



Quantitative analysis of contrast-enhanced ultrasonography of the bowel wall can predict disease activity in inflammatory bowel disease



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ABSTRACT

Purpose: To evaluate the accuracy of quantitative analysis of bowel wall enhancement in inflammatory bowel disease (IBD) with contrast enhanced ultrasound (CEUS) by comparing the results with vascular density in a biopsy sample from the same area of the intestinal tract, and to determine the usefulness of this analysis for the prediction of disease activity.

Materials and methods: This prospective study was approved by our institute's ethics committee and all patients gave written informed consent. We enrolled 33 consecutive adult patients undergoing colonoscopy and biopsy for IBD. All patients underwent CEUS and the results were quantitatively analyzed. Vessel count per high-power field on biopsy specimens was compared with colonoscopy, baseline ultrasonography, and CEUS findings, and with analysis of peak intensity, time to peak, regional blood volume, mean transit time, and regional blood flow. Results in patients with high and low vascular density were compared using Fisher's test, *t*-test, Pearson's correlation test, and receiver operating characteristic curve (ROC) analysis. Cutoff values were determined using ROC analysis, and sensitivity and specificity were calculated.

Results: High vascular density (>265 vessels per field) on histological examination was significantly correlated with active disease on colonoscopy, baseline ultrasonography, and CEUS ($p < .0001$). Quantitative analysis showed a higher enhancement peak, a shorter time to peak enhancement, a higher regional blood flow and regional blood volume in patients with high vascular density than in those with low vascular density. Cutoff values to distinguish between active and inactive disease were identified for peak enhancement (>40.5%), and regional blood flow (>54.8 ml/min).

Conclusion: Quantitative analysis of CEUS data correlates with disease activity as determined by vascular density. Quantitative parameters of CEUS can be used to predict active disease with high sensitivity and specificity.

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1. Introduction

Chronic inflammatory bowel disease (IBD) is characterized by alternating periods of active and inactive disease. However, there is currently no optimal standard for evaluating disease activity.

The Crohn's Disease Activity Index (CDAI) is used extensively in Crohn's disease, but its usefulness is controversial [1,2]. Patients are usually followed by monitoring of blood biochemistry, clinical condition, and symptoms. Diagnostic imaging is indicated in patients with unconfirmed IBD, or to determine bowel wall and perivisceral involvement in patients with IBD diagnosed by endoscopy

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and biopsy. CT and MR, due to their panoramic view of all the entire abdomen, are usually performed also to assess the extension of the disease. Serial computed tomography scanning is commonly used to evaluate disease activity, but carries risks associated with the cumulative radiation dose [3,4]. For this reason, MR is preferred technique because it is able to examine the entire small intestine without radiation hazards, but ultrasonography (US) is the least invasive imaging examination, and is easily repeatable with a proven high diagnostic accuracy [5,6]. Power Doppler US shows increased bowel wall vascularity during active disease because of an increased number and caliber of vessels [7]. Contrast-enhanced US (CEUS) and contrast pulse sequencing software have generated further interest in possible correlations between bowel wall vascularity, enhancement patterns on CEUS, and disease activity scores [8,9]. There is currently no consensus regarding the role of CEUS as a prognostic tool of disease activity. Some studies [6,9] found no correlation between vascularity detected by CEUS and clinical index of disease activity.

However, recent studies of quantitative analysis of bowel wall enhancement after contrast administration have indicated correlations between the enhancement curve and CDAI [10–13], endoscopic disease activity scores [4], or both [14]. Three previous studies by Girlich and Ripolles [15–17] have compared quantitative analysis of bowel wall enhancement by CEUS with quantitative histological findings (surgical specimens): to the best of our knowledge, no previous studies have compared quantitative analysis of bowel wall enhancement by CEUS with vascular density in biopsy sample.

This study aimed to evaluate the accuracy of quantitative analysis of bowel wall enhancement performed using contrast-enhanced ultrasound by comparing the results with vascular density in a biopsy sample from the same area of the intestinal tract. The usefulness of this analysis for the prediction of disease activity was also investigated.

2. Materials and methods

2.1. Study population

We prospectively studied 33 consecutive IBD patients who underwent colonoscopy at our institute from June 2008 to November 2009. The study was approved by the ethics committee of our institute. All patients gave written informed consent. Exclusion criteria were the well known contraindication to SonoVue: patients with recent acute coronary syndrome or clinically unstable ischemic cardiac disease, severe rhythm disorders, age < 18 years.

Indications for colonoscopy were: a clinical diagnosis of IBD needing histological confirmation, follow-up after surgery for complications of IBD, and assessment of the extent of disease during clinical recurrence after an inactive phase.

Patients comprised 18 males and 15 females with a mean age of 41.6 years (range, 18–86 years) of whom 18 had ulcerative colitis (10 males and 8 females; mean age, 38.8 years) and 15 had Crohn's disease (8 males and 7 females; mean age, 44.8 years). Of these 33 patients, 17 were symptomatic (abdominal pain and/or diarrhea) and 16 were asymptomatic at the time of investigation.

2.2. Endoscopic examination

All colonoscopies were performed by the same endoscopist (F.L.) with more than 10 years of experience. Biopsies were taken from the ileum, right colon, transverse colon, left colon, rectum, and sites with active disease [18]. In patients with Crohn's disease, the simple endoscopic score for Crohn's disease was determined

according to the presence and size of ulcerations, percentage of ulcerated surface, percentage of bowel with a pathological appearance, and the number and characteristics of strictures [19]. In patients with ulcerative colitis, the Mayo Clinic score was determined according to the presence of a rash or spontaneous bleeding, reduced or absent vascular impressions, friability, erosions, and ulcerations [20]. The endoscopist judged the disease to be active or inactive based on these scores, considering that the disease was considered active if the aphthous lesions were more than 5 mm.

2.3. Histological examination

All biopsy specimens were examined by the same pathologist (V.V.) with more than 20 years of experience, blind to the results of the other tests. The number and architecture of glandular elements, presence of ulcers or erosions, and presence of inflammatory infiltration and granulomas were assessed, and the pathologist judged the disease to be active or inactive based on these findings according to ECCO criteria [21,22]. Specimens were stained with hematoxylineosin and CD34, and the number of vessels CD34-positive per 10 high-power fields (40 \times) was counted [23].

2.4. US and CEUS

Baseline US and targeted CEUS were performed within 10 days after colonoscopy (range 2–10; mean 7 days). Patients ingested a fiber-free diet for 3 days and fasted for 6 h before the investigation.

All US investigations were performed by the same operator (L.R.) with more than 10 years of experience, using a Sequoia 512 machine (Siemens Medical Solutions Inc., Issaquah, WA).

Baseline US was performed in the supine position during spontaneous inspiration. Cross-sectional and longitudinal views of the small and large bowel were obtained, exerting moderate pressure to separate bowel loops, move intestinal gas, and detect pathological segments. Active disease was defined as bowel wall thickening > 3 mm, [6,24], or increased flow signals on power or color Doppler ultrasonography (score 2) according to the scoring system proposed by Esteban [7,25,26].

Contrast pulse sequencing software was used for CEUS. A 4C1 convex, multifrequency probe was used to optimize microbubble detection [27].

In patients with pathological characteristics on colonoscopy, the operator was informed of the biopsy sites to guide the CEUS target, but was not informed of the histological examination findings. When small bowel was involved, CEUS studies were focused on the more distal segment of the ileum, it being the only one that could be biopsied. In case of multiple pathologic segments biopsied, the best segment visible by ultrasound was chosen.

In patients without pathological findings on colonoscopy, CEUS targeted the junction of the descending and sigmoid colon, which is always clearly recognizable and was biopsied in all these patients. After injection of 2.4 mL of SonoVue followed by 10 mL of 0.9% saline, the probe was maintained in a constant position to study the target loop for 180 s. Only one bolus was administered to each patient. Microbubble wash-in and wash-out were recorded by an external camera. The enhancement pattern was subjectively analyzed by the operator on the basis of several years of CEUS experience. Wash-in was defined as rapid when microbubbles were seen < 20 s after injection and slow when microbubbles were first seen at \geq 20 s. Wash-out was defined as rapid when microbubbles washed out in < 80 s and slow when microbubbles persisted for \geq 80 seconds.

The CEUS results were converted to AVI format.

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