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## Contrast-enhanced ultrasonography for the determination of Crohn's disease activity – preliminary experience

### Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

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### Summary

#### Background:

Contrast-enhanced ultrasound (CEUS) is a recent non-invasive modality, which may partially replace currently used techniques (endoscopy, CT enterography and MR enterography) in the diagnostics and assessment of Crohn's disease (CD). The aim of the study was to analyze early experience in the use of CEUS for the measurement of activity and staging of CD.

#### Material/Methods:

Eleven patients previously diagnosed with CD were included in the study. They underwent contrast-enhanced ultrasonography (SonoVue, Bracco), low-dose CT enterography (LDCTE), assessment of laboratory markers of inflammation and clinical CD activity index (CDAI). Contrast enhancement was evaluated using a semi-quantitative method and a quantitative method that included measurement of peak enhancement (PE), enhancement curve rise time (RT) and wash-in-rate (WiR).

#### Results:

Ileal wall thickening was observed in all patients. Semi-quantitative method was used to observe CD activity in CEUS in 10 cases that perfectly matched LDCTE findings. There was a moderate positive correlation between PE and CDAI ( $r=0.65$ ,  $p<0.001$ ). There was no significant relationship between perfusion parameters and laboratory markers of inflammation.

#### Conclusions:

CEUS is a promising modality for non-invasive assessment of pathologic ileal vascularization in the course of Crohn's disease. Intensity of enhancement in CEUS reflects activity of the disease detected in LDCTE and correlates with CDAI.

#### Keywords:

Crohn's Disease • IBS • CEUS

#### PDF file:

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### Background

Crohn's disease (CD) belongs to a group of inflammatory bowel diseases that also includes entities such as ulcerative colitis and collagenous colitis. CD lesions may involve any segment of the gastrointestinal tract between the mouth and the anus [1]. The underlying disease process involves chronic granulomatous inflammation affecting all layers of the gastrointestinal tract wall. It is estimated that the incidence

of CD in the European Union is equal to 5–10/100,000/year and affects mainly individuals in the 15–25 age range [1].

The chronic nature of the disease results in the need to perform multiple follow-up examinations over the life of the patient. Hence the attempt to find new, non-invasive but effective methods of imaging in CD. Currently, besides endoscopy which is the diagnostic method of choice, MR enterography (MRE) and CT enterography (CTE) may be

used as first-line imaging studies in patients with suspected CD and to monitor the course of the disease in individuals with established diagnosis of CD [2,3]. In typical cases, these studies show segmented lesions of the small and large intestine: solitary or multiple strictures, characteristic deep ulcers and fistulas. In clinical practice, routine diagnostic imaging of CD poses a challenge. MRE study is costly, difficult to perform and carried out only at specialized centers. CTE on the other hand, exposes patients to high doses of ionizing radiation, which may reach 8–12 mSv and 2–3 mSv in case of low-dose protocols [4].

Contrast-enhanced ultrasonography (CEUS) is a relatively new technique that is gaining increasingly more clinical indications. It is based on evaluation of tissue perfusion following the administration of an intravenous micro-bubble contrast agent. Initial experiences with CEUS in patients with CD suggest that this technique may allow for the assessment of parenchymal perfusion of the gut wall and the surrounding tissues [5], thereby facilitating the detection and monitoring of inflammation and its qualitative assessment [4]. The purpose of this study is to evaluate the results of our initial experiences with CEUS in the assessment of activity and severity of CD.

## Material and Methods

The analysis included 11 patients (7 men and 4 women) ages 19 to 54 years (mean age 34.2 years) with histologically confirmed clinical exacerbation of CD. The local Bioethics Committee approved the study. Patients underwent diagnostic testing due to acute symptoms, such as abdominal pain and diarrhea. The exclusion criteria included: lack of informed consent, patient's non-cooperation preventing the examination, pregnancy, lactation, hypersensitivity to SonoVue, history of acute coronary syndrome, ischemic heart disease, heart failure stage III/IV NYHA or acute heart failure, right-to-left shunt, severe pulmonary hypertension, history of thromboembolism.

All patients underwent conventional abdominal ultrasound examination followed by CEUS. Analysis included CTE, laboratory tests (complete blood count, CRP, creatinine) along with the current Crohn's Disease Activity Index (CDAI) [10]. Low-dose CTE (LDCTE) was performed using Siemens Somatom Definition AS+ scanner with simultaneous reduction of the reference value to 105 mAs and utilization of automatic modulation mAs, which resulted in average dose reduction of 50%. The study was performed after administration of 1 L of water p.o. and 1.5 ml/kg b.w. Iomeron 400 contrast agent.

Conventional abdominal ultrasound was performed with Phillips iU22 ultrasound system using convex (C 5-2) and linear (C 9-3) transducers. Examination assessed morphology of the visible bowel loops, while quantitative evaluation was limited to the terminal ileum. Power Doppler measurements of maximal wall thickness and semi-quantitative estimation of blood flow using Esteban scale (0 – no flow, 1 – trace the flow, 2 – clear flow) were performed [6].

CEUS was performed with the same scanner using linear transducer (C 9-3). The study consisted of an intravenous administration of a 4.8 ml bolus of contrast agent SonoVue

(Bracco) through peripheral vein puncture followed by the assessment of intestinal wall strengthening. Harmonic imaging option in grayscale with MI 0.2 was used during the study. Upon identification of intestinal loop with thick wall, the screen was split into two areas for simultaneous image acquisition of conventional imagery and CEUS. The selected intestinal segment was analyzed following the administration of contrast agent for 120 s, then the images stored in cine sequences were quantitatively analyzed using VueBox v. 4.3 software (Bracco). The results are presented in the form of time intensity curves (TIC) of the selected region of interest (ROI) with the highest intensity. Calculations included: peak enhancement (PE), rise time (RT) – time from administration of contrast agent until PE, and wash-in rate (WiR) – slope of the ascending segment of TIC. Additionally, in order to facilitate the comparison with CTE, a subjective assessment of the degree of contrast enhancement similar to Esteban scale (0 – no enhancement, 1 – intermediate enhancement, 2 – intense enhancement) was made.

Compliance of parametric data distribution with normal distribution was evaluated using the Kolmogorov and Smirnov test with Lilliefors correction. Comparison of the results of CEUS and LDCTE was done using  $\chi^2$  test. Relationships between the results were analyzed using t-test for dependent variables and multivariate Friedman ANOVA test. Multiple regression analysis was used for perfusion measurement results. Compliance of parametric data distribution with normal distribution was evaluated using the Kolmogorov and Smirnov test with Lilliefors correction. Comparison of the results of CEUS and CT was done using  $\chi^2$  test. Relationships between the results were analyzed using t-test for dependent variables and multivariate Friedman ANOVA test. Multiple regression analysis was used for perfusion measurement results.

## Results

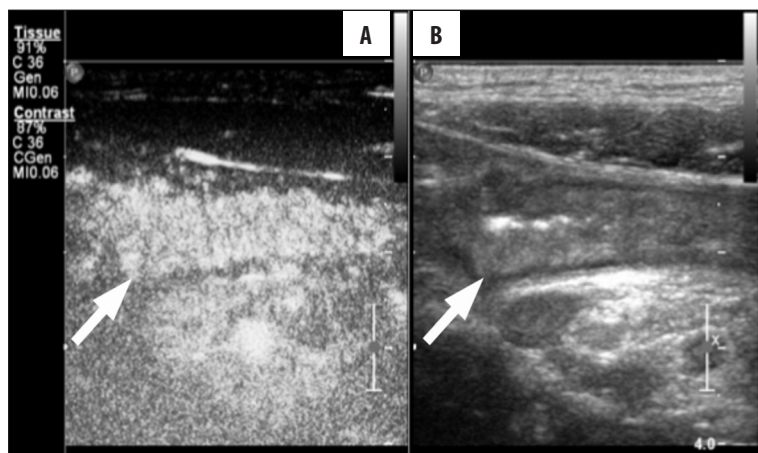
Patients underwent CEUS due to an exacerbation of CD. CDAI values computed on the day of the examination exceeded 150 (range 236–376). All patients denied the presence of other chronic diseases. In all cases, the administration of contrast agent was uneventful and no adverse effects were reported. LDCTE was carried out on the same day, also without any complications.

Terminal ileum characteristics in ultrasound, CEUS and LDCTE are shown in Table 1. Thickening of bowel wall was observed in all patients. Subjective evaluation of the intensity of contrast enhancement in CEUS (Figure 1) was consistent with the assessment of inflammatory changes made by LDCTE. Intestinal wall thickness did not correlate with CEUS perfusion indicators.

Summary of perfusion measurements and the selected laboratory parameters is shown in Table 2. In terms of PE perfusion parameters, the analysis of variance shows dependence on RT ( $p < 0.005$ , Friedman ANOVA). Multiple regression analysis shows dependence of PE on RT ( $b^* = 0.38$ ,  $p < 0.001$ ) and WiR ( $b^* = 0.91$ ,  $p < 0.0001$ , Figures 2 and 3). The existence of a moderate positive correlation between EP and CDAI ( $r = 0.65$ ,  $p < 0.001$ , Figure 4) has been shown. No relationship between perfusion parameters and laboratory test results was found.

**Table 1.** Imaging features of the distal segment of ileum in the examined patients. Table presents maximal ileal wall thickness seen in ultrasound, degree of vascularization expressed in Esteban scale, type of ileal inflammatory changes detected in LDCTE and subjective degree of contrast enhancement in CEUS.

Patient	Wall thickness	Esteban scale	Inflammatory changes in LDCTE	Enhancement in CEUS
1	5 mm	0	Active	2
2	5 mm	1	Active	2
3	7 mm	2	Active	2
4	8 mm	2	Active	2
5	7 mm	2	Active	2
6	6 mm	2	Active	2
7	6 mm	2	Active	2
8	7 mm	1	Chronic	1
9	9 mm	2	Active	2
10	7 mm	2	Active	2
11	8 mm	2	Active	2



**Figure 1.** Intensive contrast enhancement of inflamed intestine (arrows) in CEUS (A) and conventional ultrasound (B).

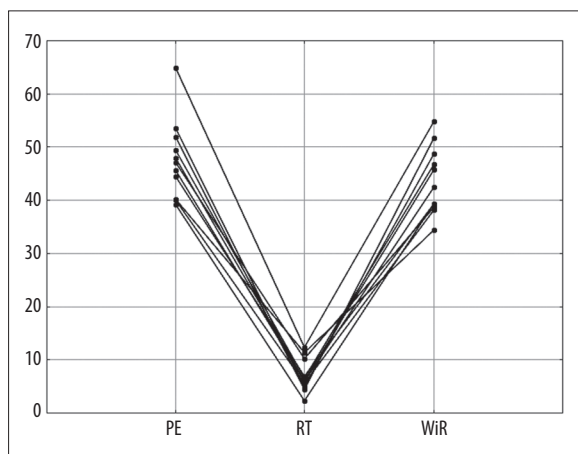
**Table 2.** Comparison of CEUS perfusion parameters and the selected laboratory results.

Parameter	Range	Median	Lower quartile	Upper quartile
PE	39.2–64.8	47.1	42.3	50.1
RT	2.28–12.34	6.2	5.3	8.6
WiR	34.4–54.9	42.5	39.1	47.8
CRP	0.4–56.5	16.0	8.5	23.9
WBC	3.5–11.7	8.6	6.5	9.5
RBC	4.3–5.4	4.8	4.5	5.2
PLT	180–560	263	225	376
CDAI	216–378	293	246	337

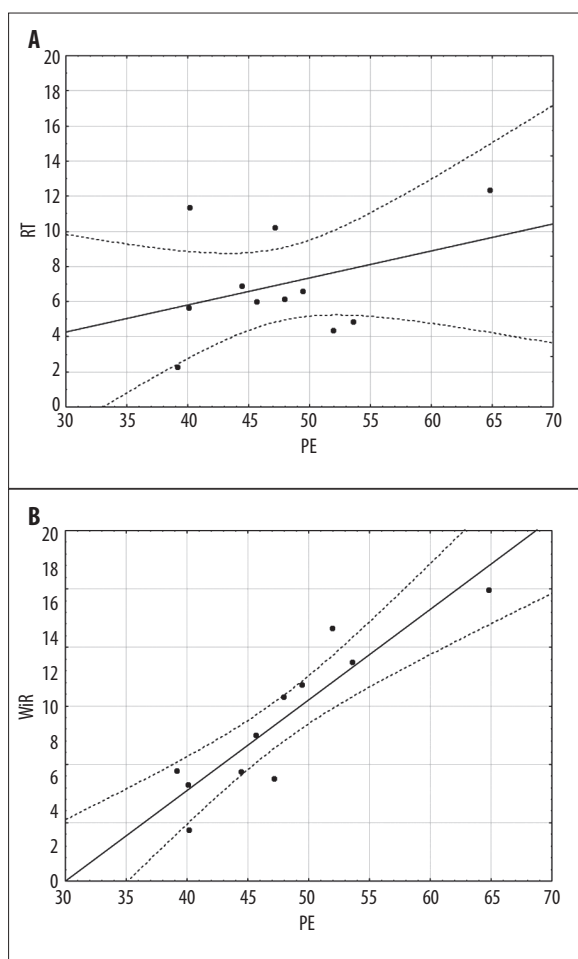
### Discussion

There is a discussion in the literature on the choice of non-invasive method of reference for the assessment of inflammatory activity in CD. CDAI is the most widely used

parameter [10]. It is a point system (0–600 pts.) with 8 variables, including 2 concerning subjective feelings. The basic elements of assessment include the number of loose bowel movements, worsening abdominal pain, general well-being, body weight, presence of a palpable abdominal tumor, the

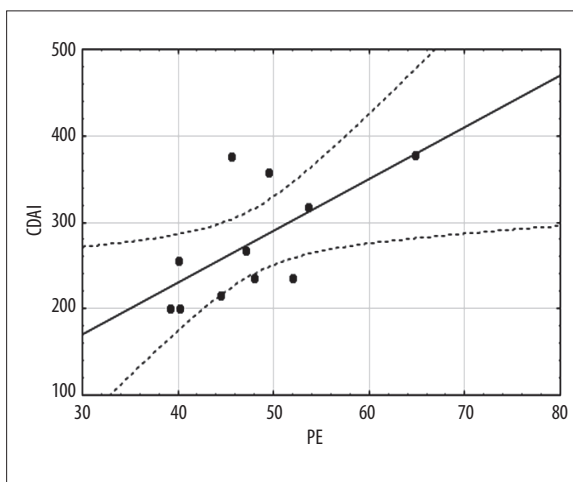


**Figure 2.** Comparison of the tested perfusion parameters in specific patients. Note the particular cases of RT prolongation.



**Figure 3.** Correlation between PE and RT (A) and between PE and WIR (B). Graphs present cases, regression line and its 95% confidence interval.

need for anti-diarrheal medications and hematocrit value. Additionally, the occurrence of parenteral complications is taken into account. CDAI score below 150 indicates remission, while score of over 450 suggests severe disease. The system has been criticized mainly for its lack of parameters, such as the quality of life or the results of endoscopy [11,12].



**Figure 4.** Correlation between PE and CDAI. Graph presents cases, regression line and its 95% confidence interval.

Thus, the quest for new non-invasive methods that would allow for monitoring of patients and especially the detection of recurrence of inflammation prior to the appearance of clinical symptoms. Besides the technical issues associated with CTE and MRE discussed in the introduction, it should be noted that these methods are strictly morphological. They use bowel wall thickness and the presence of pathological contrast enhancement as the basic criteria of inflammatory activity. These criteria indicate fully developed inflammation, which prevents their use for the detection of early stages of CD recurrence. These limitations result from low time resolution (MRE) or low time and contrast resolution (CTE).

In the technical aspect, these limitations are not present in contrast ultrasound. In the early stages of CEUS development, its use in CD was limited to the detection and semi-quantitative assessment of contrast enhancement [14,15]. According to a theory by Giangregorio et al., increased perfusion (a functional and measurable parameter) should be an indicator of active inflammation in the intestinal wall, instead of vascularization and the presence of contrast enhancement [13]. Therefore, current research concerning CEUS in patients with CD focuses on a quantitative evaluation of contrast enhancement and its relation with the clinical condition, CDAI and histopathological appearance. As with all perfusion methods, CEUS enables the plotting of contrast enhancement curve and the determination of dynamics. It is possible to record the maximum enhancement in relative or absolute values, the velocity or rise time and the time, speed and degree of contrast washout and the area under the enhancement curve [7,13].

Literature provides limited reports on the diagnostic value of quantitative assessment of intestinal perfusion in CEUS in patients with CD. Girlich et al., in their assessment of a small group of patients, have demonstrated the existence of a moderate negative correlation between the results of histopathological examination and the time to peak (TTP), as well as the ratio of TTP/PE [7-9]. However, they did not find a relationship between perfusion parameters and clinical or laboratory markers of inflammation. In turn, PE and

the area under enhancement curve (AUC) have allowed Giangregorio et al. to predict the occurrence of clinically active inflammation [13]. Quaia et al. showed significant differences in AUC and the rate of change of the graph after successful antiinflammatory therapy [16]. It should be noted that these studies, similarly to ours, have been pilot studies based on small groups of patients (15–30 subjects). Validation of the role of CEUS in the detection of inflammatory activity requires further research based on larger study populations and preferably with histopathological examination as method of reference.

## Conclusions

Contrast-enhanced ultrasound of the distal section of small intestine is a promising non-invasive method for the assessment of pathological vascularization in Crohn's disease. Subjective assessment of the intensity of contrast enhancement on CEUS corresponds with the assessment of inflammatory activity based on low-dose CTE. The intensity of enhancement appears to be dependent on CDAI. The role of CEUS in the detection of inflammatory activity requires further research on a larger groups of patients.

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