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Contrast harmonic enhanced EUS: technique and clinical outcome

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ABSTRACT

The use of ultrasound contrast agents is widespread in transabdominal ultrasound bringing a relevant clinical impact. Endoscopic ultrasound is very accurate but some limitations exist. For this reason, image enhancement with ultrasound contrast agents is expected to bring significant results also to endoscopic ultrasound. Contrast enhanced endoscopic ultrasound is performed at a high technical level with a dedicated harmonic echo; for this purpose radial and linear echoendoscopes can be used with a dedicated software. This new technique detects strong echosignals from microbubbles in vessels with very slow flow, without artifacts. In clinical experiences, the finding of a hypoenhancing mass with inhomogeneous pattern is a sensitive and accurate parameter to identify patients affected from adenocarcinoma. On the other hand, the finding of a hyperenhanced mass tends to rule out adenocarcinoma and is more suggestive of neuroendocrine tumor. Contrast harmonic enhanced endoscopic ultrasound can be used to select the lesions and/or areas within the lesion to puncture with fine needle aspiration in order to maximize the diagnostic yield.

KEY WORDS: endoscopic ultrasound, contrast agents, contrast enhanced endoscopic ultrasound

INTRODUCTION

Endoscopic ultrasound (EUS) is a very accurate technique and its impact is relevant in different diseases such as pancreaticobiliary lesions [1,2], esophageal cancer [3,4], lung cancer and lymph nodes of uncertain etiology [5,6]. Although EUS is generally more sensitive and accurate than extracorporeal imaging techniques, it has some limitations warranting the development of image enhancement. Among these, it should be quoted that EUS is highly operator dependent, tissue confirmation with fine needle aspiration (EUS-FNA) is usually required for differential diagnosis of tumors, and some pre-existing conditions (such as biliary stents, chronic pancreatitis) may hamper the detection of small lesions [7]. The use of intravenous ultrasound contrast agents (UCAs) has become standard of practice in transabdominal ultrasound for the diagnosis and follow-up of hepatic and pancreatic diseases. Experience with the use of UCAs in endoscopic ultrasound (EUS) is limited in comparison to transabdominal ultrasound. Nevertheless, the potential indications for the use of UCAs with EUS are multiple including the characterization of solid tumor vascularization in the pancreas, the differential diagnosis of lymph nodes, and the staging of gastrointestinal tumors. The purpose of this paper is to review the mechanism of action and the clinical outcome of UCAs when used in combination with EUS.

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MECHANISM OF ACTION OF UCAS AND TECHNIQUES OF SIGNAL DETECTION

The first idea of utilizing UCAs to improve ultrasound images dates back more than 40 years ago. However, several challenges have been encountered to produce microbubbles small enough to cross the lung bed and to prolong their survival. The solution is twofold. First, the gases are encapsulated in a resistant shell that can enhance the pressure that a small bubble can tolerate. Second, heavy gases are used, such as perfluorocarbons, which are less water soluble and less likely to leak out [8]. While gases are compressible, tissue is almost incompressible. When a gas microbubble is hit by an ultrasound wave it vibrates producing a strong backscattered acoustic signal that can be detected and reproduced. The mechanical index (MI) is an arbitrary value reflecting the probability of cavitation of the microbubbles: the higher the MI the faster all the microbubbles are destroyed. UCAs that are stable on passage through the lungs have been commercially available since 1995. The most studied among the first-generation UCAs, which were filled with air, is *Levovist* (Schering AG, Berlin, Germany). Second-generation UCAs, containing inert gases with low solubility in water, have been commercially available since 2001. The most studied among the second generation UCAs, which have increased the stability and duration of the contrast, is *Sonovue* (Bracco, Amsterdam, The Netherlands). The detection of signals from UCAs can be accomplished in two different modalities: a) utilizing color or power Doppler as a generic signal intensifier: contrast enhanced EUS (CE-EUS) b) utilizing a dedicated contrast harmonic: contrast harmonic enhanced EUS (CHE-EUS). The latter is the most appropriate technique as it is able to detect signals from microbubbles in vessels with very slow flow without the burden of Doppler-related artifacts, such as ballooning and over painting, which are common with CE-EUS. The first study from Japan [9] showed that low values of MI allowed a good visualization of early arterial phase, parenchymal perfusion and microvasculature in the pancreas. In comparison, CE-EUS did not depict the parenchymal perfusion images and branching vessels, whereas blooming artifacts of large vessels were observed (Figure 1). Mixed clinical conditions were studied in this pioneer experience including pancreatobiliary carcinomas, gastrointestinal stromal tumors, and lymph-node metastases.

CLINICAL EXPERIENCES WITH UCAS IN THE EUS LITERATURE

A relevant number of publications dealt with the use of contrast agents with color and power Doppler signals (CE-EUS). Although the use of UCAs without a dedicated harmonic is might be considered of limited value because of artifacts, nevertheless important clinical information has been derived from these studies. In 2 studies dating back more than 10 years ago, enhancement of B-mode images was analyzed after injection of Albunex showing for the first time that pancreatic-ductal adenocarcinoma was hypoenhancing in CE EUS [10,11]. Subsequently, larger experiences were described using Levovist as UCA. In particular, Dietrich et al. [12] used CE (color Doppler) EUS to investigate patients with an undetermined pancreatic tumor. Ductal adenocarcinoma of the pancreas showed a hypovascularity in 57/62 cases while all other pancreatic lesions revealed an isovascular or hypervascular (20 neuroendocrine tumors, 10 serous microcystic adenomas, and 1 teratoma) (Figure 2). In their experience, hypovascularity as a sign of malignancy in CE EUS obtained 92% sensitivity and 100% specificity. A comparison study among CE-EUS with Levovist vs. conventional power Doppler EUS vs. multidetector CT for the differential diagnosis of small pancreatic tumors was performed by Sakamoto et al. [13]. The sensitivity of the different techniques for differentiating ductal carcinomas from other tumors (≤2 cm) was 83% for CE EUS, 50% for multidetector CT, and as low as 11% for power Doppler EUS. Regarding the usefulness of CE-EUS with Sonovue to differentiate inflammation (focal pancreatitis) from pancreatic carcinoma, Hocke et al. [14] reported interesting results. They found that the sensitivity of EUS in the discrimination between benign and malignant pancreatic lesions was increased from 73% to 91% by the use of Sonovue.

ACCURACY OF CHE-EUS FOR THE STUDY OF PANCREATIC SOLID TUMORS

Up to now, we have studied prospectively more than 140 patients affected from solid pancreatic tumors by CHE-EUS. We have recently reported that CHE-EUS increases the accuracy for the diagnosis of solid pancreatic tumors [15]. In brief, a radial commercially available echoendoscope (GFUE160, Olympus Japan) or a linear prototype echoendoscope (XGF-UCT180, Olympus Japan) were used in conjunction with Aloka'alfa 10 unit (Aloka, Japan). The contrast agent Sonovue (Sulfur hexafluoride MBs; Bracco International BV, Netherlands) was used in every case. The protocol consisted in EUS visualization of the pancreatic area of interest, injection of a bolus of 2.4 ml Sonovue followed by a 5 ml bolus of saline. Then, evaluation and recording of Sonovue uptake/washout for at least 3 minutes was conducted. The optimal mechanical index was 0.36. The results were compared to surgical pathology or EUS-FNA. The finding of a hypoenhancing mass with inhomogeneous pattern was a sensitive and accurate identifier of patients with adenocarcinoma (96% and 82%, respectively); the vast majority of the patients with primary pancreatic adenocarcinoma had a hypoenhancing mass that was inhomogeneous and had fast washout (Figure 3). This finding was more accurate in diagnosis than the finding of a hypoechoic lesion using standard EUS. Hyper enhancement specifically excluded adenocarcinoma (98%), although sensitivity was low (39%). Of neuroendocrine tumors, 11/13 was non-hypoenhancing (9 hyper enhancing, 2 iso enhancing). Interestingly, CHE-EUS allowed detection of small lesions in 7 patients who had uncertain standard EUS findings because of biliary stents or chronic pancreatitis. Targeted EUS-FNA was performed on these lesions. Napoleon et al. [16] reported similar figures in 35 patients presenting with solid pancreatic lesions. The sensitivity, specificity, and accuracy of hypo enhancement for diagnosing pancreatic adenocarcinoma were 89%, 88%, and 89%, compared with corresponding values of 72%, 100%, and 86% for EUS-FNA.

CONCLUSIONS

CHE-EUS is feasible and safe. It is able to depict the small vessels by Sonovue enhancement without the common artifacts encountered with contrast-enhanced color- and power-Doppler EUS. Its utilization is very simple and can be used without any additional workload for the endoscopic personnel. As far as pancreatic solid tumors are concerned, the finding of a hypo enhanced lesion with inhomogeneous uptake is a sensitive and accurate predictor of pancreatic adenocarcinoma. Moreover, CHE EUS allows overcoming artifacts induced by biliary stents and chronic pancreatitis and performing targeted EUS-FNA, to improve the diagnosis of pancreatic adenocarcinoma.

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