This sign of CE-US with Sonazoid[®] is considered as malignancy. This finding is useful for differentiate between benign and malignancy. MFP is difficult to differentiate from PC. With Levovist[®], diffuse homogeneous isoperfusion pattern was characteristic of MFP, and if inhomogeneous isoperfusion pattern was shown for PC, the two could be differentiated to some extent. However, there were 4 cases diffuse homogeneous isoperfusion cases in PC. The two in this pattern is difficult to differentiate with Levovist[®]. On the other hand, with the use of Sonazoid[®] in DI and MFI contrast methods, the entry of

microvasculature into the mass that could not be visualized with Levovist[®], could now be visualized and the irregular rolling sign indicative of malignancy was not seen. Moreover, the contrast spread homogeneously in the mass showing isovascularity. This two findings are useful in differentiating between MFP and PC.

In typical PNET, the margin is clear and commonly shows a hypervascular contrast pattern. However, PNET and papillary adenocarcinoma have the same non-uniform hypervascularity, therefore, concomitant use of CT, vascular contrast imaging, and other modalities, namely, EUS, is necessary. In addition, in atypical PNET with intense hyalinization that was reported recently, the contrast reaction is weak and caution is necessary when differentiating. In 3 benign patients in whom Sonazoid was used, the contrast spread uniformly showing a hypervascular pattern with no irregular rolling sign indicating malignancy.

SPN is a rare tumor that occurs mainly in young females. In general, it is a spherical mass with a fibrotic capsule and commonly consists of both a solid area and a cystic area due to hemorrhagic necrosis. There are rare cases when a patient lacks the cystic lesion and then differentiation between acinar cell tumor and endocrine tumor becomes necessary. Solid type of SPN in our institution showed a slight delay enhancement in the Sonazoid[®] bubbles entering the mass compared to the surrounding normal pancreas, and they were contrasted to almost the same extent after that. This finding suggested that the behavior of hemodynamic in the mass is that of the tumor. The irregular vessels flow signal indicating malignancy was not seen. The existence of irregular rolling sign is useful of differentiating between benign and malignancy. Sonazoid[®] allowed visualization of the dense hemodynamics in the mass and was useful in differentiation. The dynamics of contrast imaging that varied according to the tissue of the primary lesion were captured in metastatic pancreatic tumor. The difference in contrast was more clear with Sonazoid[®] than Levovist[®]. Moreover, in metastasis of renal cancer, MFI revealed that the contrast dynamics of the mass was cotton-wool like and could be visualized in real-time. On the contrary, metastatic pancreatic tumor from lung cancer and melanoma showed the hemodynamics of hypovascularity. These were also demonstrated that by stacking the contrast images of a patient, the possibility of identifying the primary lesion was increased.

IPMN contains cystic lesions that have mucinous ingredients and are likely diagnosed by other modalities. In patients that had a nodular area internally, the septum and internal nodular components were contrasted, and the enhancement pattern showed iso-hypervascularity. It is possible to differentiate the elevation of tumor and mucus lump. With Levovist[®], it was difficult to differentiate between adenoma and adenocarcinoma. However, there was the irregular rolling sign that allowed differentiation in adenocarcinoma patients in whom Sonazoid[®] was used. It is interesting whether CE-US with Sonazoid can differentiate between adenoma and adenocarcinoma. However, the patients were few, therefore further investigation is necessary. SCN is a cystic tumor composed of a honey-combed structure of aggregated microcysts. In the B-mode that has been used to date, it was often difficult to visualize the internal structure, and then often showed low echoic mass. Therefore, it was necessary to differentiate with PC. However, the septum of the internal microcysts could be contrasted by CE-US providing clear visualization of the internal structure of the tumor. Thus, the procedure was useful in differentiation. The structure of the septum was distinctly more clear when Sonazoid[®] than Levovist[®] was used. MCN is a giant spherical cystic tumor with a thick fibrous membrane. It has usually septum and cyst in cyst structure with membrane of cyst. One of the findings is a nodular

lesion protruding into the lumen that indicates malignancy. With CE-US, the structure of the lumen was clear, showing effective contrasting of the nodular lesion.

CE-US is low invasive diagnostic procedure that can be performed easily even in an out-patient setting. Moreover, a lot of information important for diagnosis can be obtained. Therefore, it is commonly performed prior to modalities such as CT, MRI and EUS, and will likely assist in deciding on a treatment strategy such as decreasing unnecessary examinations. CE-US has brought about unprecedented changes in the diagnostic system of pancreatic disease. Accumulation of evaluations on hemodynamics using CE-US with Sonazoid® in the future is expected to bring out further improvement and generalization in the diagnostic capacity of pancreatic diseases more than CE-US with Levovist®. Furthermore, though not mentioned in this manuscript, there is the possibility that Sonazoid® will display its effectiveness even after radiotherapy and chemotherapy following high-intensity focused ultrasound (HIFU) in PC^[17,26].

CONCLUSION

The performance of CE-US with Sonazoid® in pancreatic diseases improved the diagnostic capacity better than when the conventional Levovist® was used, and was useful in the differential diagnosis.

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