

## Quantitative analysis of tissue perfusion using contrast-enhanced transabdominal ultrasound (CEUS) in the evaluation of the severity of acute pancreatitis

Adela Golea<sup>1</sup>, Radu Badea<sup>2</sup>, Mihai Socaciu<sup>2</sup>, Brîndușa Diaconu<sup>3</sup>, Daniela Iacob<sup>4</sup>

<sup>1</sup> Emergency Medicine Department, University of Medicine and Pharmacy "Iuliu Hațieganu", Cluj-Napoca, Romania

<sup>2</sup> Imagistic Department, University of Medicine and Pharmacy "Iuliu Hațieganu", Cluj-Napoca, Romania

<sup>3</sup> III Internal Medical Department, University of Medicine and Pharmacy "Iuliu Hațieganu", Cluj-Napoca, Romania

<sup>4</sup> III Pediatric Department, University of Medicine and Pharmacy "Iuliu Hațieganu", Cluj-Napoca, Romania

### Abstract

**Introduction:** contrast enhanced ultrasound provides information on the vascularization of the pancreatic parenchyma, detecting areas of inflammation, necrosis, as well as the residual parenchyma in acute pancreatitis. **The aim** of our study was to assess the role of contrast enhanced ultrasound in appreciating the severity of acute pancreatitis by quantitative analysis of the degree of vascularization and the areas of pancreatic parenchymal necrosis. **Material and methods:** The study was prospective (December 2008 - April 2010) and included 25 patients with acute pancreatitis. CEUS examination was performed with a Logiq 7 ultrasound machine, using the afferent software for the quantitative analysis of the acoustic signal. **Results:** The analysis of the average value of the maximum acoustic signal intensity (max I) after contrast injection, and of the mean time to signal enhancement appearance (mT): a) superior mesenteric artery: max I  $19.37 \pm 8.53$  dB, mT  $15.85 \pm 4.6$  sec; b) inflammation area: max I  $14.76 \pm 6.7$  dB, mT  $15.15 \pm 3.6$  sec; c) necrosis area: max I  $8.89 \pm 9.91$  dB, mT  $22.17 \pm 7.9$  sec; d) structural ill-defined hypoechoic area: max I  $12.03 \pm 5.4$  dB, mT  $21.67 \pm 4.47$  sec. The comparison of pancreatic necrosis area measured with contrast enhanced ultrasound and CT revealed a 62.5% concordance. **Conclusions:** Our study attests the usefulness of CEUS in quantifying the necrosis area in acute pancreatitis, with similar results to those obtained by CT.

**Keywords:** acute pancreatitis, contrast enhanced ultrasound, pancreatic necrosis

### Rezumat

**Introducere:** Examinarea ultrasonografică cu agenți de contrast oferă informații asupra vascularizației parenchimului pancreatic, evidențiind zonele de inflamație, necroză, precum și de parenchim restant în pancreatita acută. **Obiectivul** studiului a fost evaluarea rolului ecografiei cu agenți de contrast în aprecierea severității pancreatitei acute prin analiza cantitativă a gradului de vascularizație și a ariilor de necroză parenchimatoasă pancreatică. **Material și metoda:** Studiul de tip prospectiv (decembrie 2008 - aprilie 2010) a cuprins 25 de pacienți cu pancreatită acută. Examinarea CEUS s-a efectuat cu un ecograf Logiq 7, utilizând softul aferent de analiză cantitativă a semnalului acustic. **Rezultate:** Analiza valorii medii a intensității maxime (I max) a semnalului acustic după injectarea de contrast și a timpului mediu de atingere (Tm) a arptat: a) artera mezenterică superioară: Imax  $19.37\text{dB} \pm 8.53$ , Tm  $15.85 \text{ sec} \pm 4.6$ ; b) aria de tip inflamator: Imax  $14.76 \text{ dB} \pm 6.7$ , Tm  $15.15 \text{ sec} \pm 3.6$ ; c) aria de necroză: Imax  $8.89 \text{ dB} \pm 9.91$ , Tm  $22.17 \text{ sec} \pm 7.9$ ; d) aria hipocogenă incertă structural: Imax  $12.03 \text{ dB} \pm 5.4$ , Tm  $21.67 \text{ sec} \pm 4.47$ . Compararea ariei de necroză pancreatică măsurată ultrasonografic cu agent de contrast și prin CT a demonstrat o concordanță de 62.5%. **Concluzii:** Studiul a demonstrat utilitatea CEUS în cuantificarea ariei de necroză din pancreatita acută, cu rezultate apropiate de cele obținute prin CT.

**Cuvinte cheie:** pancreatita acută, ultrasonografia cu agenți de contrast, necroza pancreatică

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Address for correspondence:

Dr. Adela Golea  
UMP Cluj Napoca  
Emergency Medicine teaching line - U.P.U.  
1-3 Clinicilor Street  
400006 Cluj Napoca  
Tel/fax: 0264431876  
Email: adela\_golea@yahoo.com

### Introduction

Acute pancreatitis is still a pathological entity with high mortality 2% - 15% [1], ranging up to 30% in specialized centers due to severe forms in disease evolution [1,2,3]. Early detection of patients at risk of systemic inflammatory manifestations (*Systemic Inflammatory Response Syndrome - SIRS, Multiple System Organ Failure - MSOF*) and septic complications, is a chal-

lenge for *emergency medicine practitioners*, regardless of their specialty. Current research is meant to develop and improve clinical, biological and imaging criteria in evaluating the severity of the clinical form, the selection of the patients who need assistance in specialized centers for early diagnosis and management of pancreatic and extrapancreatic complications. Thus, the literature describes various scores for assessing the severity of acute pancreatitis: APACHE II (Acute Physiology and Chronic Health Evaluation), Ranson score, Glasgow score, BISAP (Bedside Index of Severity in Acute Pancreatitis), HAPS (Harmless Acute Pancreatitis Score) [4].

The diagnosis of acute pancreatitis is based on three aspects: 1) *clinical* - upper abdominal pain with sudden onset, frequently accompanied by vomiting, tachycardia, and sometimes associated with hypotension and fever; 2) *biochemical* - raised serum amylase and lipase at least three times higher than the normal value; 3) *imaging* - CT assessment of changes in the pancreatic bed, peripancreatic region or distant changes [4,5]. It is essential for the optimal therapeutic approach in emergency to classify the clinical form of pancreatitis according to the 1992 Atlanta classification [1]: a) mild acute pancreatitis, known in literature as interstitial or edematous pancreatitis (consisting of microscopic necrosis and edema), and b) severe acute pancreatitis, formerly known as hemorrhagic or necrotizing pancreatitis (consisting of parenchymal necrosis).

Ultrasonography (US), a non-invasive method, is extremely effective in the emergency approach of the patient with high clinical and biological suspicion of acute pancreatitis. 2D examination assesses the changes in pancreatic parenchyma: size, shape, echogenity, ecostructure (areas of inflammation, edema, and necrosis), Wirsung's duct, possible parenchymal or ductal calcifications (suggestive of chronic pancreatitis); thrombosis-like vascular changes on the splenic-portal-mesenteric axis. Doppler examination provides information on the vascularization of the arterial and venous arteries, as well as that at parenchymal level. It is difficult to assess the blood supply to the pancreatic parenchyma by means of Doppler examination which reveals poor or missing signal [6].

Contrast enhanced ultrasound (CEUS) is a new technique which provides information on the vascularization of the pancreatic parenchyma and can differentiate between areas of inflammation (hypervascularized) and areas of necrosis (hypovascularized or non-vascularized) [7,8,9]. Unlike pancreatic CT scan, which is the "gold standard" examination in the diagnosis of acute pancreatitis, recommended within 72 hours after the symptom onset [10], Bidimensional ultrasound (2D) transabdominal ultrasound and CEUS through its non-irradiant character and repeated dynamics provides real-time in-

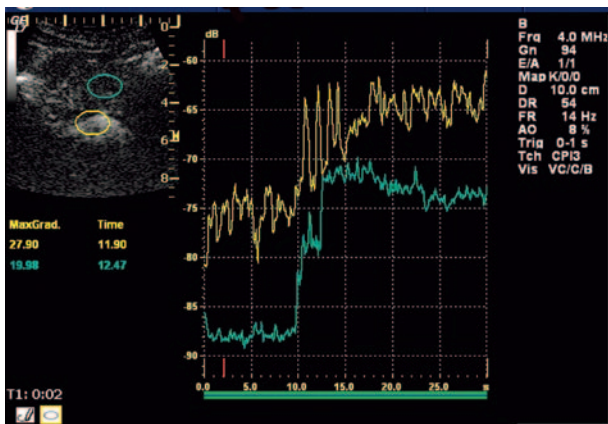
formation concordant with the clinical and biological evolution of the patient [11].

### Material and method

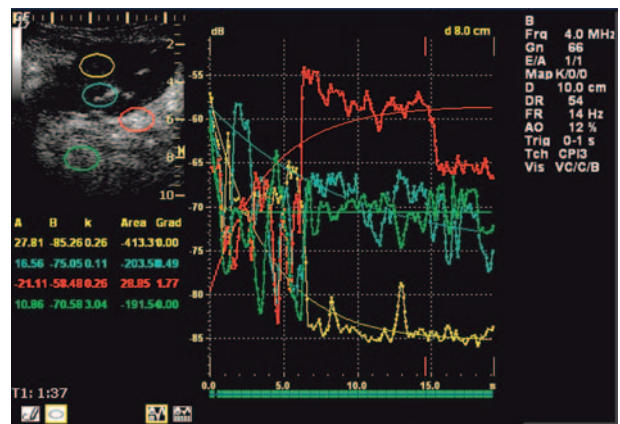
The prospective study included 25 patients admitted to "O. Fodor" Clinical Emergency Hospital, Cluj-Napoca, between December 2008 - April 2010. The patients were clinically and biologically diagnosed with acute pancreatitis. *Inclusion criteria consisted of the following:* 1. diagnostic of acute pancreatitis, suspected on clinical basis and confirmed by *amylasemia/amylasuria*; 2. 2D Doppler transabdominal US examination; 3. informed consent - signed by the patient. *Exclusion criteria consisted of the following:* 1. ultrasonic nonvisualization of the pancreatic bed in 2D mode; 2. acute heart failure; 3. acute coronary syndrome; 4. pregnancy, confinement; 5. history of allergic reactions.

2D ultrasound examination was performed on patients included in the study at their admission and 48 hours after the evolution. Contrast enhanced examination was performed 48 hours after the evolution. US examination was performed with a Logiq 7 ultrasound machine, with contrast software and with the following features: integrated mode and gain controls, coded phase inversion (ICC 3, 4), low mechanical index (MI: 0.06 - 0.1), using true agent detection in dual view. A convex transducer with a 2-5 MHz frequency has been used. We note the use of the analysis software for "wash-in"/ "wash-out" curves, incorporated into the Logiq 7 machine. The analysis of the intensity of the acoustic signal has been assessed on the video recording of the contrast enhanced examination for each patient, extracted at each 5 seconds, for 120 seconds, after contrast injection. Given the respiratory variation, the reestablishment of the region of interest was necessary for the assessment of the intensity of the acoustic signal.

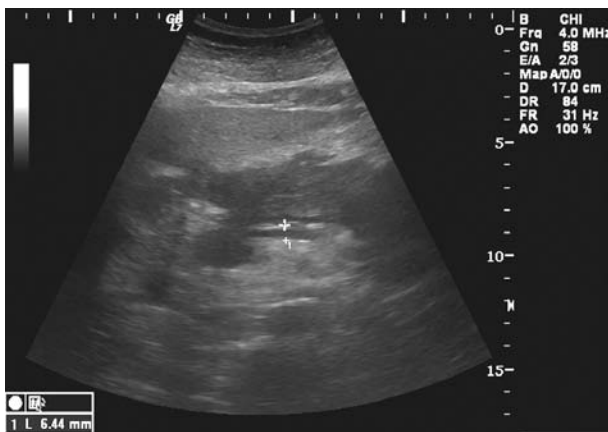
The protocol for contrast enhanced examination consisted of: setting the mechanical index to  $\leq 0.1$  values and the dynamic range to 72dB, setting the focus under the investigation area. "SonoVue" was used as contrast agent, with rapid intravenous administration of 2.4 ml, followed by a dose of 10 ml saline, using a 20G braunula, inserted in the forearm. No automatic destruction of the microbubbles has been performed. The postcontrast analysis in the first 120 seconds used 40 seconds cine-loop sequences. A standardized 12/18mm region of interest (ROI) was chosen. The maximum gradient and its enhancement time were assessed. The "wash-in" and "wash-out" curves were analyzed using Logiq 7 contrast software application. The reference used for the statistical assessment of postcontrast pancreatic parenchymal vascular changes was the mesenteric artery (fig 1, fig 2).



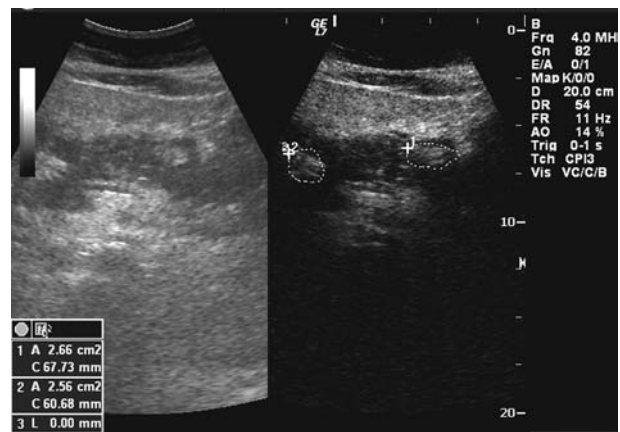
**Fig 1.** Graphic representation of the “wash in” curve in the SMA and hypovascular pancreatic parenchymal area.



**Fig 2.** Graphic representation of the “wash out” curve in the witness area (SMA - green) and different areas of structural change (necrosis - yellow, incomplete necrosis – blue, perinecrotic inflammation - red). Tardy “wash in”-like aspect in the perinecrotic inflammation area.



**Fig 3.** 2D aspect of acute pancreatitis - intense hypoechoic pancreatic area, suggesting necrosis.



**Fig 4.** Aspect of pancreatic bed after contrast administration - “dual view” of residual parenchymal areas in the extended pancreatic necrosis.

The estimation of the parenchymal, pancreatic bed and remote changes has also been tardily quantified using the “tissue contrast hybrid” application. The capsule, the pancreatic parenchymal texture, the size of the pancreas, the presence and size of hypo and non-vascularized areas, the presence of rockets and peripancreatic and remote collections have been ultrasonographically assessed (fig 3, fig 4).

The ultrasonographic diagnosis of acute pancreatitis in 2D examination was based on the gland’s increased volume, the presence of areas with suggestive inflammatory aspect (hyperechogenic) or necrotic aspect (hypoechoic/transonic with echogenic elements), possibly associated with fluid collections [4,12].

Contrast enhanced ultrasound shows a homogeneous increase in pancreatic parenchymal echogenicity in early

arterial phase in healthy subjects, with signal at 15-20 seconds after contrast injection, almost simultaneously with the enhancement of the acoustic signal in the aorta. In patients with acute pancreatitis, contrast enhanced ultrasound allows the certification of vascular parenchymal changes: the areas of inflammation have an increased acoustic signal compared to the normal parenchyma, and areas of necrosis show no vascularization. The method even allows the viewing of the residual parenchymal areas from the necrotic areas [8,13].

The limitations of contrast enhanced ultrasound are determined by the absence of sonic window, the variation of blood flow speed in the pancreatic bed, the mathematical indices of dilution varying according to the intensity of the necrotic and inflammatory process. The deep lo-

cation of the pancreas and the presence of respiratory movements make it difficult to maintain the region of interest at the same level (ROI), in order to calculate the “wash-in” and “wash out” curves, and it is necessary to use special “breathing/movement ROI correction” software or to assay the information manually.

*Contrast-enhanced* computed tomography (CECT) was performed with a Siemens SOMATOM Sensation 16 machine, using Omnipaque intravenous contrast, 1.2 to 1.5 ml/kg, with a scanning interval of one second, and a 3 mm x 3 mm reconstruction.

The statistical analysis was assessed using Excel Windows 1998, *student's t-test*, Wilcoxon matched pairs test for nonparametric tests ( $p < 0.05$  statistically significant), Spearman's rank ( $p < 0.5$  statistically significant).

**Results**

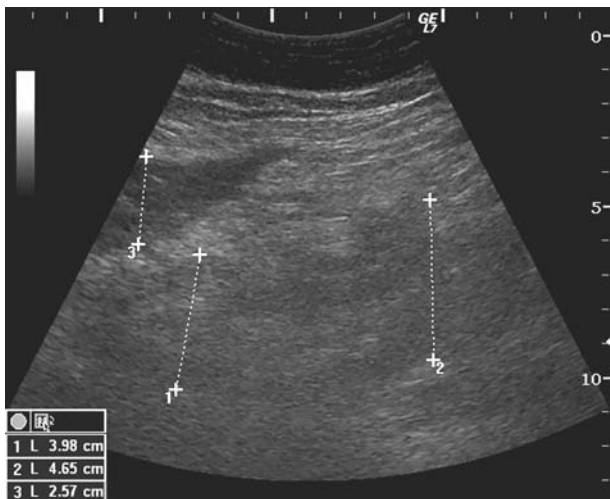
The study group consisted of 25 patients with acute pancreatitis, aged 20 to 68 (average age 46.16), 18 patients being males (72%). Body mass index (BMI) assessment allowed the classification of the patients into 42.1% overweight and 42.1% obese. The statistical analysis on this study group using Wilcoxon matched pairs test for non-parametric values showed a statistically significant correlation between the severity of acute pancreatitis assessed by means of APACHE II scores when the patients were admitted to the emergency unit, and BMI over 25 ( $n=18$ ,  $T=2.5$ ,  $Z=2.86$ ,  $p < 0.0041$ ). The main types of etiology in acute pancreatitis were detected in the analyzed group: 52% alcoholic, 32% biliary, 8% dyslipidemic.

The ultrasonographic comparison of the areas of the pancreatic segments viewed in 2D mode and with contrast agent (fig 5, fig 6), statistically analysed using the t-test, showed a significantly more accurate assessment of the pancreatic area, especially at corporeal level by means of contrast enhanced ultrasound in 2D mode ( $t=-2.99875$ ,  $dF=23$ ,  $p < 0.006409$ ). The comparison of the pancreatic necrosis area measured with contrast enhanced ultrasound and computed tomography (CT) showed a 62.5% concordance (Table I).

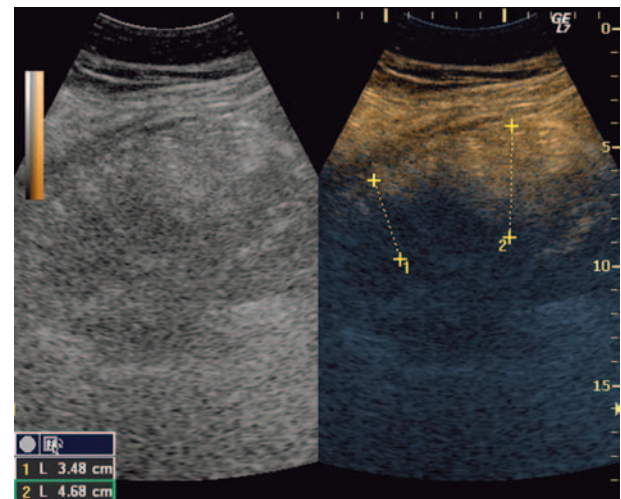
In patients with acute pancreatitis, for a similar analysis in rheological conditions to that of the vascular profile of the non-homogeneous pancreatic parenchyma, the superior

**Table I.** Comparison of the area of pancreatic necrosis measured by means of ultrasound contrast agent and computed tomography

Pt. no.	Pancreatic necrosis		Correlation
	CEUS Assessment	CT Assessment	
1	30.38	30-50	Concordant 62.5%
2	68.51	>50	
3	32.79	30-50	
4	39.94	30-50	
5	2.06	<30	CEUS underestimation 25%
6	47.88	>50	
7	28.99	30-50	CEUS overestimation 12.5%
8	33.75	<30	



**Fig 5.** 2D aspect of the pancreatic bed - increased volume, inhomogeneous, diffuse, bordered by peripancreatic fat.



**Fig 6.** Pancreatic bed aspect after contrast administration - “dual view” of vascularized parenchyma and hypovascular areas, with the optimization of the demarcation points of the pancreatic parenchyma by means of “contrast tissue hybrid” application.

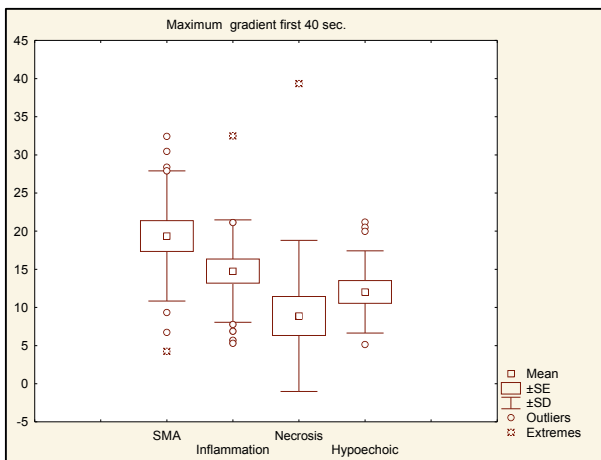
mesenteric artery (SMA) was taken as reference (control) for the contrast enhanced ultrasound examination.

For the analysis of the “wash in” curves in the first 40 seconds after contrast agent administration in the reference area (SMA), in patients with acute pancreatitis, the average value of maximum intensity (max I) was of  $19.37 \pm 8.53$  dB, and the mean time of enhancement (mT) was of  $15.85 \text{ sec} \pm 4.6$ . Comparing to the recorded acoustic signal intensity from the control area (SMA), three different patterns were assessed in the pancreatic parenchymal pathological areas for the achievement of maximum acoustic signal: a) in the inflammatory area, max I of  $14.76 \text{ dB} \pm 6.7$  achieved in a mT of  $15.15 \text{ sec} \pm 3.6$ ; b) in the necrosis area, max I of  $8.89 \text{ dB} \pm 9.91$  achieved in a mT of  $22.17 \text{ sec} \pm 7.9$ ; c) in the ill-defined hypoechoic area, max I of  $12.03 \text{ dB} \pm 5.4$  achieved in a mT of  $21.67 \text{ sec} \pm 4.47$  (table II, fig 7, fig 8).

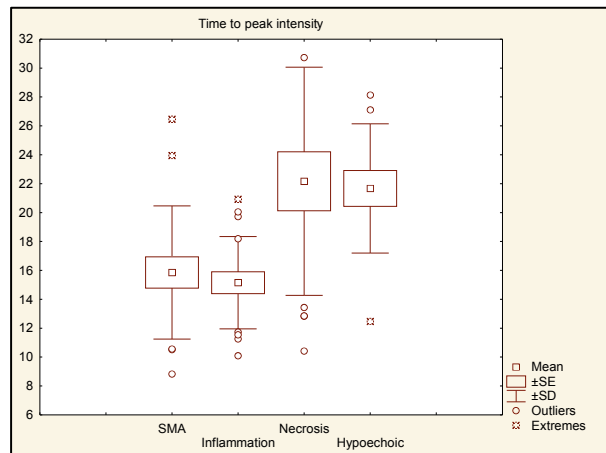
Average contrast agent filling and washing curves are shown in fig 9, 2 minutes after injection, with the intensity of the acoustic signal assayed manually in the reference area (SMA) and in the inflammation, necrosis and structural ill-defined hypoechoic areas, in the pancreatic parenchyma. We note the early contrast post administra-

**Table II.** Average maximum intensity of the acoustic signal and the mean time of its enhancement in the pancreatic interest areas

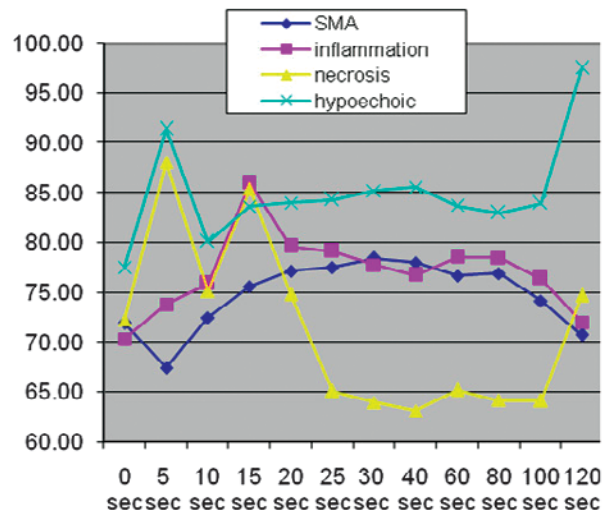
Region of Interest	Max I (dB)	mT (sec)
SMA	$19.37 \text{ dB} \pm 8.53$	$15.85 \text{ sec} \pm 4.6$
inflammation	$14.76 \text{ dB} \pm 6.7$	$15.15 \text{ sec} \pm 3.2$
necrosis	$8.89 \text{ dB} \pm 9.91$	$22.17 \text{ sec} \pm 7.9$
ill-defined hypoechoic	$12.03 \text{ dB} \pm 5.4$	$21.7 \text{ sec} \pm 4.47$



**Fig 7.** Variation of maximum intensity of the acoustic signal in the first 40 seconds after contrast administration in the witness area and in the inflammation, necrosis and ill-defined hypoechoic areas.



**Fig 8.** Variation of the mean time for reaching the maximum intensity of the acoustic signal in the first 40 seconds after contrast administration in the witness area and in the inflammation, necrosis and ill-defined hypoechoic areas.



**Fig 9.** “Wash in” and “wash out” curve of the witness area and of the inflammation, necrosis and ill-defined hypoechoic areas, assayed by hand, rearranging the area of interest in the first 2 minutes after contrast agent injection.

tion and polymorphic variations of the average acoustic intensity representation in the necrosis and structural ill-defined hypoechoic areas, due to different degrees of necrotic affection of the pancreatic parenchyma. This can be explained by correlating data from literature regarding experimental patterns of parenchymal microcirculation and capillary flow variations such of destructive-necrotic type or the capillary stasis in acute pancreatitis [14]. The statistical analysis (by means of Spearman’s correlation) of the filling and washing parameters corresponding to

**Table III.** Spearman’s rank correlation of “wash in” and “wash out” curves of the witness area and of the inflammation, necrosis and ill-defined hypoechoic areas, assayed manually in the first 2 minutes after the injection of the contrast agent

Spearman Correlation	Valid	Spearman	t(N-2)	p-level
SMA & Inflammation	12	0.643357	2.65747	0.024003
SMA & necrosis	12	-0.678322	-2.91936	0.015317
SMA & hypoechoic	12	0.090909	0.28868	0.778725

the acoustic signals, revealed a positive correlation between the reference area (SMA) and the area of inflammation ( $p < 0.042$ ), as well as a negative correlation between the references area (SMA) and the area of necrosis ( $p < 0.015$ ) (Table III).

**Discussions**

Contrast enhanced ultrasound provides a dynamic view of the “vascular pattern” through the exclusively intravascular flow of the microbubbles, assessing the aspect of increased echogenity through nonlinear signals from the microbubbles. The elimination of the contrast agent from the body is pulmonary, allowing its use in patients with acute pancreatitis and associated renal failure. Unlike the contrast agent used in ultrasonography, the contrast agent used in CT and MRI has a short intravascular remanence time, being rapidly cleared from the circulation and reaching the extracellular space, and then excreted by the kidneys [6].

CEUS technique proved to be useful in the diagnosis of liver tumors. At the moment, the guidelines for the use of CEUS in the diagnosis of tumors with various location (pancreas, kidney, mammary gland, lung) are being developed, also in the diagnosis of acute pancreatitis, in post-traumatic abdominal parenchymal lesions, and in transcranial Doppler examination [6]. Analyzing the current data from literature regarding the use of CEUS in acute pancreatitis, there are few studies, most of them qualitative. Till now, there are no published studies on the quantification of the vascular pattern in areas of inflammation and necrosis in acute pancreatitis. By analyzing the “wash-in” and “wash out” curves, we get information on the pancreatography of the residual gland and the time needed to cross the selected region of interest based on local vascular changes [15].

Our study statistically assessed a more accurate view of the limits of the pancreatic parenchyma in acute pan-

creatitis by means of CEUS examination compared to conventional ultrasound.

Rickes et al. considered the performance of CEUS in diagnosing severe acute pancreatitis to be very good compared to CT (89% specificity, 95% positive predictive value) [16]. Our study compared the detection and quantification of the areas of necrosis in acute pancreatitis through CT (gold standard diagnostic) and CEUS, and obtained a 62.5% diagnosing concordance. The ratification in using the quantitative analysis of the areas of necrosis in acute pancreatitis by means of CEUS technique on large groups of patients, will allow setting the cut off values for assessing the degree of pancreatic necrosis in areas with ill-defined ultrasonic morphology.

Our study highlighted average values of the maximum intensity (max I) of the acoustic signal rendered automatically by Logiq 7 software in SMA (19.37dB) and in the pancreatic parenchymal areas of inflammation (14.76dB). These values are higher compared to the normal value mentioned in literature for pancreatic parenchyma in a healthy adult subject (5.3dB), using Siemens ultrasound machine with Axius ACQ software [17]. For the studied group, max I was reached in a similar mean time (mT) for both SMA (15.85 seconds) and the area of inflammation (15.15 seconds). An extended mT of 22.17 seconds was recorded in the area of necrosis, certified by the reduced vascular bed.

Considering the changing location of the region of interest depending on the patient’s breathing, the analysis of the acoustic signal intensity dynamics was also performed, for the selected group, through the manual sampling of the values at regular intervals, for 120 seconds with the change in ROI. The corresponding parameters for the acoustic signals’ filling and washing curves showed an early mT for the area of inflammation compared to the references area (SMA). A negative Spearman correlation coefficient was obtained for the variation of the acoustic signal intensity in the witness area (SMA) and in the area of necrosis, partly due to the circulatory characteristics of the necrotic tissue.

A limitation of this study is the relatively small number of patients and the diversity in the ultrasonographically assessed structural changes. This data provides new information regarding the use of CEUS in assessing the extension of the lesions in acute pancreatitis. Together with other clinical and biohumoral information, these ultrasonographic parameters and their statistical analysis could help develop an ultrasonographic severity score for emergency therapy in acute pancreatitis.

**Conclusions**

An important advantage of CEUS is the possible real-time assessment of the vascular pattern with higher tem-

poral resolution than other imaging techniques. Besides, “SonoVue” administration can be repeated due to a better patient tolerance and a reduced incidence of adverse reactions.

Our study attests the usefulness of CEUS in quantifying the area of necrosis in acute pancreatitis, with similar results to those of CT. Thus, contrast enhanced ultrasound is a useful tool in the emergency diagnosis and monitoring of severe acute pancreatitis.

**Conflict of interest:** absence of conflict of interest

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