The use of contrast-enhanced ultrasound for chronic inflammatory bowel disease

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ABSTRACT
Intestinal ultrasound is a non-invasive, inexpensive, accessible imaging technique that is appropriate for the study of patients with inflammatory bowel disease (IBD). It provides an assessment of inflammatory activity and complications with a diagnostic accuracy similar to that of magnetic resonance imaging (MRI) and computed tomography (CT). Furthermore, it has proven to be of great value for the follow-up and monitoring of these patients. The addition of contrast enhancement has improved the diagnostic ability of intestinal ultrasound in the assessment of both inflammatory activity and complications. The development of dynamic studies able to quantify contrast arrival and determine a number of parameters in time-intensity curves (TICs) has increased the capability of intestinal ultrasound to identify inflammation and predict response to biologic therapy.

Keywords: Intestinal ultrasound. Contrast. CEUS. Inflammatory bowel disease. Crohn’s disease. Ulcerative colitis.
INTRODUCTION

An increased incidence of inflammatory bowel disease (IBD) and changes in treatment goals have prompted a greater demand for techniques capable of providing cross-sectional views of the bowel in the past few years. Although ileocolonoscopy is considered as the gold standard for IBD assessment, it is an invasive procedure and does not always reach the terminal ileum, does not allow the assessment of more proximal intestinal segments and cannot detect transmural inflammation or extraintestinal complications. Computed tomography (CT) and magnetic resonance imaging (MRI) have an excellent anatomical resolution and diagnostic accuracy. However, the reduced availability and higher cost of MRI, and the use of radiation in CT limit their use to assess these patients.

Intestinal ultrasound (US) has been recognized as a technique comparable to endoscopy for the identification of Crohn’s disease activity. A systematic literature review and a meta-analysis found no differences between US and CT or MRI to assess inflammatory activity, extramural complications or strictures (1,2). It offers the benefits of being accessible, non-invasive, relatively inexpensive and very well tolerated. Thus, it has a potential role as the technique of choice for systematically monitoring these patients.

Intestinal US has been routinely used since the 1980s in several European countries and is being adopted by nearly all IBD units. The European Crohn’s and Colitis Organisation (ECCO) clinical guidelines already endorse its use and recommend the technique as the first-line diagnostic examination. Over the last few decades, significant advances have been implemented to improve the diagnostic efficacy of intestinal US. One includes the use of an endovenous contrast agent, which allows to enhance the capacity of intestinal ultrasonography in the evaluation of IBD activity and complications.

INTRAVENOUS CONTRAST-ENHANCED INTESTINAL ULTRASONOGRAPHY

Intravenous contrast agents for US are made up of gas-filled microbubbles stabilized by a capsule, which is usually lipid based. Several types are available but only SonoVue® (Bracco, Milan) is authorized in Europe. It is made of sulphur hexafluoride
microbubbles covered with phospholipids and their size is similar to that of red blood cells (1-10 µm). Hence, they do not leak out to the extravascular tissue as opposed to contrast agents for CT and MRI. The half-life of SonoVue® is 5-7 minutes and it is eliminated via the respiratory tract. It has an excellent safety profile and no nephrotoxicity.

Microbubbles in the blood stream behave differently than in tissues when hit by an ultrasound beam, which allows sonography systems to separate and isolate their signals, intensifying the intravascular part. In this way, the increase in vascularization that occurs in inflammatory processes may be identified and vascular structures may be differentiated from avascular ones (3).

Contrast-enhanced US (CEUS) studies may be interpreted in different ways. Images may be qualitatively assessed, by identifying uptake patterns within the intestinal wall or evaluating uptake patterns in masses and collections. More recently, software has been developed that allows a much more accurate diagnostic approach to assess inflammation. These are dynamic studies where the amount of contrast medium reaching a region of interest (ROI) over a given period is assessed and time-intensity curves (TIC) are obtained and analyzed differently according to the equipment used. This analysis may provide a number of useful parameters to detect inflammatory activity, including the percentage increase in contrast enhancement, peak maximum intensity (PMI), time to peak (TTP), slope, area under curve (AUC), wash-in area and wash-out areas (Figs. 1 and 2) (4). Unfortunately, the wide variability extant among available equipment and software packages has limited the extrapolation of results (5).

**INFLAMMATORY ACTIVITY IN CROHN’S DISEASE (CD)**

The sonographic sign that best correlates with inflammatory activity in CD is wall thickness. Other data associated with a greater inflammation include loss of the stratified pattern at the wall, identification of ulcers, fibrofatty proliferation and the presence of adenomegalies (6).

Wall hyperemia secondary to the neovascularization that takes place in patients with CD is a key factor when assessing inflammation. The role of color-Doppler ultrasound for detection is well established but has some limitations, such as a difficult slow flow
identification in smaller vessels, in deeper bowel segments and in obese patients. Furthermore, the interpretation may be subjective. To address this issue, Limberg developed a semi-quantitative score and multiple studies showed that grades 2 and 3 were associated with disease activity (7) (Fig. 3).

The introduction of intravenous contrast has significantly improved the capacity of intestinal ultrasound to detect inflammatory activity. Initial studies, where only a qualitative assessment was performed, reported that CEUS better correlated with CD activity than color-Doppler US, exhibiting a high sensitivity (93 %) and specificity (94 %) (8). Multiple studies have reported a quantitative analysis of time-intensity curves (TICs). Ripollés et al. found in a prospective series of 61 patients that an increase in wall brightness of 46 % had a sensitivity of 96 % and a specificity of 73 % to predict a moderate-to-severe inflammation grade during endoscopy. The diagnostic accuracy of CEUS (90 %) was higher than the wall thickness measurement (79 %) and color-Doppler (69 %) (3).

De Franco et al. also found a narrow correlation between PMI and the wash-in slope coefficient (β) with inflammatory activity and both parameters were significantly elevated in patients with active ileitis (9). Recently, a multicenter study was reported in 72 patients with CD where the parameters best correlated with endoscopic activity included PMI, AUC and wash-in (10). CEUS has also been compared to vascular density in histological samples (11). Various parameters such as PMI, TTP and blood flow were higher in patients with increased vascular density. Furthermore, high vascular density (> 265 vessels per field) correlated with active disease in colonoscopy, baseline ultrasound and CEUS. In a recent series of 180 patients where color-Doppler US was compared to CEUS, Ripollés et al. found that CEUS provided an overall improvement in the diagnosis with active disease, with a very high sensitivity (99.3 %) but a lower specificity (60.5 %). Although CEUS did not represent a significant benefit for cases with grade 2/3 hyperemia, it was very useful for patients with wall thickening, where color-Doppler failed to display parietal hyperemia (12). Finally, two systematic reviews, one associated with a meta-analysis, allowed the measurement of an overall sensitivity of CEUS to identify active Crohn’s disease of 93-94 %, with a specificity of 87-79 % (13,14). These analyses have the downside of a wide technical and methodological
variability amongst studies. Furthermore, reports are available that specifically compare CEUS with MRI, and have found a high correlation between both tests, with sensitivity and diagnostic accuracy even higher for US, approaching 100 % (5). These results, together with recently reported data on gadolinium deposits in the brain and their potential adverse effects, suggest that CEUS is a good alternative for the follow-up of patients with CD.

**POST-SURGICAL RECURRENCE**

Intestinal US has also proven very useful for the diagnosis of post-operative recurrence, with a sensitivity and specificity of 94 % and 84 %, respectively. A wall thickness at or above 5 mm was the best predictor of severe recurrence (15). Information is still scarce on the role of CEUS in the diagnosis of recurrence. Paredes et al. found that an increase in wall brightness higher than 46 % increased the diagnostic yield of wall thickness with a sensitivity, specificity and diagnostic accuracy of 98 %, 100 % and 98.3 %, respectively, for the diagnosis of endoscopic recurrence when both parameters were used (16). A recent study reported by the same team found that an increase in wall thickness higher than 70 % associated with a wall thickness of 5-6 mm was useful for the identification of severe recurrence (15).

**ASSESSMENT OF COMPLICATIONS**

**Extraintestinal complications**

Extraintestinal complications in CD include fistula and inflammatory mass development. Information dealing with the role of CEUS in the detection of fistulae is restricted to isolated case reports or short series of cases. The sonographic appearance of phlegmons and abscesses may be similar, but abscesses usually have better delimited borders and a more of a cystic appearance, and commonly have gas inside. The sensitivity of US for the diagnosis of abdominal abscesses ranges from 81 % to 100 %, with a specificity oscillating between 92 % and 94 %, similar to CT and MRI. However, when located deep in the pelvis, abscesses may be harder to identify (6). Differentiating between abscess and phlegmon has a relevant impact on treatment. Using an US contrast agent is a great help to distinguish these two lesions, with a
specificity of 100 %. Phlegmons are diffusely enhanced, whereas enhancement occurs in abscesses in their periphery, with no contrast uptake in the central area. Furthermore, the contrast agent more accurately defines lesion size, which is usually smaller following contrast administration (17) (Fig. 4).

**Stricture**

Histologically, most strictures are mixed in nature and there is currently no diagnostic test to definitely assess their fibrous or inflammatory component. Some parameters, such as wall layer destructuring in B mode and hyperemia in color-Doppler mode, are suggestive of a stricture type (18). Both contrast-enhanced dynamic studies and elastography improve the ability to assess inflammatory activity (4,19). Some studies have compared TIC-related results with histology findings and found that again, PMI, TTP and enhancement percentage are the parameters that best correlate with inflammation extent in patients with strictures (5,18,19).

**MONITORING**

Presently, the goal of IBD treatment is mucosal healing, which has an impact on the condition’s natural history and even transmural healing in the case of CD. Research supports the usefulness of intestinal ultrasound for monitoring patients with IBD, showing improved sonographic parameters after only three months of therapy (20). CEUS has improved the ability to assess treatment response and several TIC parameters improve in responders, even though those used vary from one study to the next (5).

In a series reported by Quaia et al. of 50 patients assessed at six weeks after treatment onset, PMI and the wash-in slope coefficient ($\beta$) were higher in patients with active disease (21). Furthermore, Socaciu et al. studied 13 patients after three months on treatment and found that AUC was the best predictor of endoscopic improvement (22). Ripollés et al. assessed transmural healing in 51 patients with CD on biologic therapy, who underwent ultrasound at baseline, 12 weeks and one year after treatment completion. Wall thickness, color-Doppler grade, contrast enhancement and the presence of stricture and/or extraparietal complications were assessed.
Remarkably, short-term sonographic changes allow to predict the sonographic and clinical response in the long term, so that patients with improved sonographic parameters at week 12 had better outcomes at one year of follow-up (85% vs 28%) (23). These promising results suggest that CEUS is a useful technique for monitoring patients during treatment.

THE ROLE IN ULCERATIVE COLITIS (UC)

The role of intestinal US in UC has been less investigated, as UC exhibits a greater correlation between the clinical picture and endoscopic activity and the study of the colon with endoscopy is much more accessible. Furthermore, the rectum is usually inadequately visualized with intestinal US using the transabdominal approach. In any case, intestinal US has shown an adequate correlation with endoscopy findings, with wall thickness and hyperemia being the most useful parameters (24). With regard to contrast enhancement, only two papers have reported a comparison of CEUS with endoscopic findings. Girlich et al. found a good correlation between TTP/PMI ratio and histology in eleven patients with UC (25). Socaciu et al. compared CEUS with clinical and endoscopic parameters in 65 patients, and found a correlation between AUC and endoscopic activity (22). AUC was also the parameter that best identified treatment response in one third of these patients who were evaluated after three months.

CONCLUSIONS

Using an intravenous contrast agent for intestinal US optimizes intestinal assessment in different clinical situations, regarding both the diagnosis and follow-up of patients with IBD, particularly with CD. It allows a better assessment of both intestinal and extraintestinal micro-vascularization, thus improving the diagnostic yield of sonography’s to assess inflammation. In addition, its potential for quantitative studies is of great value for monitoring treatment response. There are ambitious goals in the treatment of IBD, including mucosal healing and transmural healing. Thus, bearing in mind the clinico-pathological discordance observable in this disease, there is a growing need for repeat procedures during the follow-up of these patients. Intestinal US, with and without contrast enhancement, is an accessible procedure that provides an
accurate, minimally-invasive, radiation-free, well-tolerated examination of the bowel.

REFERENCES


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Fig. 1. Time-intensity curve (TIC) shapes. A. TIC parameters analyzed. PMI: peak of maximum intensity; TTP: time to peak; wash-in slope: reflects the rate at which contrast reaches the PMI; wash-out slope $\beta$: reflects wash-out rate; AUC: area under curve, including wash-in area and wash-out area. B. Analysis of percentage of increase in wall brightness. Calculation: $\left(\frac{\text{post-contrast brightness} - \text{pre-contrast brightness}}{\text{pre-contrast brightness}} \times 100\right)$.

Fig. 2. TICs from patients with Crohn’s disease. A. Patient with ileal activity. The ROI is placed on the contrast-enhanced intestinal wall. The TIC and some measured parameters (TTP, AUC, wash-in area) may be seen on the right side. B. Patient with inactive disease. The curve shape is similar to the above, but parameter measurements differ, correlated with the absence of significant inflammatory activity.
Fig. 3. Limberg score, modified. Examples. A. Grade 0: absence of flow in color-Doppler mode. B. Grade 1: presence of 1-2 vessels per cm$^2$ of intestinal wall. C. Grade 2: presence of 3-5 vessels per cm$^2$ of intestinal wall. D. Grade 3: presence of intense vascularization of the wall, even of surrounding mesenteric fat.

Fig. 4. Example of CEUS use for extraintestinal complications. A. In B mode, a predominantly hypoechoic heterogeneous mass is identified with a well-delimited wall. B. After IV contrast administration uptake is absent from much of the mass, and enhancement is only seen peripherally, which provides a diagnosis of an abscess. Both in B mode and contrast mode hyperechoic foci suggestive of gas may be seen inside
the abscess.