The value of real-time contrast-enhanced ultrasonography (Sonovue) when characterizing the microcirculation in pancreatic disease

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Purpose

Contrast-enhanced ultrasonography (CEUS) is an imaging method useful for the assessment of slow blood flow in small vessels from areas of interest like parenchymatous organs or tumors. CEUS brings functional information and better, more credible images.

Many studies have shown the CEUS usefulness in liver tumors assessment [1,2,3,4,5]. Contrast-enhanced examination of the pancreas has been recently introduced into the clinical practice [6,7,8], its main indications being: acute pancreatitis, benign and malignant pancreatic tumors and pseudotumours.

The main purpose of this study was the evaluation of the utility of CEUS in the diagnosis of pancreatic disorders as an imaging procedure used routinely in a clinical ultrasound department. A second aim was to assess the usefulness of a supplementary tool like "time-intensity curves" evaluation in order to make the procedure more objective and less operator dependent.
Methods and Materials

Patients:

Sixty-two consecutive patients (mean age: 58.16±11.7 years, male/female: 63%/37%) with suspected pancreatic lesions during native US were assessed prospectively between December 2008 and November 2009 using CEUS (SonoVue), contrast-enhanced CT and/or endoscopic ultrasonography (EUS)/EUS-fine needle aspiration (FNA).

Contrast-enhanced US examination-SonoVue

The ultrasonographic machine was a GE Logiq 7 equipment (with contrast software from 2007) and a 1.5-5.5 MHz convex broadband transducer (4C).

The examination of the pancreas included two phases:

(a) native phase regarding the area of interest (details of the parenchyma structure, presence of a defined lesion, its texture, overall pancreatic echoes, collections, Wirsung duct, cysts or calcifications), the study of collections in acute pancreatitis, signs of vascular thrombosis (in inflammations) or vascular invasions (neoplasia) of the portal and splenic veins, involvement of the liver and spleen (ischemia, metastases).

(b) contrast phase regarding the enhancement pattern of the pancreatic vascular supply, the assessment of the retroperitoneal vessels permeability (thrombosis or vascular invasion), the liver vascular supply and the possible existence of hepatic and splenic metastases.

All the patients were injected with the same quantity of Sonovue (2.4ml/patient, regardless of body weight), always followed by 10 ccm saline injection according to the EFSUMB recommendations [9]. The US equipment was set for a contrast examination program which produces a suppression of the tissue echoes and detects the microbubbles harmonic echoes. The mechanical index was set at 0.09-0.11, while the focus was positioned below the area of interest in order to avoid the bursting of the bubbles. Due to the particularities of the pancreatic vascularization which is entirely arterial, the CEUS phases were easy to identify: arterial/early 10 - 30 seconds (concomitant with the abdominal aorta and or superior mesenteric artery, and venous/late 30 - 120 seconds interval (contrast agent noted in the spleen and mesenteric veins). The assessment of the contrast agent in the interest area was made using the normal pancreatic parenchyma as reference. The examination included the scanning of the liver and spleen in order to detect small metastases (over 90-120 seconds) [10].
Research methodology and quantification technique

Video clips were recorded on the hard disk of the equipment, at precise times, the identification and analysis of wash-out curves was made on the recording. The quantitative analysis of the pancreatic vascularization consisted in time-intensity curves which were created in the selected areas in arterial vessel, focal lesion and normal pancreatic parenchyma. RAW curves data was exported on a workstation, where interpolated fitted curves have been obtained using a technical software (Origin 8). CEUS parameters were than measured from the fitted curves.

The CEUS parameters are presented in Table 1.

<table>
<thead>
<tr>
<th>Pancreatic lesions</th>
<th>CEUS qualitative analysis</th>
<th>CEUS quantitative analysis</th>
</tr>
</thead>
</table>
| Solid lesions      | - enhancement pattern in pancreatic solid lesion  
                     - the identification of the arterial, venous and late phase  
                     - the scanning of the liver and the spleen (over 90-120 seconds);  | Contrast curves in  
                     - selected area inside the solid lesion  
                     - pancreatic normal parenchyma  
                     - arterial vessel  
                     - Parameters for each contrast curve: time to peak (TTP), peak intensity (PI), ascending path, descending path, area under the curve. |
| Cystic lesions     | - enhancement pattern in pancreatic cyst wall  
                     - enhancement pattern in the septa  
                     - the identification of the arterial, venous and late phase  
                     - the scanning of the liver and the spleen (over 90-120 seconds);  | Contrast curves in  
                     - selected area in the cyst wall and septa  
                     - pancreatic normal parenchyma  
                     - arterial vessel  
                     - Parameters for each contrast curve: time to peak (TTP), peak intensity (PI), ascending path, descending path, area under the curve. |
<table>
<thead>
<tr>
<th></th>
<th>descending path, area under the curve.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute pancreatitis</td>
<td>- enhancement pattern in pancreatic tissue and/or in necrotic areas</td>
</tr>
<tr>
<td></td>
<td>- the identification of the arterial, venous and late phase</td>
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<tr>
<td></td>
<td>-Contrast curves in</td>
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<tr>
<td></td>
<td>-selected area in the pancreatic tissue and/or necrotic areas</td>
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<tr>
<td></td>
<td>-pancreatic normal parenchyma</td>
</tr>
<tr>
<td></td>
<td>-arterial vessel</td>
</tr>
<tr>
<td></td>
<td>- Parameters for each contrast curve: time to peak (TTP), peak intensity (PI), ascending path, descending path, area under the curve.</td>
</tr>
<tr>
<td>Other lesions</td>
<td>- enhancement pattern in selected area</td>
</tr>
<tr>
<td></td>
<td>- the identification of the arterial, venous and late phase</td>
</tr>
<tr>
<td></td>
<td>-Contrast curves in</td>
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<td></td>
<td>-selected area</td>
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<td></td>
<td>-pancreatic normal parenchyma</td>
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<td>-arterial vessel</td>
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<tr>
<td></td>
<td>- Parameters for each contrast curve: time to peak (TTP), peak intensity (PI), ascending path, descending path, area under the curve.</td>
</tr>
</tbody>
</table>

**Table 1:** The CEUS parameters

For a better reproducibility, additional "normalized ratios" have been obtained from the parameters, using the formula: \( \text{Param Index} = \frac{(\text{Param lesion} - \text{Param artery})}{(\text{Param parenchima} - \text{Param artery})} \).

Resulting parameters have been subsequently compared between several subgroups (carcinomas vs. pseudotumoral chronic pancreatitis, pseudocysts vs. cystic adenomas, carcinomas vs. metastasis), using the Fischer 2-sample test and 2-way ANOVA test.
Contrast-enhanced CT/ EUS-FNA

Contrast-enhanced CT was performed with a multi-slice CT scanner (Siemens SOMATOM Sensation 16) (Fig.1). EUS was performed using a linear echoendoscope (GF-UCT 140 AL5; Olympus) in conjunction with Aloka alpha 10 ultrasound unit. In case of unresectable pancreatic tumors EUS-FNA was performed (median of three passages, using needles of 22 G) to obtain samples from the pancreatic masses for cytology or histology. (Fig. 2)

Histopathology

In pancreatic malignant lesions histology based on EUS-guided fine needle biopsy or surgery was obtained. The cellular blocs obtained on EUS-FNA and the resected specimens were immediately fixed and embedded in paraffin. The paraffin sections were stained with hematoxylin and eosin. (Fig. 3).
**Fig. 0:** CT: Pancreatic tumor with the invasion of celiac trunk

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Fig. 0: EUS examination: a. pancreatic adenocarcinoma, b. chronic pancreatitis, c. pancreatic cyst with EUS-FNA, d. pancreatic pseudocyst

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Fig. 0: Pancreatic adenocarcinoma: cytology (hematoxylin and eosin).

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Results

The final diagnosis has been reached in 57 cases: pancreatic adenocarcinoma (31), chronic pancreatitis (7), pancreatic pseudocyst (5), acute pancreatitis (4), cystadenoma (4), pancreatic metastasis from hypernephroma, gastric and ovarian cancer (3), neuroendocrine tumor (1), intrapancreatic varices (1), lymphoma (1).

The qualitative analysis showed that a hypoenhancing pattern was characteristic for adenocarcinoma (29/31 cases - 93.54%) and 6 new cases of liver metastasis and 2 new cases of spleen metastasis were identified. Table 2. Fig. 1, 2, 3.

<table>
<thead>
<tr>
<th>Patients (no)</th>
<th>Pancreatic lesions</th>
<th>Hypovascular CEUS pattern</th>
<th>Isovascular CEUS pattern</th>
<th>Hypervascular CEUS pattern</th>
<th>Observations</th>
</tr>
</thead>
</table>
| 31            | Pancreatic adenocarcinoma | 29/31 (93.54%) | - | 2/11 | -Liver metastasis (6) undetected by US 
- spleen metastasis (2) undetected by US 
-The tumor limits better observed Fig. 1 a |
| 7             | Chronic pancreatitis | 3/7 | 4/7 66% | - | Fig. 1 b |
| 4             | Acute pancreatitis | - | - | 4/4-100% | Lack of irrigation in the necrotic tissues Fig. 1 c |
Table 2. The final diagnosis and CEUS pattern in the pancreatic lesions

Subjective findings were backed by corresponding changes in TIC parameters. Statistic results can be seen in Table 3.
| Lesion AUC | -4393,7 | -4632,5 | **0,0420** | -3529 | -4890,3 | **0,0195** | -4393,7 | -4076,6 | **0,0533** |
| Normalized AUC | 26,70 | 1,36 | **0,0013** | -1,5 | 19,18 | **0,0094** | 1,70 | 1,0 | 0,1865 |
| Lesion TTP | 30,16 | 32,91 | 0,1698 | 37,22 | 51,46 | 0,0998 | 30,16 | 38,10 | 0,1201 |
| Normalized TTP | 69,13 | 1,05 | **0,0010** | 1,17 | 1,48 | 0,0754 | 0,43 | 0,10 | **0,0339** |
| Lesion GRAD | 0,84 | 1,05 | 0,2089 | 0,82 | 0,31 | 0,1303 | 0,84 | 1,18 | 0,1585 |
| Normalized GRAD | 0,85 | 2,35 | **0,0039** | 1,23 | -0,15 | **0,0095** | -0,85 | 4,42 | 0,2040 |
| Lesion TTG | 17,68 | 14,23 | 0,2145 | 24,02 | 39,76 | 0,1521 | 17,68 | 20,46 | 0,2621 |
| Normalized TTG | 0,03 | 1,77 | **0,0130** | 0,49 | -4,96 | **0,012** | 0,03 | -27,22 | 0,2510 |

**Table 3.** Results from statistic tests (Fischer) concerning the variance and average of TIC parameters (see Method) in cases of pancreatic carcinomas (PC), pseudotumoral chronic pancreatitis (CP), pseudocysts (PsCy), cystic adenomas (CA) and pancreatic metastases (Met). Tests with p<=0.05 have been highlighted.

It is noteworthy that good to very good differentiation between the studied subgroups with significant p values can be obtained especially when comparing the normalized indexes of the parameters. Best results were obtained for AUC and GRAD parameters (Fig. 4,5,6,7,8).
Fig. 0: CEUS images with main pathological findings: a. Hypoenhancing lesion in pancreatic carcinoma; b. Isoenhancing nodular focus of chronic pancreatitis; c. Diffuse, intense hyperenhancement in acute pancreatitis; d. Non-enhancing lesion with hyperenhancing rim in pancreatic pseudocyst.

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Fig. 0: Differentiating CEUS features in cystic lesions: a. Cystic pancreatic adenoma with normal enhancement in the walls; b. Time-intensity curves from the cyst (yellow), pancreas (green) and artery (red) shows lack of enhancement inside the tumor; c. Pancreatic pseudocyst with contrast uptake in the rim; d. Time-intensity curves show a level of enhancement in the rim (yellow) in between the artery (red) and the tissue (green).

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**Fig. 0:** Pancreatic enhancing metastasis from a renal cell carcinoma: a. Complete enhancement in the arterial phase; b. Wash-out in the venous phase.

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Fig. 0: Descriptive statistics for AUC from pancreatic carcinomas vs. chronic pancreatic pseudotumors show a better differentiation with a very good statistic relevance when comparing the normalized ratios.

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Fig. 0: Descriptive statistics for maximum ascending gradients (GRAD) in pancreatic carcinomas vs. chronic pancreatic pseudotumors show a very good differentiation when using the normalized ratios.

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Fig. 0: Descriptive statistics for AUC calculated in the wall of pancreatic pseudocysts vs. cystic adenomas show a very good differentiation of the populations, especially after normalization.

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**Fig. 0:** Descriptive statistics for maximum ascending gradients (GRAD) calculated in the wall of pancreatic pseudocysts vs. cystic adenomas show a very good differentiation of the populations after normalization.

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Fig. 0: Average differentiation of pancreatic metastases from primary tumors using AUC parameters.

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Conclusion

1. Most of the pancreatic tumors are hypovascular and better seen on CEUS.

2. The examination of the liver in sinusoidal phase allows the detection of small metastasis, unapparent in conventional ultrasound.

3. In addition, CEUS allows better visualization of mass-forming chronic pancreatitis, necrosis in acute pancreatitis and intrapancreatic circulatory abnormalities in segmentary portal hypertension.

4. Mathematical modeling of time-intensity curves parameters can lead to a better differentiation between several pathology subgroups.

5. The best results (p<0.005) were obtained by measuring area under the curve and maximum ascending gradient for the lesions and calculating a “normalized index”.


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