

The Added Value of Real-time Harmonics Contrast-Enhanced Endoscopic Ultrasonography for the Characterisation of Pancreatic Diseases in Routine Practice

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Abstract

Endoscopic ultrasonography is an imaging method used in the diagnosis of pancreatic diseases. The differentiation between inflammatory tumor-like masses and pancreatic adenocarcinoma still remains difficult. Contrast enhanced harmonic endoscopic ultrasonography (CEH-EUS) is a new technique, recently available in commercial use and less evaluated. It is used to characterize the microcirculation in pancreatic disorders - hypervascularized masses such as neuroendocrine tumors or hypovascularized masses such as adenocarcinomas - and to better visualize the necrotic areas in acute pancreatitis and the vascularisation of mural nodules and septa in pancreatic cystic lesions.

Key words

Endoscopic ultrasonography – harmonics – contrast – enhanced – pancreatic tumors – chronic pancreatitis – acute pancreatitis.

Introduction

Starting in 1980, radial endoscopic ultrasonography (EUS) has been described as a very good tool for high resolution diagnosis of pancreatic masses. Later on, the EUS guided fine needle aspiration (EUS-FNA) was introduced, for obtaining cytology or histology from these masses. The technology used for EUS also progressed, from mechanical radial transducers to digital electronic transducers with contrast-enhanced power Doppler assessment possibility [1]. Recent evolution of transducers and ultrasound equipment allow the harmonics contrast-enhanced (CE) assessment [2].

The main indications of this technique are: the depiction of the pancreatic lesions' size and margins including its relationship with adjacent vessels, the characterization of adenocarcinomas and neuroendocrine tumors, the differential diagnosis between pseudocysts and cystic tumors and differentiation of the vascular (solid) or avascular (liquid/necrotic) components of the lesion [3, 4].

The ultrasound contrast agents (UCA)

Are defined as exogenous substances which are administrated in a blood vessel to improve the ultrasound contrast. They consist of microbubbles filled with gas and surrounded by a hydrophilic shell which generates two types of response when hit by an US wave: a reflection between microbubbles and surrounding tissue and a vibration of the microbubbles dependent on the type of gas, the flexibility of the shell and the acoustic power of the US reflected by the mechanical index (MI). When the MI is lower than 0.1, the oscilation is symmetrical and the scattered signal is equal with the emitted sound waves (linear response). For a MI between 0.1-0.6 the expansion of microbubbles under US is higher than compression and returning signal contains multiples of emitted signal, called harmonic frequencies (nonlinear response). For MI higher than 0.6, the microbubbles are destroyed, resulting a transient very strong echo [5].

Among fluoro-gas-containing agents the major experience in CE-EUS is with Sonovue[®], which consists of phospholipids-stabilized microbubbles of sulfurhexafluoride (SF₆) with stability and resistance to pressure. Sonovue[®] is isotonic, with a viscosity similar to blood and does not contain protein-based materials. It does not diffuse into the extravascular compartment remaining within the blood vessels until the gas dissolves and is eliminated in the expired air [5].

UCAs increase the signal from the blood and improve the detectability of small vessels flow by using CE Power Doppler endosonography (CE-PD-EUS). However, the main limitations of this method are its high sensitivity for motion artifacts (the signal intensity from blood flow is

Received: 20.01.2010 Accepted: 02.02.2010

J Gastrointestin Liver Dis

March 2010 Vol.19 No 1, 99-104

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low compared to that of tissue movements), the blooming effects (due to the turbulence flow in large vessels), the angle-dependent color display and the rapid destruction of microbubbles.

Contrast-enhanced harmonics endoscopic ultrasonography (CEH-EUS) technique

The harmonic frequencies obtained during CEH-EUS are different from those transmitted by the transducer and are the result of non-linear oscillation of microbubbles. The image obtained is an addition of the signal created by the distortion of the microbubbles and the tissue-derived signal [5]. This can be optimized by using low MI, which allows minimum bubble destruction and complete “subtraction” of the tissue-derived signal, obtaining a high resolution continuous real-time assessment of the microvascularization during the contrast uptake period [6-8]. CEH-EUS allows a more precise location of vascular structures within the parenchyma and focal abnormalities, with better delineation of pancreatic lesions than EUS, though not with better detection.

The CEH-EUS examination of the pancreas consists of two phases: a. a native phase showing the interest area, the surrounding parenchyma and the neighboring major vessels; b. a contrast phase showing the enhancement pattern of the pancreatic vascular supply. Continuous scanning is performed at a frequency of 7.5 MHz and a MI of 0.3-0.4. After optimizing the settings, the echoenhancing agent (Sonovue®) is injected at a standardized dose of 2.4-4.8 ml/patient followed by a 10 ml saline solution. The contrast phases are identified: arterial phase - early 10-30 seconds (concomitant with the enhancement in abdominal aorta, celiac trunk or superior mesenteric artery) and venous phase - late 30-120 seconds (enhancement in splenic vein, portal vein and superior mesenteric vein). The examination must include scanning of the liver in order to detect small metastases (after 90-120 seconds). The assessment of the contrast agent in the area of interest is made using normal pancreatic parenchyma as reference and the assessment of the arterial/venous vessels. Real-time evaluation after injection of contrast includes: pancreatic morphology, pancreatic circulation, tumor size and invasion of adjacent

major vessels, study of the liver and spleen in the sinusoidal phase (over 120 s).

The mass after contrast injection can be hypovascular homogeneous (low contrast uptake, but the lesion remains completely hypoechoic with no hyperechoic spots inside), hypovascular inhomogeneous (some of contrast uptake, the mass remains hypoechoic after injection, but with some hyperechoic spots inside), hypervascular (mass hyperechoic after injection) or avascular (no uptake).

The CEH-US examination is stored in a video system and later reviewed by a reader who was not present during the examination. The quantification is obtained by digital analysis of the image or by using a specialized software.

Application of CEH-EUS in pancreatic diseases

Acute pancreatitis

The applicability of CEH-EUS in the evaluation of necrotic areas in acute pancreatitis has not been evaluated yet. In acute edematous pancreatitis the filling of the vascular supply is diffuse leading to a homogeneous iso- or hypervascularised enhancement [9]. In severe acute pancreatitis CEH-EUS allows the identification of the necrotic areas as hypovascularised regions (Fig. 1).

Chronic pancreatitis

For focal pancreatitis, the vessel architecture is regular, with both arterial and venous vessels, so one can expect an iso-vascular homogeneous pattern during CEH-EUS, as seen in some studies [5, 10, 11]. However, the pattern of vascularisation depends on the amount of necrosis, inflammation and fibrosis [9]. Edema and inflammation requires extended vascular supply, whereas fibrosis produces a decrease of vascularisation [6, 12, 13]. The fibrosis might be an explanation in cases of severe chronic pancreatitis which displays a hypovascular pattern (Figs. 2, 3) [11].

The use of Sonovue® during CE-EUS facilitates the differential diagnosis between inflammatory lesions and ductal adenocarcinoma, based on perfusion characteristics of microvessels. Hocke et al [10] used the following criteria for chronic pancreatitis without neoplasia: no detectable vascularisation or regular appearance of vessels over a

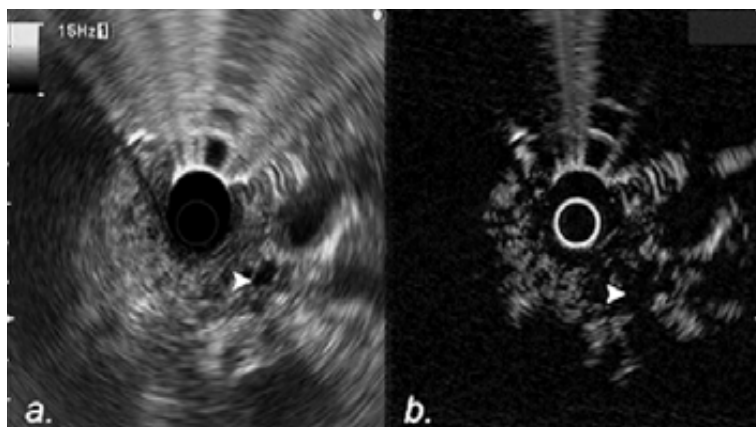


Fig 1. Necrotic areas in acute pancreatitis. **a.** Conventional EUS: a small hypoechoic area (arrow); **b.** CEH-EUS: a larger hypovascular homogeneous area after contrast injection (arrow).

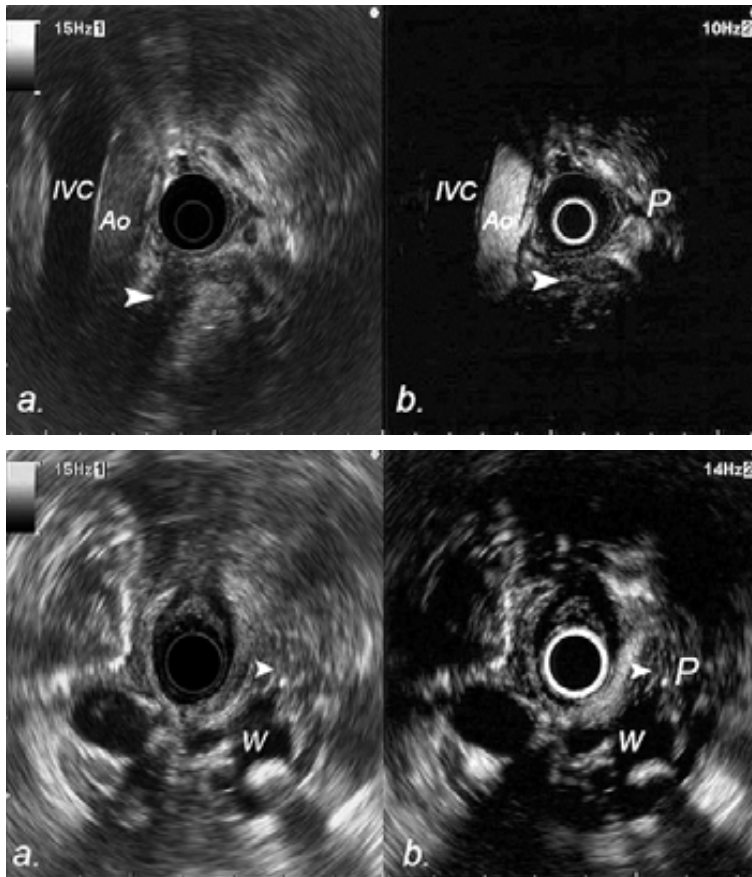


Fig 2. Mass-like chronic pancreatitis. **a.** Conventional EUS. Hypoechoic inhomogeneous mass in the pancreatic head (arrow). Ao - Aorta, IVC- inferior caval vein. **b.** CEH-EUS. During the arterial phase (20 sec after contrast injection) the abdominal aorta becomes hyperechoic and the mass is hypovascular (arrow) in comparison to the surrounding parenchyma (P).

Fig 3. Chronic pancreatitis. **a.** Conventional EUS. Inhomogeneous parenchyma of the pancreatic body (arrow) with dilated Wirsung duct (W) and intraductal lithiasis. **b.** CEH-EUS. Isovascular pattern in the target area (arrow) with the surrounding parenchyma (P) and better view of multiple lithiasis in a very dilated Wirsung duct.

distance of at least 20 mm before and after injection of Sonovue® and detection of arterial and venous vessels in the CE phase. The sensitivity of the discrimination between benign and malignant pancreatic lesions increased from 73.2% by EUS to 91.1% using CE-PD-EUS. The specificity increased from 83.3% to 93.3%. Use of CE-PD-EUS to characterize vessels within the pancreatic masses is superior to the analysis of vascularisation intensity by native Power Doppler EUS alone as demonstrated by Becker et al [1].

For autoimmune pancreatitis, using Sonazoid® during CE-EUS, the isovascular pattern was noticed in 75% of cases, while hypoenhancement was described in 25% of cases [14].

Pancreatic adenocarcinoma

The first experiences with CE-EUS used Albunex® and showed that the pancreatic adenocarcinoma was hypoenhancing [15, 16].

Initial studies used microparticles with galactosis (SHU508 A-Levovist) and CE-PD-EUS; the hypovascular pattern of the pancreatic mass compared to surrounding tissue was considered a sign of malignancy (sensitivity of 82-97% and specificity of 89-100%), although the isovascular and hypervascular pattern was seen in 8% of patients [17]. The hypovascular pattern was considered to have a good value for differentiation of adenocarcinomas from inflammatory masses (sensitivity of 94%, specificity of 100%) [1, 18], for detection of tumors smaller than 2 cm (sensitivity of 94%) or for differentiation from other pancreatic tumors (sensitivity

of 83.3%) [19].

A sensitivity and a specificity of 91.1% and 93.3%, respectively were obtained using CE-PD-EUS with Sonovue® in 86 patients for differential diagnosis between malignant pancreatic tumors and chronic pancreatitis [10,20]. Hocke et al used the following criteria for malignancy: no detectable vascularisation before injection of Sonovue®, irregular appearance of arterial vessels over a short distance after injection of Sonovue® and no detection of venous vessels in the lesion, assuming a malignant lesion if all criteria were detectable [10].

The first study regarding CEH-EUS included only 6 patients [2]. In a larger study on 77 patients, the MI of 0.4 and the scanning interval longer than 2 seconds were considered the optimal conditions for visualizing the pancreas. The same study assessed 27 patients with adenocarcinoma and found a hypovascular pattern with irregular network-like vessels in most of the cases, allowing the differentiation from neuroendocrine tumors which were hypervascular (Figs. 4, 5) [9].

Other studies showed that the hypovascular pattern represented a significant predictive factor for malignancy [21, 22], but also noticed the hypervascular pattern in some pancreatic adenocarcinomas [23, 24].

Neuroendocrine tumors

Previous reports that used CE transabdominal US indicated that 80% to 87% of endocrine tumors exhibited hypervascular pattern [25, 26]. CE-PD-EUS showed iso-

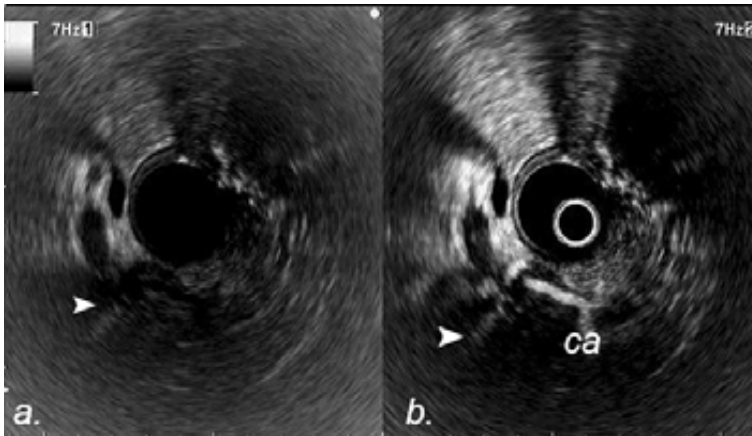


Fig 4. Pancreatic adenocarcinoma: **a.** Conventional EUS: a hypoechoic lesion in the pancreatic body (arrow) **b.** CEH-EUS: a hypovascular homogeneous lesion (arrow) with the encasement of celiac artery (ca).

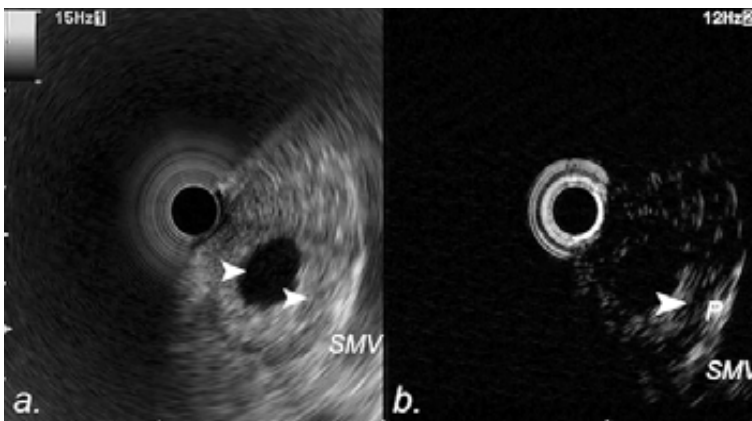


Fig 5. Adenocarcinoma with central necrosis. **a.** Conventional EUS: a hypoechoic lesion with anechoic central region (arrows), without the involvement of the superior mesenteric vein (SMV). **b.** CEH-EUS: a hypovascular mass with lower contrast uptake (arrow) compared to non-tumoral parenchyma (P) situated in the SMV proximity.

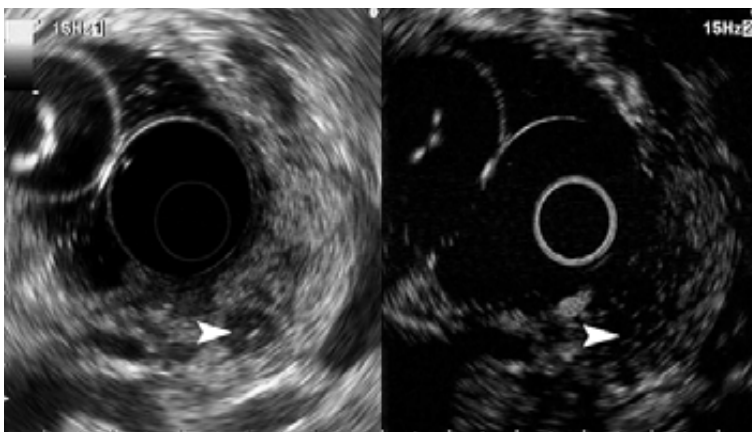


Fig 6. Neuroendocrine tumor. **a.** Conventional EUS: a small hypoechoic lesion (arrow) situated in the pancreatic body between the anterior capsule and the splenic vein. **b.** CEH-EUS: an isovascular pattern of the entire area without delineation of the lesion (arrow).

or hypervascularity of the tumor compared to surrounding tissue [17]. The hypervascularity as a sign of tumors other than adenocarcinomas was found to have a sensitivity of 100%, specificity of 92% and accuracy of 95% [18]. CEH-EUS showed isovascular enhancement in one case of a neuroendocrine tumor [9]. In our experience, CEH-EUS showed an isovascular pattern in one case of neuroendocrine tumor (Fig. 6).

Metastatic pancreatic tumor

Pancreatic metastases display a hypovascular homogeneous pattern [9] or a hypervascular aspect in case of renal-cell metastatic carcinoma [12].

Cystic lesions

Pancreatic pseudocysts

Pseudocysts appear like single unilocular cysts, without internal septa, parietal or central calcifications and have a sharply delineated wall. CEH-EUS may add information for the differential diagnosis with oligocystic serous cystadenoma, mucinous cystadenoma, branch duct IPMN. Pancreatic pseudocysts are avascular on CEH-EUS with absence of intermittent (perfusion) imaging (Fig. 7) [9]. They might have a solid component without any contrast uptake. The communication with the pancreatic duct is not better visualized as compared to the conventional EUS. Hypervascularised walls are seen in ‘young cysts’, while



Fig 7. Pancreatic pseudocyst after an episode of acute pancreatitis. **a.** EUS-linear view. Hypoechoic, large, round lesion (large arrow), quite well delineated, without vascularisation, near gastroduodenal artery (small arrow) **b.** Conventional EUS-radial view. Round hypoechoic lesion (arrows) in the head of the pancreas, nearby SMV. **c.** CEH-EUS: an avascular pattern of pancreatic pseudocyst (arrows), with no contrast uptake compared to the surrounding parenchyma (P).



Fig 8. Branch duct IPMN located in the pancreatic neck. **a.** EUS-linear view. Two anechoic lesions, separated by a septa, with some hyperechoic content (arrow) and communication with Wirsung duct (W). **b.** Conventional EUS-radial view. An inhomogeneous hypoechoic lesion (arrows) situated close to the Wirsung duct, with some hyperechoic content (mucus? solid lesion?). **c.** CEH-EUS: an avascular aspect of the lesion, corresponding to a multilocular branch IPMN (arrows).

hypovascularised walls may be seen in 'old cysts' [7].

Intraductal papillary-mucinous neoplasia (IPMN)

The main duct IPMN can reveal during CE-PD-EUS enhancing neoplastic nodules [17]. During real-time imaging on CEH-EUS branch duct IPMN can show a homogeneous avascular aspect, with some spotty nodules when they become malignant (Fig. 8) [9].

Serous microcystic adenomas

They can appear sometimes as solid masses, due to the submicroscopic size of the cysts. On CEH-EUS the septa are better visualized and the absence of papillary projections gives the honeycomb aspect.

Mucinous cystadenomas

They have thick walls, thick septa, mural or septal calcifications which are the most important findings associated with malignancy.

Conclusions

Contrast-enhanced harmonics endoscopic ultrasonography of the pancreas represents a new development of endoscopic ultrasonography. It can better differentiate chronic pseudotumoral pancreatitis from pancreatic adenocarcinoma.

This technique might improve the staging of pancreatic cancer by better visualization of tumoral delineation and vascular invasion. In acute pancreatitis, CEH-EUS is useful for in the identification of necrotic areas.

Conflicts of interest

None to declare.

Acknowledgements

We are grateful to Olympus and Aloka for furnishing the equipment used in this study. The study was partially funded by a research grant SONODIG and PAGEN PNII/2008 from the Romanian Ministry of Education.

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