CLINICAL IMAGING

Contrast-Enhanced Ultrasound of the Pancreas –a Method Beyond its Potential or a New Diagnostic Standard?

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Abstract

Contrast-enhanced ultrasound is a relatively new technique, currently used for liver tumors diagnosis. Newer contrast agents are composed of stabilized micro-bubbles capable of traversing the capillary circulation. Lately, the method has also been used in the assessment of pancreatic disorders. Pulse inversion harmonic imaging allows the assessment of the hypervascularised masses as neuroendocrine tumors, of the hypoperfused masses as adenocarcinomas and of the necrotic areas in acute pancreatitis. Also, this imaging method allows a better assessment of the pancreatic tumor resectability and the identification of septa inside the cystic lesion. Contrast-enhanced ultrasound might represent a valuable additional imaging method to contrast CT for selected cases.

Key words

Contrast enhanced ultrasonography– pancreas – pancreatitis – neoplasm – cystic tumors

Introduction

The diagnosis of pancreatic disorders is mostly based on sectional imaging techniques – CT, MRI, ultrasonography (US), other such as endoscopic US and intraductal US being added whether needed [1-6]. Ultrasound examination is the first imaging method used in the assessment of abdominal pain and abdominal emergencies. Non-invasive and non-radiating, it is easily accepted by patients and has proven to be a very good diagnostic tool if performed by an expert. Lately, it has been used as an extension of the clinical examination, shortening the diagnostic time [7, 8]. The disadvantages of this technique are the difficulty of a complete examination in overweight patients, operator dependence, and low reproducibility. The limits of transabdominal US in the diagnosis of pancreatic diseases are in case of tumors <10 mm diameter and in the assessment of the necrotic and ischemic areas in acute pancreatitis, even when harmonic techniques are used [9-12]. The use of contrast agents has further improved the diagnostic accuracy [13].

The contrast agents are stabilized gas micro-bubbles with a diameter of <10 microns. They are injected into the systemic circulation, traverse the pulmonary capillary circulation and reach the organ vascular supply and remain at this level, unlike the contrast agents used in CT or MRI. Based on the Doppler principle and secondary harmonics, the micro-bubbles are detected following vibration and bursting and increasing the signal-to-noise ratio. The contrast agents are non-embolizing and non-toxic and mild adverse reactions are recorded [14, 15].

The SonoVue (Bracco) substance is a second generation contrast agent used with modern sophisticated ultrasound equipment. Echoes are received in a wide range of values concomitant with pulse inversion, which improves discrimination between non-linear micro-bubble and linear tissue echoes. Lowering the mechanical index (acoustic pressure of the ultrasounds emitted by the transducer), the bubbles can be distinctly visualized concomitant with the parenchyma extraction from the image, resulting a real time and longer time (range of minutes) improved visualization of the vascular supply.

The main indications of the method are the qualitative and quantitative assessment of parenchyma perfusion and optimal visualization of slow blood flow in small vessels difficult to assess by Doppler ultrasound. While a large number of studies have showed the CEUS usefulness for liver tumor assessment, studies regarding pancreatic disorders are scant and inconclusive [16-20]. The main indications are acute pancreatitis, pancreatic neoplasm and pseudotumours.

Examination technique. The ultrasound examination of the pancreas consists of two phases: (a) a native phase regarding the area of interest selection and (b) a contrast

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phase regarding the assessment of the enhancement pattern of the pancreatic vascular supply. Concomitantly, the operator should assess the retroperitoneal vessels permeability (thrombosis or vascular invasion), the liver vascular supply and the possible hepatic dissemination. The amount of contrast agents injected is standardized (2.4 ml/patient, regardless of body weight), or adapted to each individual, always followed by 10 cc saline administration. The US equipment is set for a contrast examination program which suppresses the tissue echoes and detects the micro-bubbles harmonic echoes. The mechanical index is set at 0.09-0.11, while the focus is positioned below the area of interest in order to avoid the bursting of the bubbles. Due to the entirely arterial pancreatic system, the contrast phases are easy to identify: arterial / early 10–30 seconds (concomitant with the abdominal aorta), and venous / late 30–120 seconds interval (contrast agent in the splenic and mesenteric veins). The assessment of the contrast agent in the area of interest is made considering the normal pancreatic parenchyma as reference. The examination must include scanning of the liver and spleen in order to detect small metastatic lesions (> 90-120 seconds).

Application of contrast enhanced ultrasonography (CEUS) in pancreatic diseases

Acute pancreatitis. In acute edematous pancreatitis the filling of the vascular supply is diffuse, leading to an overall increase of echogenicity [21] (Fig.1).

This part of the examination represents a true "parenchymatography". There is a sinusoidal filling of the vascular supply which leads to a late enhancement of the pancreas, about 3-5 minutes after the i.v. administration of the contrast agent, thus improving the conventional ultrasound image (Fig. 2).

In severe forms of pancreatitis, CEUS allows the identification of ischemic areas and thus improves the assessment of the parenchymal necrosis (Fig. 3).

The performance of CEUS in the diagnosis of severe acute pancreatitis is very good compared to the CT Balthazar score (82% sensitivity, 89% specificity; positive predictive value: 95%, negative predictive value: 67%) [18]. The advantages of contrast agents include the lack of radiation, lower cost and utility for the patients in whom contrast CT is contraindicated – renal failure, iodine contrast allergy and pregnancy [18].

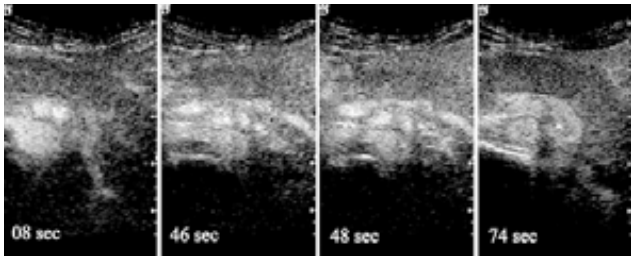

Fig 1. Pancreatic vascular bed filling in acute pancreatitis. A progressive and diffuse increase of parenchyma echogenicity is noted in the first 60 seconds, followed by a "wash-out" of the pancreatic bed up to the 74th second.

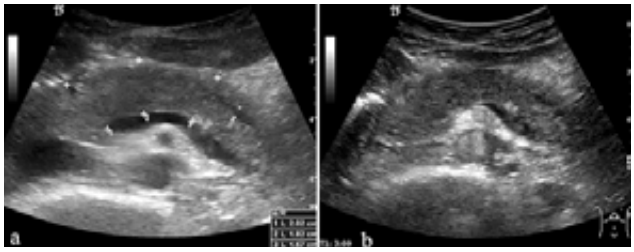

Fig 2. Comparative examination of the pancreas in a case of acute pancreatitis, using conventional ultrasonography (a) and after the administration of contrast at about 240 seconds (without the specific software!) (b). The image on the right has a better accuracy due to the contrast agent at the level of the interstices in the neighbouring structures and microcirculation in the pancreatic parenchyma.

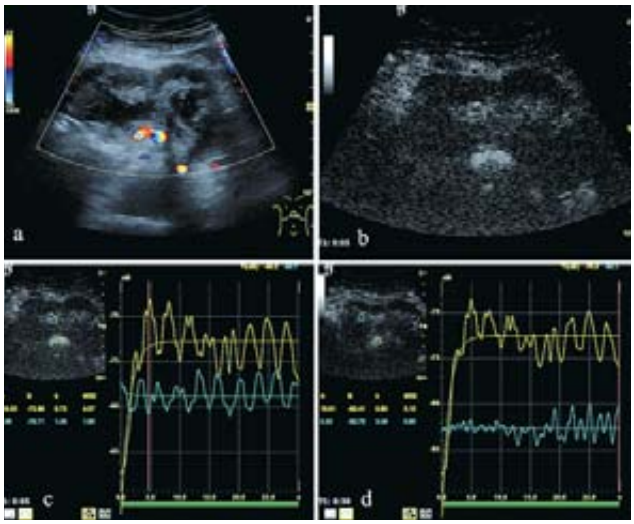

Fig 3. Acute necrotic pancreatitis. Conventional examination (a) evidences signs of severity (enlarged pancreatic bed, hypoechogenic areas suggesting necrosis of the parenchyma); non-homogeneous contrast fill confirms necrosis (b); analysis of the contrast curves evidences viable (c) and necrotic (d) tissues (contrast curves use the signal in the upper mesenteric artery as control).

Pancreatic pseudo-tumors might occur following acute or chronic pancreatitis and might be misdiagnosed as pancreatic neoplasms due to the compression of the pancreatic duct or the retroperitoneal organs [22]. At conventional US examination they appear as an imprecise, hypoechoic tumor mass. Following contrast administration, there is a slow and diffuse enhancement of the pseudo-tumor in over 90% of cases [21], similar in pattern and intensity with the normal parenchyma, thus excluding the presence of tumors (Fig. 4).

The extent of the vascular supply filling is in inverse proportion to the duration and intensity of the inflammatory process, which might represent an indirect sign of the degree of fibrosis and of the presence of parenchyma inflammation and necrosis (21). The diagnostic accuracy of the technique

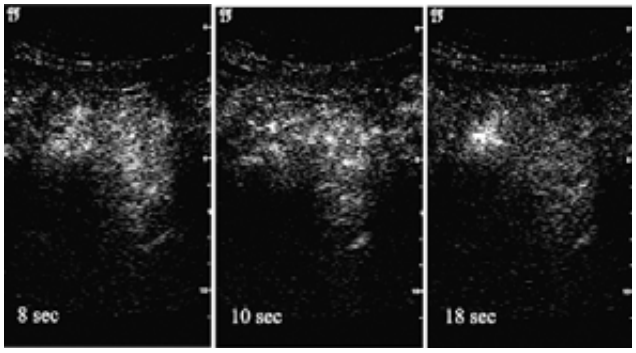

Fig 4. Pseudotumoral chronic pancreatitis. Progressive and diffuse filling of the parenchyma, small in intensity in the first 10 seconds, when a "pancreatogram" type pattern occurs, followed by early and non-homogeneous "wash-out" at 18 seconds.

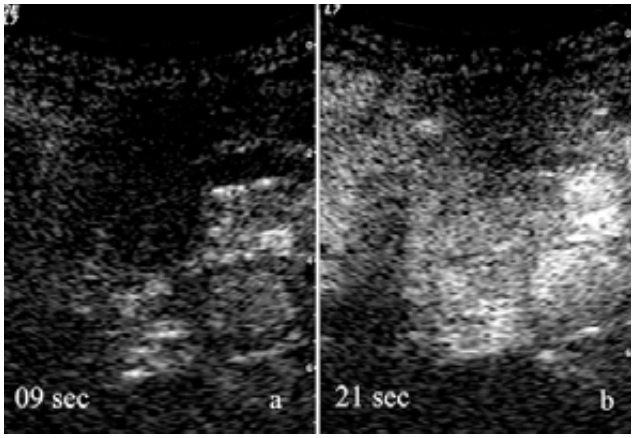

Fig 5. Pancreatic adenocarcinoma. Slow filling of the vascular bed (a), with an intensity peak at 20-30 seconds (b).

regarding pancreatic tumors is: 88.6% sensitivity, 97.8% specificity, 91.2% positive predictive value, 97.1% negative predictive value, general accuracy 96% [21].

Pancreatic adenocarcinoma appears as a hypoechoic mass at conventional ultrasound. Following the contrast agent administration, the signal appears in the large tumor arteries at 9–11 seconds, followed by a slow and diffuse filling of the vascular supply, reaching a maximum intensity at 20–30 seconds. Filling is non-homogeneous, while the overall enhancement remains low compared to the surrounding parenchyma. Thus the typical tumor pattern is hypoechoic, as found in 90% of adenocarcinomas [23- 25] (Fig. 5).

This filling pattern is due to the poor vascularity and the fibrous content of the tumor, which further slows filling [25]. The circulatory model differences between the tumor and the normal parenchyma enhances the tumor margins, more common in hypoechoic adenocarcinomas compared to the isoechoic tumors, thus increasing the diagnostic accuracy (Fig. 6). About 77% of the tumors with negative resection margins presented a hypoechogenic filling pattern in a group of 67 cases of pancreatic adenocarcinoma assessed by this technique and subsequently resected. Only 50% of the tumors with positive resection margins had this filling pattern [2].

The enhancement pattern might lead to an increased echogenicity similar to that of the normal pancreas parenchyma (isoechogenic filling pattern) in 10% of the cases. This pattern might also occur in chronic pancreatitis, thus allowing differential diagnostic errors [13]. In all cases, retroperitoneal vascularization is better emphasized and arterial invasion becomes obvious (Fig. 7).

Kitano classified the pancreatic tumors according to the vascular pattern and behavior after contrast infusion: type I – no vessels in the arterial time and no enhancement on the perfusion image; type II – a few vessels and scattered signal intensity increase in the hypovascular area on the perfusion image, vascularization less intense than in the neighboring pancreatic parenchyma; type III – vascularization similar to the neighboring parenchyma and homogeneous increase of

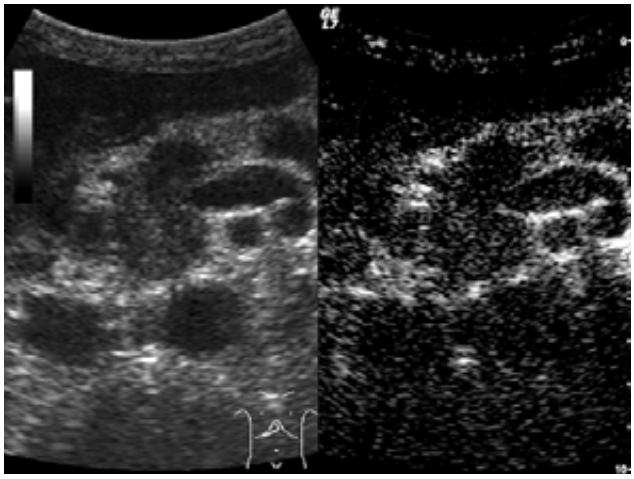

Fig 6. Optimization of the pancreatic mass (adenocarcinoma) visualization after i.v. administration of the contrast agent (SonoVue). The left image is grey-scale, the right one was taken 7 min. 38 seconds after the i.v. infusion.

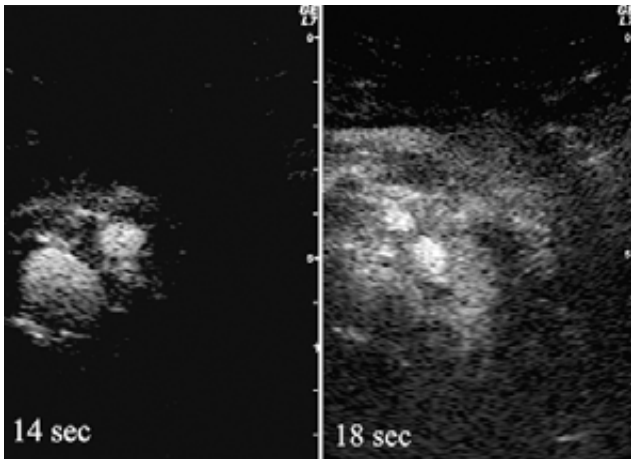

Fig 7. Optimization of the tumoral invasion visualization after i.v. administration of the contrast agent (SonoVue). Hypoechogenic aspect of the parenchyma around the upper mesenteric artery 14 seconds after injection (left). This parenchyma is "filled by contrast" after 18 seconds, at the same time with the tumours, which suggests the common nature of the two structures (right).

signal intensity on the perfusion image; type IV – abundant vessels in the arterial time and hypervascularization on the perfusion image [17]. Most of the adenocarcinomas belong to types I and II (hypovascular tumors), while the other pancreatic tumors are iso- or hypervascular (Fig. 8).

Contrast-enhanced US can detect small (< 2 cm) pancreatic tumors with a sensitivity similar to endoscopic ultrasound (95%) and higher than that of CT (68%) [17]. The technique is sensitive enough to discriminate between patients with abundant tumor vascularization associated with better response to therapy and patients with hypovascularized tumors, with lower therapeutic efficiency and unfavorable prognosis [2].

Neuroendocrine tumours are very small in size (in about 50-70% of the cases the insulinoma diameter is less than 1.5 cm), hypo- or isoechogenic, and almost impossible to detect by conventional US [28-30]. They usually have a very rich vascularization. Using contrast agents, the arterial phase is characterized by a rapid and marked enhancement [31], with a hyperechogenic pattern compared to the surrounding parenchyma. The tumor might be homogeneous or non-homogeneous, depending on the presence of necrotic or cystic areas. During the venous phase the contrast is washed out, leading to a hypoechogenic pattern compared to the surrounding parenchyma. The examination may be performed percutaneously, or during an intraoperative angiography; tumors of up to 1 cm might be detected [29]. Studies have reported a sensitivity of 94%, specificity 96%, a positive predictive value of 75% and negative predictive value of 99% [32] (Fig. 9).

Pancreatic metastases are rare. The most frequent cause of pancreatic metastasis is renal carcinoma. Contrast agents might demonstrate the hypervascularization pattern, concomitant with the detection of liver metastases [33, 34] (Figs.10, 11).

Cystic tumours present a particular filling pattern, but the definite diagnosis requires integration of CT and MRI findings [11]. Microcystic adenoma appears as a well delineated mass with small cysts inside. Following contrast administration septa are enhanced, the tumour showing a mulberry-like or honeycomb pattern [35]. Pancreatic pseudocyst is better diagnosed at contrast administration with the enhancement of the surrounding parenchyma vascular supply. Peripheral circulatory signal might by more enhanced in older pseudocysts [30, 36]. Mucinous cystadenomas are characterized by cystic areas separated by septa, with parietal nodules and papillary wall protrusions. The parietal nodules might not be detected by conventional US due to the rich mucinous content. Also, the differential diagnosis with large pseudocysts might be difficult. Using CEUS, there is an increase of the parietal nodule and intracystic septa vascular signal intensity, allowing the differential diagnosis with pseudocysts (Fig. 12).

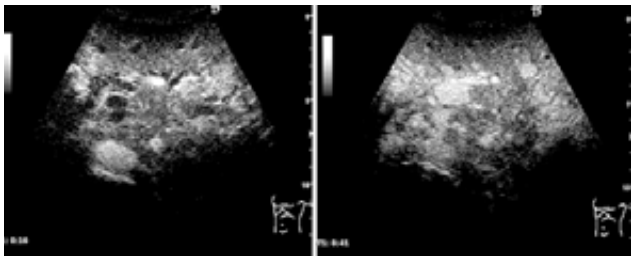

Fig 8. Pancreatic adenocarcinoma with marked filling at the level of the large vessels and peripheral hypoperfusion (fill pattern IV according to Kitano's classification) (left – early arterial time; right – late portal venous time).

Fig 9. Neuroendocrine tumour (insulinoma) (left – conventional examination; right – enhanced contrast US).

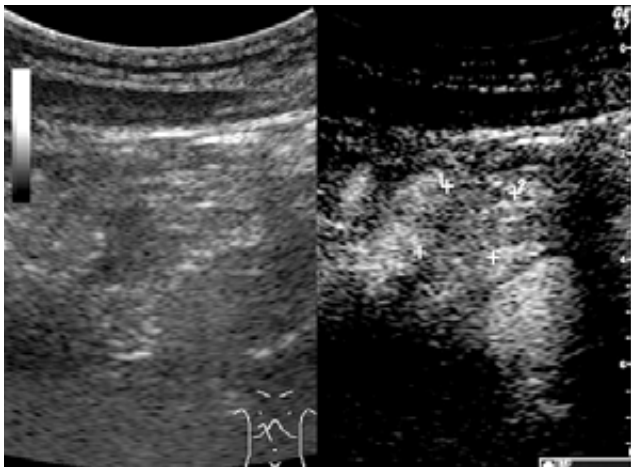

Fig 10. Pancreatic metastasis of a Grawitz tumour.

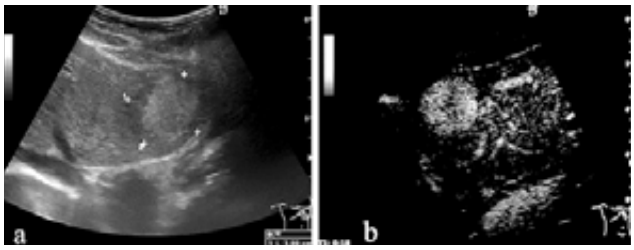

Fig 11. Liver metastasis of a Grawitz tumour (same case as fig. 10).

Mucinous intraductal papillary tumours are rarely detected at US. They appear as a non-homogeneous mass just below a dilated duct when they are large. Contrast agents might show the intraductal growth [31].

Intrapancreatic circulation abnormalities are rare. Among these, there are intrapancreatic varices caused by high portal hypertension. They appear as intrapancreatic hypoechogenic areas corresponding to the dilated vessels completely filled during CEUS venous phase (Fig. 13).

The limits of CEUS in evaluating pancreatic disorders are in differentiating tumors with similar macroscopic aspect, such as cystic tumors. The technique is useful only when the area of interest is also well delineated at conventional US.

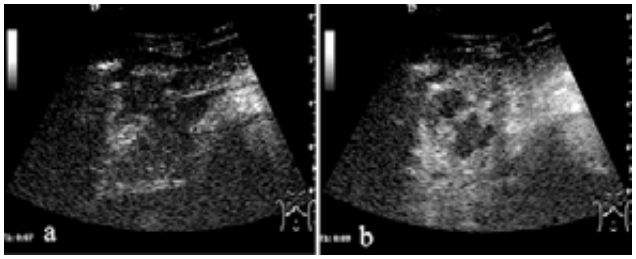

Fig 12. Pancreatic cystic tumour (a – unchanged aspect in early arterial time; b – perfusion of the septa and walls 9 seconds after i.v. contrast injection).

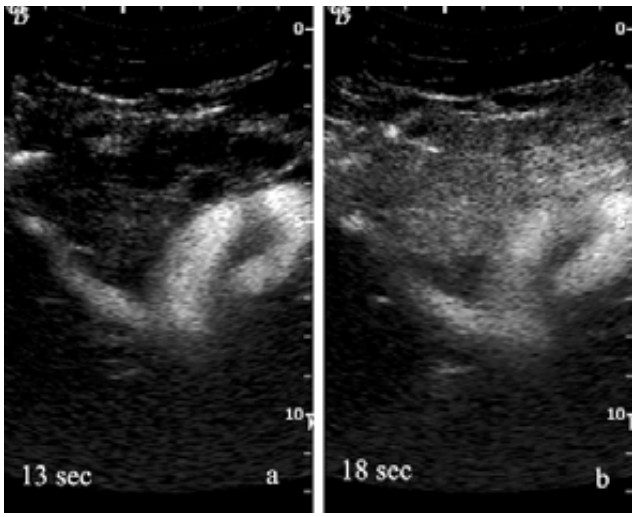

Fig 13. Intrapancreatic collateral circulation evidenced by i.v. contrast. Hypoechogenic aspect of the pancreas during the arterial time (a). Complete filling of the parenchyma during venous time (b).

Conclusions

Contrast-enhanced ultrasonography of the pancreas represents a new development of conventional ultrasonography. Its main indications are the assessment of the solid tumors according to the enhancement pattern following the contrast agent injection, and the differential diagnosis between pseudotumoral chronic pancreatitis and pancreatic adenocarcinoma. The technique might improve the tumor staging by a more precise delineation of the resection margins. The neuroendocrine tumors pattern after contrast administration is highly characteristic, increasing the diagnostic accuracy. In acute pancreatitis the method is useful for the identification of necrotic areas and for the differentiation of pancreatic pseudocysts from cystic neoplasms by evidencing the vascularized septa.

Conflicts of interest

None to declare.

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