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MINIREVIEWS

Current status and future applications of contrast-enhanced endoscopic ultrasonography

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Abstract

Endoscopic ultrasonography (EUS) is currently an integral investigation of many gastrointestinal disorders. It has been shown to have a higher efficacy than conventional computed tomography in detection and characterization of small lesions especially in the pancreas. Much effort has been put to further improve the sensitivity, specificity and overall accuracy of EUS. One of the major advances is the utilization of contrast agents for better delineation of the vascularity and tissue perfusion of the target lesion. This article describes the basic principles of ultrasound contrast agents and the different modalities used in contrast-enhanced EUS (CE-EUS) including contrast-enhanced Doppler EUS (CED-EUS) and contrast-enhanced harmonic EUS (CEH-EUS). In addition, the current applications of contrast enhanced EUS in different gastrointestinal conditions were discussed. Furthermore, the future development of hybrid approaches combining CE-EUS with other imaging modalities and the potential therapeutic aspect of using it as a vector for drug delivery were also discussed.

Key words: Endoscopic ultrasonography; Contrast-enhanced endoscopic ultrasonography; Advanced endoscopic ultrasonographic imaging

Core tip: This article provides a focused update on the current applications of contrast enhanced endoscopic ultrasonography in the gastrointestinal tract. Recent advances and future developments in contrast enhanced EUS are discussed.

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INTRODUCTION

Endoscopic ultrasonography (EUS) is currently an integral investigation of many gastrointestinal disorders. It has been shown to have a higher efficacy than conventional computed tomography in detection and characterization of small lesions especially in the pancreas[1]. Much effort has been put to further improve the sensitivity, specificity and overall accuracy of EUS. One of the major advances is the utilization of contrast agents for better delineation of the vascularity and tissue perfusion of the target lesion. This article aims to review the current status of contrast enhanced EUS and to provide insights into future applications of the technology in the gastrointestinal tract.

ULTRASOUND CONTRAST AGENTS

Contrast agents used in EUS are gas-containing microbubbles encapsulated in a resistant shell[2]. This shell decreases dissolution or disruption of the microbubbles in the blood stream. When hit by an ultrasonic wave, the microbubbles would oscillate and generate an acoustic signal that would be detected and reproduced on an ultrasound image[3,4]. At a low acoustic power, a non-linear return signal containing multiples of the resonating frequency would be detected[5]. These higher frequency components, known as harmonics, are fundamental to the "enhancement" detected when performing contrast-enhanced harmonic ultrasonography[6].

Three generations of ultrasound contrast agents have been developed based on their capability of transpulmonary passage and half-life in the human body (Table 1)[7]. First generation agents are microbubbles filled with air, but they generally require high acoustic power to produce oscillation or break its microbubbles. Second generation agents, including the commonly used SonoVue™ and Sonazoid™, are composed of gases that are less soluble and less likely to leak out from microbubbles, thereby lasting longer in the circulation. These agents can be oscillated or broken by lower acoustic power, and thus are more suitable for EUS because of the limited acoustic power produced by the small transducer. Third generation agents (Echogen™) are capable of phase shifting from liquid to gas form once they reach body temperature. These agents are not widely used in EUS of the gastrointestinal tract as yet. Ultrasound contrast agents are generally safe, and adverse reactions are rarely observed. The macromolecules within the agent could lead to allergic reactions, which mostly are mild. There is also minimal clinical significance regarding the toxic or embolic potential and biological effects of these ultrasound contrast agents[5].

Table 1 Contrast agents for ultrasonography[7]

Contrast agent	Composition	Manufacturer
First generation		
Albunex	5% Sonicated serum albumin with stabilized microbubbles	Mallinckrodt
Echovist (SHU 454)	Standardized microbubbles with galactose shell	Schering
Levovist (SHU 508)	Stabilized, standardized microbubbles with galactose, 0.1% palmitic acid shell	Schering
Myomap	Albumin shell	Quadrant
Qantison	Albumin shell	Quadrant
Sonavist	Cyanoacrylate shell	Schering
Second generation		
Definity/luminity	C3F8 with lipid stabilizer shell	Bristol-Myers Squibb Medical Imaging
Sonazoid	C4F10 with lipid stabilizer shell	GE Healthcare
Imagent-Imavist	C6F14 with lipid stabilizer shell	Alliance
Optison	C3F8 with denatured human albumin shell	GE Healthcare
Bisphere/cardiosphere	Polylactide-coglycolide shell with albumin overcoat	Commercially unavailable
SonoVue	SF6 gas with lipid stabilizer shell	Bracco
AI700/imagify	C4F10 gas core stabilized with polymer shell	Acusphere
Third generation		
Echogen	Dodecafluoropentane (DDFP) liquid in phase shift colloid emulsion	Sonus Pharmaceuticals

CATEGORIES OF CONTRAST ENHANCED ENDOSCOPIC ULTRASONOGRAPHY

After intravenous contrast injection, sonographic assessment of the target of interest could be performed by two methods: contrast enhanced color/power Doppler imaging (CED-EUS) and contrast enhanced harmonic imaging (CEH-EUS). Contrast injection in conventional B-mode ultrasound is not recommended as it would not improve imaging quality and the detection of contrast agents is poor in the presence of surrounding tissue. When contrast agents are used with Doppler EUS, it would allow detection of intratumoral vessels with enhancement of tumor vascularity[8-14]. However, vessels with slow flow are still poorly depicted, as this mode has a low sensitivity to low blood flow[6,9,15]. Blood flow from surrounding vessels can also create motion and blooming artifacts, increasing the difficulty in evaluation of tumor vascularity. Motion artifacts refer to low signal intensity of flowing blood when compared to that of tissue movement, while blooming artifacts refer to the widened appearance of a blood vessel with power Doppler[6].

CEH-EUS was recently developed to overcome the difficulties experienced with Doppler EUS. As mentioned above, the harmonic component refers to the return signal of multiples of the fundamental frequency. The harmonic component derived from microbubbles is higher than that from tissues, and the harmonic imaging technique detects these signals. It also filters signals that originate from the tissue by selectively detecting the harmonic components, thereby producing images that depict vessels with very slow flow without Doppler related artifacts[6].

Dietrich *et al*[16] first reported the use of CEH-EUS in 2005. In their study, they demonstrated the possibility of arterial, portal venous and parenchymal contrast enhancement after injection of a second generation contrast agent. Kitano *et al*[17,18] also reported their initial experience with a novel echoendoscope (XGF-UCT260W; Olympus Medical Systems Co. Ltd., Tokyo, Japan) that was equipped with a broadband transducer and extended pure harmonic detection mode. Pancreatic parenchymal perfusion and branching vessels were only observed after contrast injection with the harmonic mode but not the power-Doppler mode, enabling further improvement in accuracy of assessment of tissue vasculature (Figure 1). Since then, numerous studies have reported the use of this novel technique for assessment of different gastro-

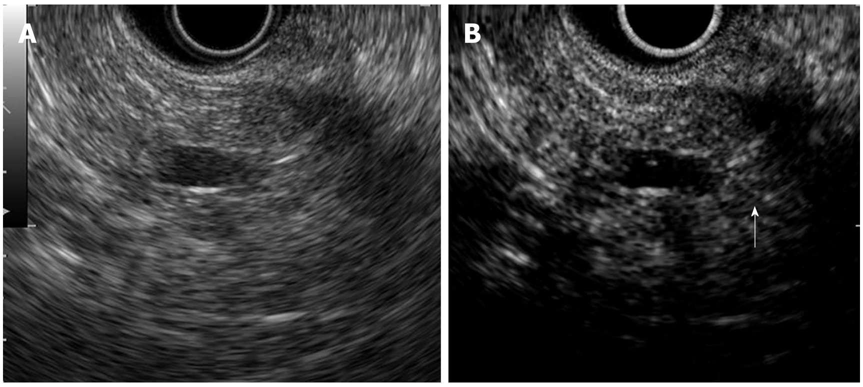

Figure 1 Contrast-enhanced harmonic-endoscopic ultrasonography images of pancreatic parenchymal perfusion. A: Conventional B-mode image; B: Contrast-enhanced harmonic image. Arrowhead indicates pancreatic parenchyme with small vasculature.

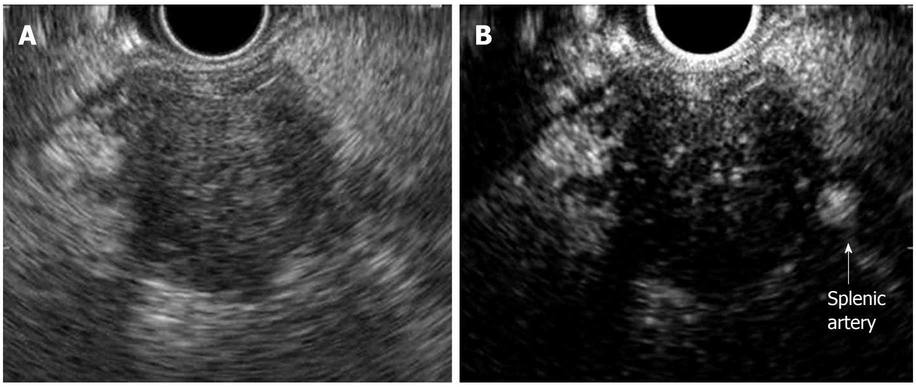

Figure 2 Hypoenhancing pancreatic tumour. A: Conventional B-mode image; B: Contrast-enhanced harmonic image.

intestinal and pancreatic pathologies. However, inter-observer agreement of CEH-EUS was only found to be fair to moderate[19]. Upon a review of 80 EUS videos by 15 endosonographers, overall inter-observer agreement was moderate for the uptake of contrast agents (k = 0.567) and fair for the pattern of distribution (k = 0.304) and the washout velocity (k = 0.369). This finding highlighted a major limitation of the technique that qualitative image analysis of contrast enhanced images is subjected to individual interpretation.

CURRENT APPLICATIONS OF CONTRAST-ENHANCED EUS

Pancreatic solid lesions

Differentiation between pancreatic ductal carcinoma and other pancreatic pathologies such as autoimmune pancreatitis and neuroendocrine tumors is difficult by conventional EUS. By CEH-EUS, four types of enhancement patterns have been reported previously: non-enhancement, hypo-enhancement, iso-enhancement and hyper-enhancement[20]. Hypo-enhancement pattern has been identified as the most common distinguishing feature of pancreatic adenocarcinoma (Figure 2). A recent meta-analysis including studies of both contrast enhanced Doppler EUS and contrast enhanced harmonic EUS reported an overall high sensitivity of 94% (95%CI: 0.91-0.95) and specificity of 89% (95%CI: 0.85-0.92) in diagnosing pancreatic adenocarcinoma[21-26]. Kitano *et al*[20] reported the largest series of 277 patients with solid pancreatic lesions who underwent contrast enhanced harmonic EUS with Sonazoid™. When compared with multi-detector contrast enhanced computed tomography, CEH-EUS yielded a significantly higher accuracy in diagnosing pancreatic adenocarcinomas that were less than 2 cm in size, with a sensitivity of 91.2% (95%CI: 82.5-95.1) and specificity of 94.4% (95%CI: 86.2-98.1). Furthermore, CEH-EUS was also superior in predicting the T-stage of pancreatobiliary tumors as compared with conventional EUS. In particular by CEH-EUS, the wall of the portal vein was better depicted, enabling better visualization of portal vein invasion and providing valuable information for surgical planning for vascular resection[27]. In patients with unresectable carcinoma of the pancreas, CEH-EUS has also been demonstrated to aid in predicting efficacy of chemotherapy. The presence of intratumoral vessels predicted a better progression free and overall survival after chemotherapy[28].

On the other hand, a hyper-enhancing pattern was identified to be a common feature in pancreatic neuroendocrine tumors (PNETs), with a sensitivity of 78.9% and a specificity of 98.0%[20] (Figure 3). The presence of filling defects within an enhancing pancreatic lesion cor-

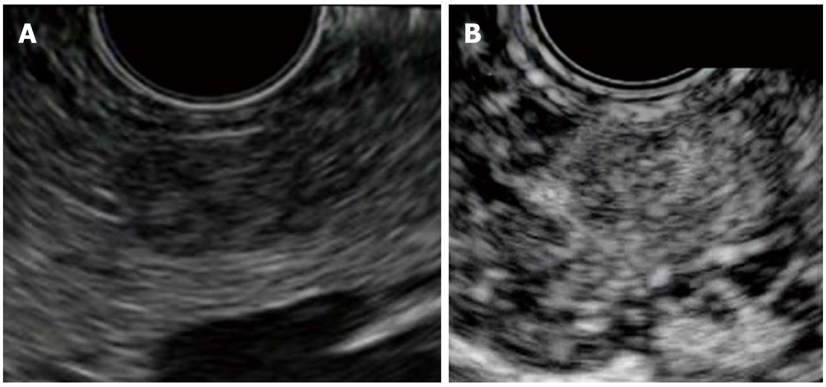

Figure 3 Hyperenhancing pancreatic insulinoma. A: Conventional B-mode image; B: Contrast-enhanced harmonic image.

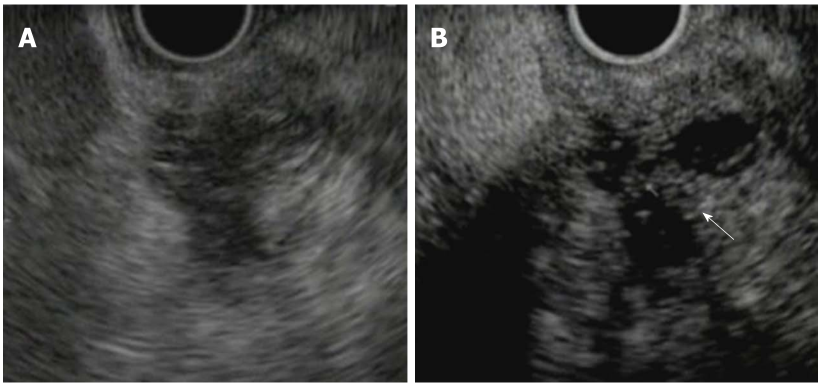

Figure 4 Contrast enhancing mural nodules of a pancreatic cystic neoplasm. A: Conventional B-mode image. B: Contrast-enhanced harmonic image. Arrow indicates mural nodule.

responded to hemorrhage or necrosis of malignant diseases as seen on pathological examination. This may have a potential role in differentiating benign versus malignant PNETs[13].

Pancreatic cystic lesions

The differentiation between benign and malignant intraductal papillary mucinous neoplasms (IPMNs) of the pancreas is difficult. Mural nodules have been identified as one of the most important indicator in the prediction of malignancy. A study published in 2009 demonstrated the ability of contrast enhanced EUS in characterizing mural nodules found in IPMNs[29] (Figure 4). Mural nodules were classified into four types based on the CE-EUS findings, and types Ⅲ (papillary nodule) and Ⅳ (invasive nodule) patterns were more frequently associated with invasive cancer, at 88.9% and 91.7%, respectively. A subsequent series by the same group of authors also found that only CE-EUS identified the presence of mural nodules in 27.3% of cases with proven malignant IPMNs after surgical resection[30]. Accurate differentiation between true mural nodules from mucous clots could also be achieved by contrast enhanced EUS[31].

Gastrointestinal stromal tumors

In a study of 17 patients with gastro-esophageal submucosal lesions, CEH-EUS was able to differentiate between gastrointestinal stromal tumors (GISTs) and other benign submucosal tumors such as leimyoma or lipoma by the pattern of contrast enhancement[32]. All 9 histologically proven GISTs showed hyperenhancement after contrast injection.

CEH-EUS has also been utilized to differentiate between low grade versus high grade malignant GISTs. In a study by Sakamoto *et al*[33], two distinctive vascular patterns were identified by CEH-EUS. Type Ⅱ pattern demonstrating irregular vessels on vessel image and heterogeneous enhancement on perfusion image was more commonly found in high grade malignant GISTs (Figure 5). The overall sensitivity, specificity and accuracy in prediction of malignant risk were 100%, 63% and 83%, respectively. A significantly higher sensitivity of CEH-EUS in detecting intra-tumoral vessels among high-grade malignant GISTs was also demonstrated when compared with multidetector computed tomography (CT) and power-Doppler EUS.

Gallbladder and bile duct lesions

The utilization of CEH-EUS in differentiating cholesterol polyps, gallbladder adenoma and gallbladder carcinoma has been studied. The sensitivity and specificity of CEH-EUS for differential diagnosis of gallbladder adenoma and cholesterol polyps based on the enhancement pattern were 75.0% and 66.6%, respectively, according to a study

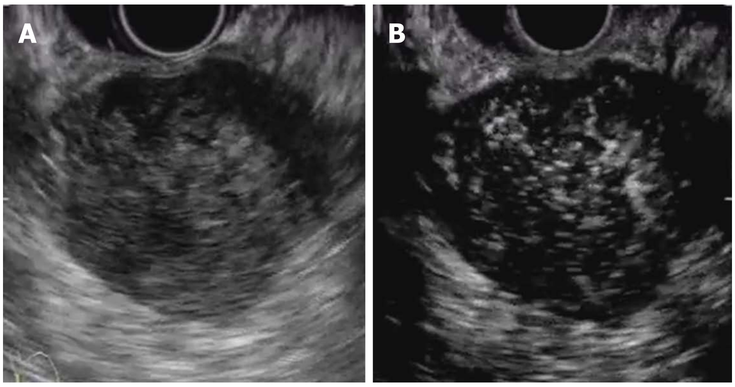

Figure 5 Heterogeneous enhancement with perfusion defects present in high grade gastrointestinal stromal tumors. A: Conventional B-mode image; B: Contrast-enhanced harmonic image.

by Park *et al*[34]. In another study of 93 gallbladder polyps > 1 mm, identification of irregular intratumoral vessels and perfusion defect aided in diagnosing malignant from benign gallbladder polyps, with a sensitivity of 93.5% and a specificity of 93.2%[35].

Bile duct thickening is a common feature in both benign and malignant biliary conditions such as primary or secondary sclerosing cholangitis and bile duct carcinoma. Studies have shown that contrast enhancement in the bile duct wall corresponds to non-neoplastic changes of the bile duct as in cholangitis[36,37].

Intra-abdominal lesions of undetermined origin

Contrast enhanced EUS has been found to be useful in differentiating benign versus malignant intra-abdominal lesions of unknown origin. In a study published by Xia *et al*[38], 43 patients with such a condition underwent CEH-EUS. Correlating with FNA results, the differentiation of malignancy was made by identifying heterogeneous enhancement within these lesions, with a sensitivity, specificity and accuracy of 96.3%, 100% and 97.6%, respectively. Of note, most lesions in the series were indeed intra-abdominal lymphadenopathies with benign or malignant changes.

Visceral vascular assessment

In a small study of 12 patients, all visceral vascular lesions were accurately diagnosed by the use of combined Doppler and CEH-EUS, including one undefined lesion by abdominal CT. The findings of EUS helped determine the appropriate intervention without radiation exposure[39].

Contrast enhanced EUS has also been utilized in other upper gastrointestinal diseases, including the depth of invasion in gastric carcinoma[40] and hemodynamic assessment of esophageal varices[41,42].

FUTURE DEVELOPMENT OF CONTRAST ENHANCED ENDOSCOPIC ULTRASONOGRAPHY

As stated previously, contrast enhanced EUS has been criticized for its qualitative nature. Quantitative methods have been proposed to improve the reliability. Two groups of authors reported the results with time intensity curve (TIC) of contrast uptake in differentiating pancreatic diseases[43,44]. According to Matsubara and colleagues, pancreatic carcinoma, in contrast to other pancreatic pathologies, yielded the greatest echogenic intensity reduction rate from the peak at 1 min after contrast injection. The diagnostic accuracy of EUS in combination with TIC reached 94.7% in their study[44].

A hybrid approach combining EUS with other imaging modalities has also been investigated recently. It was based on electromagnetic position tracking of the EUS transducer position and co-registration with a planar reconstructed image from those obtained on CT or magnetic resonance imaging[45,46]. A preliminary study has demonstrated that estimation of tumor angiogenesis through combining different imaging modalities was possible[47]. It may also increase the diagnostic accuracy through direct comparison of the target lesion by different imaging techniques. Furthermore, improved selection and enhanced visualization are possible for EUS guided FNA of lesions that are not clearly visible in the EUS field[48]. Contrast enhanced EUS could also help determine the likelihood of a false negative FNA result for pancreatic solid lesions.

The therapeutic potential of contrast enhanced ultrasonography has also been explored. Drug substances, such as plasmid DNA, could be delivered within the microbubbles of ultrasound contrast agents. Upon exposure to ultrasonic waves with very high acoustic power, rapid disintegration of microbubbles would occur and the drug within the microbubbles could be released. When combined with endoscopic ultrasound, the technique may aid in targeted drug delivery in pancreatic tumors[5,49,50].

CONCLUSION

With the recent advances in contrast enhanced EUS and CEH-EUS, better characterization of different gastrointestinal pathologies could be achieved. Furthermore, contrast enhanced EUS could play an increasingly important role in diagnosis and management of these conditions in the future.

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