

Contrast-Enhanced Ultrasonography (CEUS) for the Evaluation of the Inflammation of the Digestive Tract Wall

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Abstract

The evaluation of digestive wall lesions has benefited in latter years from advanced, noninvasive techniques such as contrast enhanced ultrasound (CEUS). This method appreciates the microcirculation in inflamed bowel segments in terms of qualitative and quantitative parameters. Based on precise and reproducible criteria it evaluates the extension and the activity of disease, as well as the presence of complications. Monitoring studies using quantitative measurements of inflammation could lead to the development of prognostic factors regarding the treatment efficacy. The performance of this method can be improved by the use of intraluminal contrast media.

Key words

Contrast enhancement ultrasound – inflammatory bowel disease – tuberculosis – diverticulitis – pseudomembranous colitis.

Introduction

Inflammatory bowel diseases (IBD), ischemic colitis, diverticulitis, infectious diseases like ileo-cecal tuberculosis or pseudomembranous colitis, have as common features the involvement of the distal digestive tract and the diarrhea syndrome, but they differ in evolution, type of complications and treatment. Positive and differential diagnosis requires a combination of endoscopic and imaging procedures, histology and biological investigations. The assessment of the involved digestive wall, as well as the quantification of the inflammatory process and detection of complications

(perforation or stenosis) are of major importance for prognosis and for therapy. Endoscopy with additional histology is the main technique for the differential diagnosis of the inflamed bowel wall and for monitoring the disease activity in IBD [1]. However, it may not be used in patients with severe activity because of the risk of perforation [2]. Imaging modalities such as computer tomography (CT), magnetic resonance imaging (MRI) or ultrasonography (US) enable the visualization of the intestinal wall as well as of the extraintestinal structures, being able to assess the mural and perivisceral inflammation and to differentiate fibrosis from edema, with good specificity (about 90%) [3, 4].

US techniques

Ultrasonography is a noninvasive, non-ionizing imaging modality, well tolerated by patients with inflammatory bowel pathology. US examination by means of high-resolution linear or convex array transducers (7 – 12 MHz) allows the identification of the layers of the digestive wall [5, 6]. The method requires a clinical suspicion (the examiner must be informed of the existence of a digestive disease) and should be followed by a systematical search for all digestive tract segments [7]. Gradually applying pressure ensures dissociation of the intestinal loops, emphasizing the involved intestinal segment, small quantities of fluid and inflamed perivisceral fatty tissue. The so-called “hydrosonography” allows more detailed imaging of the bowel wall, mucosal surface and lumen [8-10].

In conventional gray scale US, the digestive wall has five layers: perivisceral fat and serosa (hyperechogenic), smooth muscle layer (hypoechoic), submucosa (hyperechogenic), muscularis propria (hypoechoic) and mucosa (hyperechogenic). The US criteria systematically used in the evaluation of a bowel disease are: thickness of the wall (normal 4–5 mm), echogenicity of the layers, haustration, parietal motility, aspect of the peritoneal serosa and perivisceral fat, presence of perivisceral fluid and enlarged mesenteric lymph nodes.

The presence of inflammation, suggested by a thickening of the intestinal wall of over 5 mm with preserved parietal

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multilayered structure is detectable with a sensitivity of 91 – 94% and a specificity of 67 – 88% [11, 12].

Color and power Doppler techniques may provide additional information about the vascularization of the inflamed bowel wall according to the intensity of color signals and by the analysis of Doppler curves, with measurement of resistivity index, obtained from intraparietal vessels. In IBD, using Doppler measurements it is possible to differentiate the active from the inactive disease, without being able, however, to assess the severity of the disease [13]. This limitation is explained by the fact that Doppler techniques can detect only the large arteries feeding the microscopic vascular bed.

There are several ways to improve the sensitivity of digestive tract US diagnosis. Among these, contrast-enhanced ultrasonography (CEUS) characterizes the microcirculation in various inflammatory bowel conditions, after i.v. administration of a contrast agent (CA) by means of a US equipment having a contrast specific real-time imaging technology. It can be combined with hydrosonography, small amounts of the same CA micro-bubbles being added to the water [10].

CEUS technique

After identifying the inflamed area using gray scale and power Doppler technique with the lowest available pulse repetition frequency, CEUS is performed by using high frequency transducers, the i.v. CA SonoVue (Bracco) and “Tissue Harmonic Imaging” technique in the presence of a low mechanical index (MI). SonoVue CA consists of stabilized gas micro-bubbles (1-7 μ m) which remain in the circulation and produce a non-linear harmonic response that can be separated from the tissue signal using contrast harmonic US. The use of a multi-band probe with independent transmission and registration frequencies optimizes the capture of the non-linear harmonics produced by micro-bubble resonance. Using a low mechanical index the destruction of micro-bubbles is minimal and the arterial and venous phases can be registered continuously. After bolus injection of 4.8ml of CA in a peripheral vein, the capillary filling by a CA is suggested by an enhancement of the wall echogenicity that starts approximately in 10-15 seconds and proceeds up to 30 seconds, when a peak intensity (PI) is reached (arterial phase) (Fig. 1).

This phase is followed by the venous phase, in which the CA is distributed to the whole capillary bed and the concentration slowly decreases followed by the excretion of CA through the lungs.

Contrast enhancement pattern within the intestinal layers should be noted: particularly the submucosa and/or the entire bowel wall, according to the degree of inflammation.

Information regarding US signal intensity during contrast examination is stored on the machine in lossless format as a CineLoop. Two CineLoop clips, 30 seconds long are saved during the arterial and venous phase. A time-intensity curve is obtained by plotting the average intensity of the signal inside the area of interest, along the time axis. Raw data can

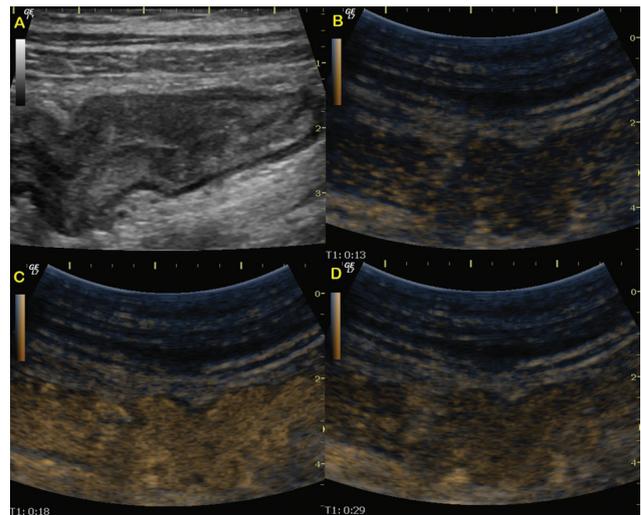


Fig 1. Examination of the intestinal wall microcirculation using a 2nd generation i.v. contrast (SonoVue) in a patient with severe ulcerative colitis: (A) B-mode showing inhomogeneous wall thickening. The capillary filling occurs in 10-15 seconds (B) and the peak is reached in around 20 seconds (C). Beyond this moment, the parietal echogenicity starts to decrease due to “washout” of the agent (D).

be exported and processed by digital analysis. Mathematic modeling using multiple fitting functions allows calculating specific parameters: time to peak – TTP, the PI, the time to maximum gradient - TTG and the area under curve – AUC (Fig. 2).

The circulatory pattern defined by the combined use of qualitative and quantitative parameters is different in inflammation as compared to that obtained in malignancies. It also discriminates between active inflammation and remission and evaluates therapy efficacy [14, 15].

Hydrosonography, using water enema with addition of a small amount of CA micro-bubbles (SonoVue) depicts better the mucosal surface and the luminal diameter (Fig. 3). The received harmonics from the tissues and the gaseous micro-bubbles are transformed into images that allow a better visualization of the lumen. The lesions are more accurately identified thanks to assessment of peristalsis and distensibility of the affected area. The phase inversion technique identifies pseudo-polyps and ulcerations by creating a good contrast to the interface between the lumen and mucosa [10].

Applications of CEUS in inflammatory bowel pathology

Crohn’s disease (CD)

US findings in CD consist of significant (usually > 10 mm) circumferential thickening of the digestive wall, spanning over several cm, with decreased or absent peristaltic waves [16]. The submucosa and muscularis propria are thickened and the delineation between them is imprecise. The submucosa can be interrupted by linear hyperechogenic structures, with gas content, corresponding

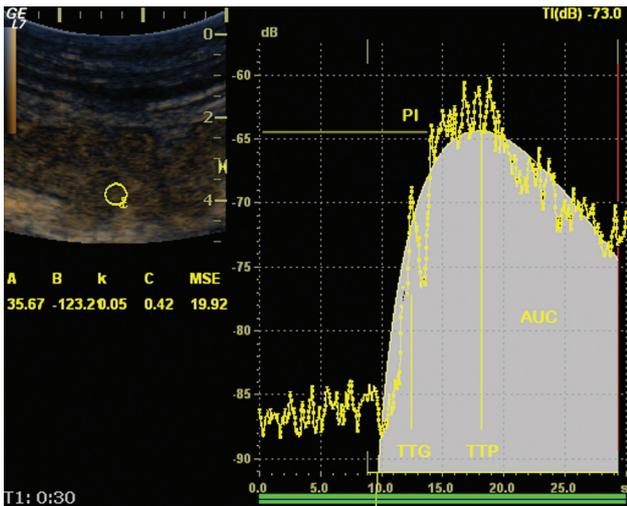


Fig 2. The time progression curve of the contrast agent in the circulatory bed of the intestinal wall. The maximum gradient time (TTG), the time to peak (TTP), the peak intensity (PI) and the area under the curve (AUC) are quantifiable parameters for the characterization of the microcirculation.

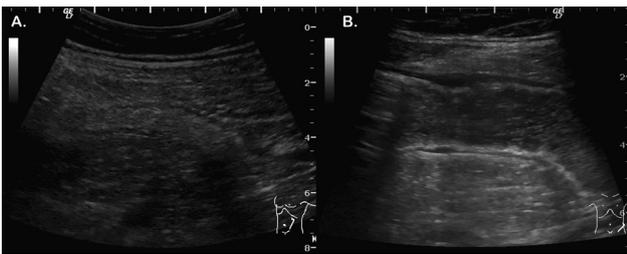


Fig 3. Ultrasound examination of the descending colon (sigmoid) in baseline conditions (A) and after administration of contrast agent via the anus - hydrosonography (B). A significant improvement of image quality after luminal dilatation occurs. The intestinal wall can be better measured and described.

to deep ulcerations. The surface of the serosa appears irregular, due to hyperechogenic perivisceral fat.

The development of capillaries in the intestinal wall can be identified with Doppler techniques. The color flow map (CFM) technique shows an increased vascular signal in the affected walls, and can also differentiate inflammatory areas (exhibiting a color signal) from intraabdominal abscesses, which only have a peripheral vascular signal [17].

Marked hypoechoic wall thickening without recognizable wall layers is usually associated with high disease activity, while preserved layering may suggest the presence of fibrosis [18]. The CEUS technique assesses the pattern of the neovascularization within the intestinal layers, allowing a better discrimination between active and inactive disease [14], between the inflammatory or fibrotic strictures [19] and between inflammatory pseudo-tumors and abscesses [20, 21]. The quantitative analysis of the TIC curves yields a linear enhanced pattern of the vascular signal in the submucosa in the inactive disease and in the entire intestinal wall in active disease. Monitoring these quantitative parameters, treatment efficacy may be predicted [22, 23].

The characteristic features described by hydrosonography using water enema combined with SonoVue in CD are: significant transmural wall thickening, narrowed lumen (the degree of the stenotic segment is more evident) and decrease in peristaltics, with a better characterization of mucosal surface, deep ulcerations and mural fistulas which become more evident (Fig. 4).



Fig 4. Luminal contrast examination (SonoVue) in Crohn's disease. Stenosis revealed by the SonoVue enema, showing only a narrow stream of bubbles passing through.

Ulcerative colitis (UC)

In UC the thickening of the colonic wall is less marked than in CD. The lesions are superficial and include thickening of the mucosa (hypoechoic) and of the submucosa (hyperechogenic), without involvement of the muscularis propria or adipose tissue [8]. Identifying the selective involvement of parietal layers - the mucosa alone in UC - is possible after administration of luminal CAs. The hydrosonographic criteria for the differentiation between CD and UC are: irregularities of the mucosa or pseudo-polyps for UC and loss of layering of a thickened wall for CD [24]. Phase inversion imaging identifies pseudo-polyps, by creating a very good contrast at the lumen/mucosa interface and ulcerations by microbubbles accumulation in ulcerated areas [10] (Fig. 5).

The use of i.v. CA increases the echo intensity in the microvascularization, allowing for better discrimination between mucosal thickening due to the disease activity or to

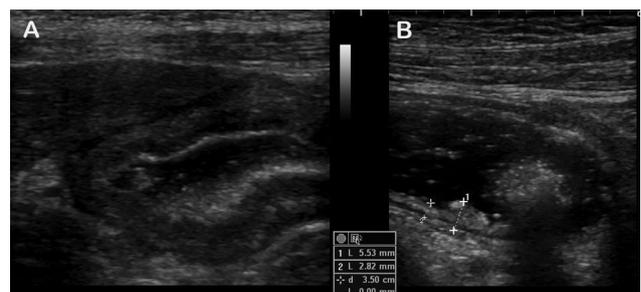


Fig 5. Hydrosonography of the descending colon in ulcerative colitis: irregular thickening (A) and pseudopolyps (B).

the fibrosis, during the healing process [25]. In moderate or severe disease activity, the arterial phase shows rapid filling 20 seconds after administration of the CA, of relative high intensity in the mucosa and submucosa, and persistence of the agent during the venous phase (without filling defects or rapid washout). The quantitative analysis performed on the time-intensity curves (TIC) allows the noninvasive monitoring of the evolution and the response to therapy [10, 26]. Favorable outcome after therapy can be anticipated by the decrease of TIC parameters (Fig. 6).



Fig 6. Microbubble-enhanced hydrosonography in sigmoid diverticulosis showing contrast entrapment inside the pouches.

Acute diverticulitis

In acute diverticulitis involving the left colon, US detects hyperechoic structures communicating with the bowel wall. Extensive hypoechogenic thickening of the colonic wall is a frequent finding in diverticulitis [27]. The luminal contrast hydrosonography is of great value in acute inflammation since it identifies the diverticula as breaches in the intestinal wall, protruding beyond the echogenic serosa. Decreased luminal distensibility suggests the presence of fibrosis, induced by recurrent relapses (Fig. 7).

Infectious colitis

Infectious colitis can be suspected in patients with marked and extensive thickening of the mucosa. The lumen can be either distended due to abundant fluid content, or narrowed with a more pronounced haustration, as is the case of pseudomembranous colitis.

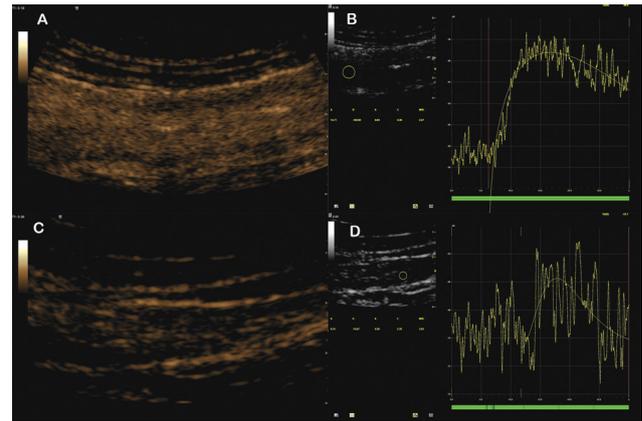


Fig 7. CEUS in a patient with severe ulcerative colitis before and after treatment: (A) B-mode showing inhomogeneous wall thickening before treatment. (B) The time progression curve of the contrast agent in the circulatory bed of the intestinal wall before treatment. (C) B-mode showing normal parietal echogenicity. (D) Favorable outcome after therapy can be observed by the decrease of TIC parameters.

Ileocecal tuberculosis

It is characterized by diffuse or segmental hypoechoic bowel wall thickening (> 5mm), increased echogenicity of the mesentery, peri-ileal enlarged lymph nodes and ascites [28]. CEUS reveals an enhanced signal of the CA in the affected areas and the surrounding fat and may suggest the areas of necrosis, where the enhancement is lacking (Fig. 8).

The US signs of severe pseudomembranous colitis are: diffuse thickening of the colonic walls, loss of layering, intramural gas echoes narrowing of the lumen, free pericolic fluid [29]. In CEUS there is an important enhancement of the vascular signal in the colonic wall (Fig. 9) and the luminal contrast US detects extensive ulcerations in the mucosa.

Conclusions

The use of i.v. contrast agents in the inflammatory pathology of the digestive tract allows a better quantification of the microvascularization, providing noninvasive parameters for the characterization of the inflammatory activity and evaluation of treatment efficacy. Hydrosonography with addition of a contrast agent provides details that the conventional ultrasonography cannot offer, such as

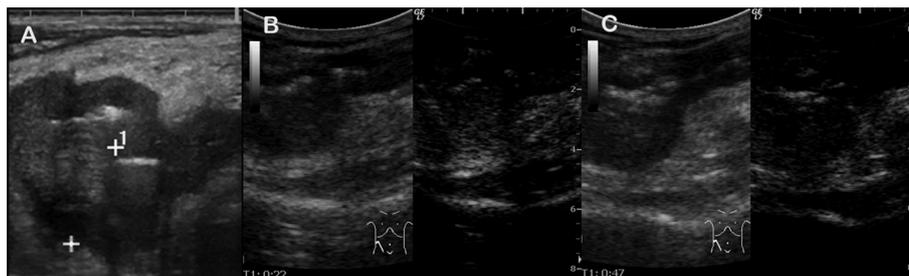


Fig 8. Ultrasound aspect in ileocecal tuberculosis (A). Mild contrast uptake in the thickened terminal ileum, with fast washout (B and C).

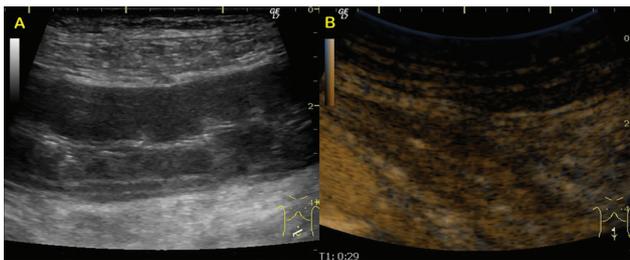


Fig 9. Ultrasound aspect of infectious colitis (pseudomembranous), revealing diffuse thickened walls, with loss of differentiation (A), high contrast enhancement (B).

a clear delineation of the mucosal surface with excellent visualization of its irregularities, erosions or ulcerations, an optimized image of the lumen and of the relationship of the studied organ to the neighboring structures.

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Conflicts of interest

None to declare.

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