Intravenous contrast-enhanced ultrasonography of the pancreas – current state of the method, indications, performance, limitations

R. Badea, Andrada Seicean, M. Tanțău, Zeno Spârchez, Brîndușa Diaconu, M. Socaci, Roxana Stan-Iuga
Medical Clinic III, “Iuliu Hațieganu” University of Medicine and Pharmacy, Cluj-Napoca, România

Abstract
Contrast-enhanced ultrasonography is a relatively new technique, currently used for in the diagnosis of liver tumours. Contrast agents are stabilized micro-bubbles that fill the vascular bed. In the last years the method has also been found useful for the assessment of pancreatic disorders. The equipment will detect harmonic echoes using pulse inversion, which allows the visualization of hyperirrigated areas in the neuroendocrine tumours, or the hypoorrigated or necrotic ones in pancreatitis. In the case of neoplasms, the technique allows a better definition of the tumour and the identification of septa in the cystic forms. In addition, it is highly accurate in detecting liver metastases. Contrast-enhanced ultrasound may represent a convenient alternative to contrast CT in well selected cases.

Keywords: Ultrasonography – Intravenous contrast – Pancreas – Pancreatitis – Neoplasm

List of abbreviations:
CAUS – contrast agents used in ultrasonography
CEU – contrast-enhanced ultrasonography
CT – computed tomography
ERCP – endoscopic retrograde cholangiopancreatography
MRCP – magnetic resonance retrograde cholangiopancreatography
US – ultrasonography

Conflict of interest: None

Acknowledgements: The authors would like to thank Mrs. Zsoka Szasz for helping with this study

Introduction
Pancreatic diseases, both inflammation, acute or chronic, and neoplasms, represent an important health problem [1]. The diagnosis of pancreatic diseases is mostly based on sectional images – CT, MRI, US – which attempt to identify any alterations as early as possible, so that therapy, costs and patient’s suffering to be minimal. Spiral CT assesses the pancreatic bed as a mass and its extensions, or as parenchymatous necrosis, vascular complications and serous collections in the case of acute pancreatitis, being considered the gold standard for such disorders [2]. The technique has the disadvantage of an iodine contrast substance, which is good for assessing circulation but bad for the kidneys. Moreover, they can also affect pancreatic microcirculation, as evidenced by experimental studies [3]. Other techniques are endoscopic
retrograde cholangiopancreatography (ERCP) and MRI cholangiopancreatography (MRCP), each of them with limitations regarding the diagnosis of masses, being either invasive, or with low specificity [4]. Ultrasound examination is often the first method used in abdominal pain and even abdominal emergency. High-resolution portable equipment is current in emergency units, and they also exist in gastroenterology units, independently from medical imaging sections. Diagnostic performance of US is high if in experimented hands, while its noninvasive and non-radiation nature make it very well accepted by patients. Ultrasonography is an extension of the clinical examination, often shortening the diagnostic process [5, 6].

The most common forms of acute pancreatitis are mild to moderate, with reversible oedema. However, about 10-25% of cases evolve to necrosis, pseudocysts and infections, which require complex management: surgery, endoscopy and/or radiology [7, 8]. The signs at the basis of the US diagnosis are enlarged pancreatic bed, non-homogeneous parenchyma (not characteristic), and abdominal collections [9]. The association with the harmonic technique enhances image quality, while color Doppler detects vascular pseudoaneurysms and venous thromboses, without evidencing pancreatic microcirculation. Therefore evidencing ischemic and necrotic areas in acute pancreatitis is not possible with conventional equipment [10]. In the case of tumours, US evidences masses over 10 mm especially when hypoechogenic or cystic. With this size the US aspect is not characteristic and does not discriminate between adenocarcinoma and other tumours such as microcystic adenoma, focal pancreatitis, or cystic adenoma, cystic mucinous neoplasm and intraductal mucinous tumours [11].

Generally speaking US examination is difficult in overweight patients and depends on the operator, which makes it practically irreproducible. Technical progress is represented by echo-endoscopy and intraductal US, but they are not routine examinations, and even less emergency ones [12,13].

All these considerations make any attempt to enhance conventional US worthwhile, one of the methods being the use of i.v. contrast agents.

Contrast agents (CAUS) are stabilized gas micro-bubbles less than 10 microns in size. They are injected into circulation, go through pulmonary microcirculation then systemic one and reach the vascular bed of all organs, and remain at this level, unlike contrast agents used in CT or MRI. By vibration and bursting the ratio signal-sound is markedly increased, which allows their detection based on the Doppler principle and secondary harmonies. These substances are non-embolizing and non-toxic, while adverse reactions are reduced [14, 15].

The main indications of the method are the qualitative and quantitative assessment of circulation in parenchymatous organs and optimal visualization of the vessels in which blood flow is slow or difficult to view by Doppler ultrasound. A high number of studies have shown the CAUS utility in liver tumours [16], while for pancreatic diseases such studies are still undergoing [17].

There are several types of contrast agents on the European market, among which Optison (GE Healthcare) and Luminiity (Bristol Myers Squibb), with cardiac applications, and Levovist (Schering) and SonoVue (Bracco) for abdominal organs. The SonoVue (Bracco) preparation is a contrast agent of the second generation whose use imposes sophisticated modern equipment. Echoes are received in a wide range of values concomitantly with inverse oscillation pulse emission, which facilitates the “discrimination” of linear echoes at the tissue level from the non-linear ones coming from the micro-bubbles. By the very marked lowering of the mechanical index (acoustic pressure of the ultrasounds emitted by the transducer), the bubbles can be distinctly visualized concomitantly with the “extraction” of the parenchyma from the image, which results in an improved visualization of the vascular bed for a long period of time, in the range of minutes. The information is obtained and analyzed during the phenomenon, which makes it a “real-time” investigation. An important limitation is the situation in which conventional US examination is poor. However, in obese patients tissular harmonics may be used to enhance the image quality [18].

Contrast-enhanced examination of the pancreas has been recently introduced [19, 20], its main applications being represented by acute pancreatitis, benign and malignant pancreatic tumours and pseudotumours.

Examination technique Ultrasound examination of the pancreas includes two times: (a) native time consists of study of the pancreatic bed (details of the parenchyma structure, presence of a defined lesion, its texture, overall pancreatic echoes, collections, Wirsung’s duct, cysts or calcifications), the study of collection migration in case of acute pancreatitis (peripancreatic, omental sac, supra- or submesothelial level, pleura and pericardium), signs of vascular disorders by thrombosis (in inflammations) or vascular invasions (neoplasia), involvement of other solid organs (ischemia, metastases). This time is mandatory as it selects the area of interest. (b) contrast time consists of the examination and the features of the filling of the pancreatic vascular bed, the assessment of retroperitoneal vessels permeability (thrombosis or vascular invasion), and the filling of the liver vascular bed and hepatic masses (dissemination at this level). The amount of injected CAUS may be standard (2.4 ml/patient, regardless of body weight), or adapted to each
individual patient, being always followed by the injection of 10 ccm saline. The US equipment is set for a special contrast examination program which produces a suppression of the tissular echoes and detects harmonic echoes at the level of micro-bubbles. The mechanical index is set at 0.09-0.11, while the sound focus is positioned below the area of interest in order to avoid the bursting of the bubbles. Due to pancreatic vascularization, entirely arterial, the filling times with CAUS are easy to identify: arterial/early 10 – 3- seconds (concomitant appearance with the one in the abdominal aorta, and venous/late 30 – 120 seconds (with appearance of the contrast in the splenic and mesenteric veins). The assessment of the contrast in the interest area is made using the normal pancreatic parenchyma as reference. The examination must end with scanning the liver and the spleen in order to detect small metastatic lesions or pre-existing tumours.

Contrast-enhanced US examination must observe a set of principles: (a) examination consist of “real-time” follow-up of the vascular bed filling and its subsequent wash-out; (b) each area of interest will require different administration of the contrast agent; (c) video clips should be recorded on the hard disk of the equipment, as precise times, identification and analysis of wash-out curves being easier on the recording, in the patient’s absence; (d) total duration is about 10 minutes, which will include the examination of the specific area as well as the neighbouring parenchymatous organs (liver, spleen).

The applications of the technique in pancreatic diseases

Acute pancreatitis. In acute edematous pancreatitis the filling of the vascular bed is diffuse, which leads to an overall increase of echogenicity [21] (fig. 1).

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.

This part of the examination has the significance of a true “parenchymatography”. Even without using the contrast software, after about 3-6 minutes from the i.v. administration, i.e. late, the pancreatic bed is is better defined, which in fact represents an optimization of the conventional ultrasound image (fig. 2).

Fig.2. Ultrasound examination of the pancreas in a case of acute pancreatitis, using conventional ultrasonography after administration of contrast without the specific software. The image has a better accuracy due to the contrast agent at the level of the interstices in the neighboring structures and microcirculation in the pancreatic parenchyma.

In severe forms of pancreatitis, in the presence of parenchymal necrosis, the value of contrast ultrasonography increases significantly by the identification of ischemic areas. (fig. 3).

In a study of 31 patients with acute pancreatitis comparing contrast US with contrast CT and in which a severity score similar to Balthazar’s score was used the performance in the was very good (82% sensitivity, 89% specificity; positive predictive value: 95%, negative predictive value: 67%) [18]. In patients with contraindications of contrast CT – renal failure, allergy to iodised substances, pregnancy - this technique could be of choice. A larger number of studies is necessary to assess its value in relation to CT in acute pancreatitis, two arguments making it very attractive: non-radiating nature and possibility to repeat it, and the relatively lower cost than that of the CT [18].

Pancreatic pseudotumours. They represent well delimited growths of the pancreatic parenchyma, with a substrate of interstitial fibrosis and chronic inflammatory infiltration. They occur after repeated bouts of acute pancreatitis of alcoholic etiology or in chronic alcoholic or autoimmune pancreatitis. Similarly to tumours, they
compress the pancreatic duct or the retroperitoneal organs (vessels, duodenum, nerves). Differential diagnosis with neoplasms is difficult due to similarities [22]. At conventional ultrasound examination the aspect is of an imprecise, hypoechogenic tumoral mass. By contrast examination, in over 90% of cases [21] there is a slow and diffuse filling of the pseudotumour, similar in pattern and intensity with the normal parenchyma, which helps to exclude the neoplastic tissue (fig. 4 a,b,c,d).

The extent of the vascular bed filling is in inverse proportion with the duration and intensity of the inflammatory process, which may represent an indirect indicator of the degree of fibrosis and the presence of parenchymatous inflammation and necrosis [21]. The diagnostic performance of the technique for pancreatic tumours is: 88.6% sensitivity, 97.8% specificity, 91.2% positive predictive value, 97.1% negative predictive value, general accuracy 96% [21].

Pancreatic masses. Their behaviour after contrast i.v. administration is defined in relation to the initial aspect of the tumour and the normal neighbouring parenchyma. It may be hypoechogenic, isoechogenic or hyperechogenic [11]. Adenocarcinoma has a hypoechogenic aspect with conventional examination. After the i.v. administration of the contrast agent, the signal appears in the large arteries of the tumour after about 9-11 seconds, followed by a slow and diffuse filling of the vascular bed, reaching a maximum intensity after 20 – 30 seconds. Filling is non-homogeneous, while the overall intensity remains low as compared to the neighbouring parenchyma, which
leads to the conclusion that the typical tumoral pattern is hypoechoic (fig. 5).

It is found in 90% of the cases of adenocarcinoma [23,24,25] and is independent of the contrast agent, 1\textsuperscript{st} generation (Leovist, Schering), or second generation (Sonovue, Bracco). The explanation for this filling pattern is the poor vascularization and the fibrous content of the tumour, which slows the filling [25]. The difference in irrigation between the tumour and the normal parenchyma emphasized the tumour limits, more marked in hypoechoic adenocarcinomas as compared to the isoechoic ones, which actually raises diagnostic performance (fig. 6 a,b,c,d).

Thus, in a group of 67 cases of pancreatic adenocarcinoma examined with this technique and subsequently resected, 77% of the tumours with negative resection margins presented a hypoechoic filling pattern, while only 50% of the tumours with positive resection margins had this filling pattern [26]. In about 10% of the cases filling may lead to increased echogenicity, similar to that of normal pancreas (isoechoic filling pattern), something that may also occur in chronic pancreatitis, which might lead to differential diagnostic errors [11]. In all the cases retroperitoneal vascularization is better emphasized and arterial invasion is clearer.

Kitano classified pancreatic tumours according to
the vascular pattern and behaviour after the injection of contrast: type I – no vessels in the arterial time and no intensification on the perfusion image; type II – a few vessels in the vascular image and scattered increase of the signal in the hypovascular area on the perfusion image, with vascularization remaining less intense than in the neighbouring parenchyma; type III – vascularization similar to the neighbouring tissue and homogeneous increase of the signal on the perfusion image; type IV – abundant vessels in the arterial time and hypervascularization on the perfusion image [17]. The majority of adenocarcinomas belong to types I and II (hypovascular tumours), while the other pancreatic tumours are iso- or hyper-vascular.

In Kitano’s study, in 67% of the cases CUS evidenced intratumoral vessels which contrast CT misses; it also visualizes small (< 2 cm) pancreatic tumours with a sensitivity similar to echoendoscopy (95%) and higher than CT (68%) [17]. In another study Dietrich et al. showed that poor vascularization as a sign of duct adenocarcinoma has 90% sensitivity and 100% specificity [25]. Exploration of intratumoral circulation may represent an indicator of the efficiency of chemotherapy in patients with adenocarcinoma. The technique is sufficiently sensitive to discriminate between patients with abundant intratumoral circulation, with a better response to therapy, and patients with hypovascularized tumours, in which therapeutic efficiency is lower and prognosis poorer [27].

Neuroendocrine tumours are very small in size (in about 50-70% of the cases the insulinoma diameter is less than 1.5 cm), with hypo- or iso-echogenic aspect, which makes
them impossible to detect by conventional examination [28,29,30]. They usually have a very rich vascularization. With CAUS the arterial phase is characterized by a rapid and marked filling [31,32], a hyperechogenic pattern as related to the control parenchyma. The tumoral aspect may be homogeneous or non-homogeneous, depending on the presence of necrotic or cystic degeneration areas. During the venous time the contrast is washed out, which induces hypoechogenicity in relation to the neighbouring parenchyma. The examination may be performed percutaneously, or during an intraoperative angiography; tumours of up to 1 cm may be detected [29]. Sensitivity is 94%, specificity 96%, positive predictive value 75%, negative predictive value 99% (fig. 7).

Secondary pancreatic findings are rare, the most frequent being in the case of renal carcinoma. CUS evidences their hypervascularization at the same time with the detection and visualization of liver metastases [33,34] (fig. 8).

Cystic tumours may present a particular filling pattern. Microcystic adenoma appears as a well delineated mass with small cysts inside. After the administration of contrast, septa are filled, which evidences a mulberry-like or honeycomb pattern [35]. Pancreatic cysts and pseudocysts do not present peripheral vascularization, while cystic tumours present a signal at the periphery and intracystic septa [36]. The peripheral circulatory signal may by more expressed as the pseudocyst is older [30]. Large cystic tumours with abundant solid content, as well as cystic neoplasms are difficult to differentiate by CUS because of their great resemblance in the macroscopic aspect. Mucinous cystadenomas are
characterized by the presence of cystic areas, separated by septa, with parietal nodules and papillary protrusions. Due to the rich mucinous content it is possible that the parietal nodules be not detected by conventional US, and the differentiation from large pseudocysts is difficult. By CAUS there is an increase of the vascular signal at the parietal nodule and intracystic septa levels, which will allow the differential diagnosis with pseudocysts (fig. 9).

*Mucinous papillary intraductal tumours* are rarely evidenced by ultrasound. When they are large, they appear as a non-homogeneous mass below a duct dilation. CAUS may evidence the intraductal growth through the vascularization

Fig. 8. Pancreatic metastasis (gastric neoplasm).
However, for most cystic masses CUS is not sufficient for the differential diagnosis, CT and MRI being also required [11].

**Intrapancreatic circulation abnormalities** are rare. Among these there are intrapancreatic varices caused by high portal hypertension. They appear as hypoechoic areas in the pancreas, corresponding to the dilated vessels which are completely filled at the venous time of the contrast examination (fig. 10).

![Fig. 10. Intrapancreatic collateral circulation evidenced by i.v. contrast.](image)

**Diagnostic improvement and added value of the technique.** The results of the studies on CUS used for the diagnosis of pancreatic diseases are presented in Table 1, and they demonstrate high values of the sensitivity, specificity, positive and negative predictive values in the diagnosis of acute pancreatitis, pancreatic pseudotumours, adenocarcinoma, neuroendocrine tumours and cystic tumours. Associating liver examination in the tissular time significantly increases the performance of the ultrasound technique in detecting liver metastases – competitive with CT and MRI.

**The limitations of contrast-enhanced ultrasonography in pancreatic diseases**

are represented by tumours with very similar macroscopic aspect, such as cystic tumours – pseudocyst, oligocystic cyst-adenoma, without septa inside, or serous cystadenoma. The technique is only useful when the interest area is clear by grey-scale ultrasonography as well.

**Conclusions.** Contrast-enhanced ultrasonography of the pancreas represents a direction of development of conventional ultrasonography. It is mainly indicated for establishing the nature of solid tumours according the filling pattern of the

<table>
<thead>
<tr>
<th>Disease</th>
<th>Author</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute pancreatitis</td>
<td>Rickes, 2002, 2006</td>
<td>82.85%</td>
<td>89.99%</td>
<td>95.97%</td>
<td>67.94%</td>
</tr>
<tr>
<td>Pseudotumours</td>
<td>D’Onofrio, 2006</td>
<td>88.6%</td>
<td>97.8%</td>
<td>91.2%</td>
<td>97.8%</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>Rickes, 2002</td>
<td>87%</td>
<td>94%</td>
<td>89%</td>
<td>93%</td>
</tr>
<tr>
<td>Neuroendocrine tumours</td>
<td>Rickes, 2003</td>
<td>94%</td>
<td>96%</td>
<td>76%</td>
<td>99%</td>
</tr>
<tr>
<td>Cystic tumours</td>
<td>Rickes, 2004</td>
<td>95 – 100%</td>
<td>92 – 100%</td>
<td>95 – 100%</td>
<td>92 -100%</td>
</tr>
</tbody>
</table>
vascular bed by the contrast agents, and the discrimination between pseudotumoral chronic pancreatitis and pancreatic adenocarcinoma. The technique optimizes tumour staging by a more precise definition of the resection margins. The aspect of neuroendocrine tumours after the contrast administration is characteristic, which increases diagnostic reliability. In acute pancreatitis the method is useful for identifying necrotic areas and differentiating pancreatic pseudocysts from cystic neoplasms, by evidence of the vascularized septa.

References


