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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 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), and 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
Increased incidence of IBD and changes in treatment goals have prompted over the past few years a greater demand for techniques capable of providing cross-sectional views of the bowel. Although ileocolonoscopy is considered the gold standard for IBD
assessment, it is an invasive procedure that not always manages to reach the terminal ileum, does not allow the assessment of more proximal intestinal segments, and can detect neither transmural inflammation nor extraintestinal complications. CT and MRI possess excellent anatomical resolution and diagnostic accuracy. However, the lower availability and higher cost of MRI, and the use of radiation in CT limit their use for assessing 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 in assessing inflammatory activity, extramural complications, or strictures (1,2). It offers the benefits of being accessible, non-invasive, relatively inexpensive, and very well tolerated, which points at its potential role as the technique of choice for systematically monitoring these patients. Intestinal US is routinely used since the 1980s in several European countries, where it is being adopted by nearly all IBD units. The ECCO (European Crohn’s and Colitis Organisation) clinical guidelines already endorse it, and recommend the technique as first-line diagnostic examination. Over the last few decades significant advances have been implemented to improve the diagnostic efficacy of intestinal US. One of them included the use of an endovenous contrast agent, which allowed 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 lipidic. 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 cell (1-10 μm), hence they do not leak out to the extravascular tissue as opposed to contrast agents for CT and MRI. SonoVue® half-life is 5-7 minutes, and 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, 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 in assessing 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 that was used. This analysis may provide a number of useful parameters for detecting inflammatory activity, including percentage of increase in contrast enhancement, peak of maximum intensity (PMI), time to peak (TTP), slope, area under curve (AUC), wash-in area, and wash-out area (Figures 1 & 2) (4). Unfortunately, the wide variability extant among available equipments and software packages has limited 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 greater inflammation include loss of stratified pattern at th wall, identification of ulcers, fibrofatty proliferation, and presence of adenomegalies (6).

Wall hyperemia secondary to the neovascularization that takes place in patients with CD is a key factor when it comes to assessing inflammation. The role of color-Doppler ultrasound in its detection is well established but has some limitations, such as difficulty for slow flow identification in smaller vessels, in deeper bowel segments, and in obese patients. Furthermore, interpretation may be subjective. To address this issue Limberg developed a semiquantitative score, and multiple studies showed that grades 2 and 3 were associated with disease activity (7) (Figure 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 was better correlated than color-Doppler US with CD activity, exhibiting a high sensitivity (93 %) and specificity (94 %) (8).

Multiple studies have reported a quantitative analysis of TICs. Ripollés et al, in a prospective series of 61 patients, found that an increase in wall brightness by 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 wall thickness measurement (79 %) and color-Doppler (69 %) (3).

De Franco et al also found a narrow correlation between PMI and wash-in slope coefficient (β) with inflammatory activity, with both parameters being significantly elevated in patients with active ileitis (9). Recently a multicenter study was reported on 72 patients with CD where 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 highly useful for patients with wall thickening where color-Doppler failed to display parietal hyperemia (12).

Finally, two systematic reviews, one of them associated with a meta-analysis, allowed to measure an overall sensitivity of CEUS for identifying active Crohn’s disease of 93-94 %, with a specificity of 87-79 % (13,14). These analyses have as downside a wide technical and methodological variability amongst studies.

Also, reports are available that specifically compare CEUS with MRI, and find a high correlation between both tests, with sensitivity and diagnostic accuracy being 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, with wall thickness at or above 5 mm being 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 in 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 more of a cystic look to them, and commonly have gas inside. The sensitivity of US for the diagnosis of abdominal abscesses ranges from 81 % to 100 %, with 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 of great help in distinguishing these two lesions, with a specificity of 100 %. While phlegmons are diffusely enhanced, in abscesses enhancement occurs in their periphery, with the central area exhibiting no contrast
uptake. Furthermore, the contrast agent more accurately defines lesion size, which is usually smaller following contrast administration (17) (Figure 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 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 best correlated 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 has been reported that supports the usefulness of intestinal ultrasound for monitoring patients with IBD, showing improved sonographic parameters after only 3 months of therapy (20). CEUS has improved the ability to assess treatment response; several TIC parameters improve in responders, even though the ones used vary from one study to the next (5). In a series reported by Quaia et al, including 50 patients assessed at 6 weeks after treatment onset, PMI and the wash-in slope coefficient (β) were seen to be higher in patients with active disease (21). Furthermore, Socaciu et al studied 13 patients after 3 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, at 12 weeks, and at 1 year after treatment completion. Wall thickness, color-Doppler grade, contrast enhancement, and presence
of stricture and/or extraparietal complications were assessed. Remarkably, short-term sonographic changes allowed 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 1 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 since UC exhibits a greater correlation between 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. At any rate, intestinal US has shown an adequate correlation with endoscopy findings, with wall thickness and hyperemia being the most useful parameters (24). As regards 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 11 patients with UC (25). Socaciu et al compared CEUS with clinical and endoscopic parameters in 65 patients, and found 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 3 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, most particularly with CD. It allows a better assessment of both intestinal and extraintestinal micro-vascularization, thus improving sonography’s diagnostic yield in assessing inflammation. In addition, its potential for quantitative studies is of great value for monitoring treatment response. With ever more ambitious goals in the treatment of IBD, including mucosal healing and transmural healing, and bearing in mind the clinico-pathological discordance observable in this disease, there is a growing need for repeat procedures over the years in the follow-up of these patients. Intestinal US, with and without contrast enhancement, is an accessible procedure that provides
an accurate, scarcely-invasive, radiation-free, well-tolerated examination of the bowel.

REFERENCES


