The diagnostic value of small bowel wall vascularity after sulphur hexafluoride-filled microbubble injection in the differentiation of inflammatory and fibrotic stenoses in patients with Crohn's disease

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Purpose

To assess the value of small bowel wall vascularity on contrast-enhanced US to differentiate inflammatory from fibrotic stenoses in patients with Crohn's disease (CD).
Methods and Materials

Patients

This prospective study was approved by the ethics committee at our institute (equivalent to the Institutional Review Board). Informed consent was obtained from all patients at the time of scanning.

During a 36-month period (between December 1, 2008, and December 1, 2011) thirty-four consecutive patients (22 male and 12 female; mean age ± SD, 42.6 ± 17.83 years; range 16-82) who were known to have or were suspected of having CD US, and who were undergoing specific anti-inflammatory treatment from 2 months up to 14 months, were routinely scheduled to undergo CT and/or MR enterography and colonoscopy. Patients with active colonic disease were preliminarily excluded to avoid misinterpretation of clinical and laboratory activity indexes. Among these patients twenty-eight patients were proven to have an ileal CD based on endoscopy and were referred to our hospital to undergo an US examination which included also CEUS examination of the intestinal wall. Patients underwent both CEUS and endoscopy within a 30-day period. The indications for endoscopy were (a) to establish the extent and severity grade of lesions in clinically suspected exacerbation of disease activity during medical treatment (n = 12), and (b) to confirm diagnosis of CD (n = 16).

Patients had a CDAI >150 (n=10 patients) or <150 (n=18). Clinical status and the CDAI according to reference criteria [9] were defined a reference gastroenterologist within five days before the US examination (unenhanced gray-scale US, color or power Doppler US, and CEUS) and no more than two days after starting corticosteroid therapy. On MR imaging or CT-enterography or -enteroclysis (n=22 patients). CD involved a single intestinal loop in 20 patients only, while in 8 patients multiple bowel loops were affected.

Exclusion criteria were pregnancy, age < 18 years, recent acute or chronic heart failure, and ileal disease that was not appreciable at US. We excluded 4 patients owing to the interval of more than 30 days between CEUS and colonoscopy. Therefore, 28 patients (15 male and 13 female; mean age ± SD, 48.5 ± 17.17 years; range 21-76) were finally included in our study.

US examination

In each patient the thickest ileal loop was scanned after intravenous injection of sulfur hexafluoride-filled microbubbles (SonoVue, Bracco, Milan, Italy). CEUS was then used to assess intramural vascularization in a well-visualized terminal ileal loop exhibiting (a) aperistalsis, (b) wall thickness of more than 3 mm (regardless of the length of the thickened segment) (15), and (c) intramural Doppler signals if present. The location of
the loop was photographically documented so that it could be readily identified during subsequent studies.

The US equipment was a 512 Sequoia US unit (Siemens-Acuson Mountainview, CA, USA) with a 1-5 MHz frequency convex-array and 8-14 MHz frequency linear-array probe equipped with frequency compounding technology. Unenhanced gray-scale US and color/power Doppler US were performed by one on-site board-certified diagnostic radiologist with 10 years of experience in US of the abdomen. Color Doppler US was carried out with the lowest possible wall filter and pulse repetition frequency settings enabling detection of very low flows without generating motion artefacts.

The convex-array probe was used to perform CEUS examinations by using Cadence Contrast Pulse Sequencing (CPS) software. CPS detects all the non-linear responses from the microbubble contrast agent, including the non-linear fundamental frequencies. The prepared solution of sulfur hexafluoride-filled microbubbles was injected as a bolus in a vein of the arm in 2.4 mL amounts. By using a low transmit power insonation (MI: 0.06-0.08), the first-pass dynamic enhancement of the bowel wall was monitored in real time during breath-holding to avoid breathing-related movements for, at least, 8 seconds. Technical parameters were: dynamic range 65 dB, temporal resolution between frames 75-100 ms (10 - 13 frames for second), echo-signal gain below noise visibility, signal persistence turned-off and one focus below the level of the tumor. We used a dynamic video intensity (VI) range of 38-42 and intermediate temporospatial resolution. The general echo signal gain setting, which varied with the patient and the depth of the area being explored, was adjusted (#80 VI) to eliminate visualization of parenchymal structures before contrast material injection. The focus position (which influences bubble rupture and, therefore, determines enhancement duration) was always set below the area to be examined with contrast enhancement (ideally at the bottom of the transducer's field of view).

From, 5-10 seconds after microbubble injection, distinct consecutive digital cine-clips for CEUS, each 30 seconds in duration, were stored on a PC (Intel, Pentium 4, Santa Clara, CA, USA) connected to the US equipment as an uncompressed Digital Imaging and Communications in Medicine (DICOM) multiframe cineclip format (15 frame per seconds) which were stored on Picture Archiving and Communications System (PACS). Cine-clips were subsequently stored on digital video discs (DVDs) after the end of the scan.

**Image visual analysis**

The digital cine-clips were reviewed on screen (Intel, Pentium 4 with 19 inch TFT display, Santa Clara, Calif, USA) by the three reference radiologists during one consensual reading session in one sitting. These readers were not involved in the US scanning and were blinded to the patients' identification, clinical histories, biopsy results and other imaging findings. All readings were performed on the same computer (Intel, Pentium 4
with 19 inch TFT display, resolution 2560 x 1600 pixels, Santa Clara, Calif, USA) by using the Power-DVD software (CyberLink Corporation, Fremont, CA, USA).

The surface extension (expressed in mm) of the affected bowel was evaluated. When several segments located in different loops were involved their total length was measured. A bowel wall thickness >3.5 mm was considered as the threshold value for pathology. During the color Doppler US examination the submucosal, mural and perivisceral vessels were identified. The small bowel vascularity was visually assessed and scored (0 = absent, 1 = limited to the submucosa, or 2 = diffuse transparietal contrast enhancement beginning a) from submucosa or b) from perivisceral vessels) and correlated with CDAI by non-parametric correlation analysis.

**Image quantitative analysis**

The first-pass dynamic enhancement of the wall of the terminal loop was quantified in grey-scale levels (0 - 255) by a dedicated software and a manually-drawn region of interest encompassing the thickened bowel wall. From 1 to 2 days after visual analysis, the radiologist responsible for the study performed the quantitative analysis of echo-signal intensity by a proprietary software package (Q-ontrast; e-AMID - release 4.0 - Advanced Medical Imaging Development, distributed by Bracco, Milan, Italy). This software is able to quantify the contrast enhancement from a time sequence of perfusion frames and to generate chromatic map that allow immediate evaluation of the perfusion properties of regions of interest (ROIs) as selected by the operator. The quantification procedure was performed for each pixel encompassed by the ROI on the frame sequence during the selected time period. If peristalsis-related movements were evident in the scanned volume, those frames which appeared off-site to the reader were virtually excluded from the computation of the color map.

The color map from the CPS technique was automatically converted to a gray-scale map. In each image a polygonal (4,100 - 40,110 pixels, mean 21,430 pixels) a manually-defined ROI was drawn encompassing the thickened ileal anterior wall avoiding the lumen and the external layer. The US video-intensity was measured in gray-scale levels, from 0 (black pixels) to 255 (white pixels), through histograms analysis expressing the mean ± SD videointensity of pixels comprised in each ROI. Time-intensity curves were compared with the theoretical gamma variate curve obtained with the following formula: 

\[ SI(t) = At e^{-at} + C, \]

where \( SI(t) \) = signal intensity vs time; \( A \) = amplitude of the curve above baseline; \( a \) = initial slope of the ascending tract of the curve; \( C \) = echo-signal intensity at the baseline (the zero crossing point of the y-axis). The different kinetic parameters, including the maximum enhancement (expressed as a percentage of the highest possible achievable enhancement value), the time to the peak enhancement (calculated from the time of microbubble arrival in the scanning plane up to the peak enhancement), and the area under the time-intensity curve related to the regional blood volume were averaged in each patient. The area under the time-intensity curve was measured for the first 20 seconds after the microbubble arrival in the scanning plane.
Endoscopy

Endoscopy (Olympus, probe CF-H180AI/L, Hamburg, Germany) with biopsy of the terminal ileal loop was performed in all cases. All patients had bowel preparation using polyethylene glycol administered the previous day, and were fasted overnight. Immediately after the procedure, the endoscopic score was assigned according to the Crohn's disease endoscopic Rutgeerts's modified grading system (0, no lesions; 1, aphthous ulcers; 2, aphthous ulcers with normal mucosa between lesions; 3, aphthous ulcers with diffuse inflamed mucosa; 4, diffuse inflammation with already large ulcers, nodule and/or stenosis) (Rutgeerts et al. 1990). Using the surface histology, we further classified each patient's disease as quiescent (score of 0 or 1) or active (score of 2, 3, or 4).

The disease was classified as active (on the basis of assessments performed #2 weeks before contrast-enhanced US) when (a) there was evidence of presence of ileal ulceration at retrograde ileoscopy; (b) small bowel enema or small-bowel follow-through examination showing apthous or linear ulcers, cobblestone mucosa, sinus tracts, fistulas with extraluminal fluid collections, or fold thickening and/or CT or MR enterography showing mucosal hyperenhancement, mural stratification, comb sign, ulceration, fistulas with extraluminal fluid collections, and perienteric fat with increased attenuation at CT and/or high signal intensity at T2-weighted MR imaging.

Statistical Analysis

A biostatistician participated in the statistical analysis performed by a computer software package (XLSTAT, version 2010.5.08, Addinsoft, NY, USA).

We compared the results of the visual and quantitative analysis with the CDAI using a non parametric Spearman's sign rank test.

To assess the effect of the potential risk factors for inflammatory stenosis separate univariate logistic regressions (Gareen and Gatsonis 2003) were first conducted to determine the relationship between stratified echo pattern or hypoechoic pattern, transparietal contrast enhancement, and submucosal enhancement by keeping as the outcome variable the diagnosis of inflammatory stenosis. These regressions produced odds ratios (OR) with 95% confidence intervals (Campbell and Machin 1999; Sistrom and Garvan 2004).

The different kinetic parameters, including the percentage of the maximal enhancement compared to baseline, the time to the peak enhancement, and the regional blood volume related to the area under the time-intensity curve measured in patients with inflammatory and fibrotic stenosis were compared by Mann Whitney U test.
Receiver operating characteristic (ROC) curves were constructed to determine the optimum threshold for each parameter. To compare the different parameters, the areas under the ROC curves were compared by using the method of DeLong et al. (1988). The cutoff values obtained from the ROC analysis were applied to each patient, and the sensitivities and specificities were calculated for each parameter and compared by the McNemar tests.

For all tests a P value < .05 was considered to indicate a statistically significant difference.
Fig. 1: Figure 1a-c. Scheme of echo-signal quantitation with the Q-ontrast software. Selection of the plane; Image segmentation with a ROI drawn over the anterior wall and excluding the bowel lumen; the time-intensity curve resulting from image analysis.

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Results

The correlation between CDAI, wall thickening, length of the diseased segment, parietal vascularity visual score yielded a value of $r = 0.4 - 0.6 \ (P>0.05)$ in all patients. In particular, no significant correlation ($P > 0.05$) between the visual score and CDAI was found. An inflammatory origin of stenosis correlated significantly with a high CDAI ($P< .01$), and the length of stenosis ($P< .01$).

Inflammatory stenosis was identified in 12 patients, while fibrotic stenosis was identified in 16 patients. No morphologic parameter was significantly correlated to the diagnosis of inflammatory stenosis on univariate regression analysis (Table 1).

Table 1 - Univariate logistic regression analysis

<table>
<thead>
<tr>
<th>MR imaging findings</th>
<th>Odds Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stratified echo pattern</td>
<td>0.001 (0– 0.003)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Hypoechoic echo pattern</td>
<td>0.001 (0– 0.003)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Transparietal enhancement</td>
<td>0.001 (0– 0.003)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Submucosal enhancement</td>
<td>0.001 (0– 0.003)</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

Table 2: Table 1 - - Odds ratio according to the different MR imaging parameters. C.I. = confidence intervals.

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Table 1.

After microbubble contrast agent injection, patients with inflammatory stenosis revealed a transparietal enhancement (Figure 1) in all cases, while patients with fibrotic stenosis revealed transparietal (n=10) or submucosal enhancement (n=4 patients) (Figure 2), or also complete absence of enhancement (n=2).

Table 2 shows the results of the quantitative analysis.
The time to peak enhancement was not significantly different in the inflammatory and fibrotic stenosis ($P > 0.05$), while the percentage of maximum enhancement and the area under time-intensity curve were significantly lower in fibrotic loops ($P < 0.05$).

The ROC analysis of the blood volume produced the highest value for the area under the ROC curve and the selected cutoff produced a sensitivity of 73% and a specificity of 62% to discriminate inflammation from fibrosis.

### Table 2 – Average values of the different kinetic parameters

<table>
<thead>
<tr>
<th></th>
<th>Inflammation</th>
<th>Fibrosis</th>
<th>$P$§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of enhancement (*)</td>
<td>45.86 ± 5.32</td>
<td>37.33 ± 16.24</td>
<td>0.027</td>
</tr>
<tr>
<td>Time to peak (**)</td>
<td>9.25 ± 4.21</td>
<td>12.01 ± 7.34</td>
<td>0.44</td>
</tr>
<tr>
<td>Area under curve (***))</td>
<td>1168.25 ± 437.65</td>
<td>570.47 ± 323.08</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 1: Table 2: Average values of the different kinetic parameters. * = The level of absolute enhancement expressed as a percentage of the maximum possible value ** = Time to achieve the highest level of contrast enhancement (seconds). *** = Measured for the first 20 seconds after the microbubble arrival in the scanning plane, expressed in absolute units, and related to the regional blood volume. § Mann Whitney U test

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Table 2. Average values of the different kinetic parameters.

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** = Time to achieve the highest level of contrast enhancement (seconds).

*** = Measured for the first 20 seconds after the microbubble arrival in the scanning plane, expressed in absolute units, and related to the regional blood volume.

§ Mann Whitney U test
**Fig. 2:** Figure 2a - c 55-years old man with ileal Crohn's disease. (a) Unenhanced gray-scale ultrasound. Stratified echo pattern (arrows) of the involved ileal loop. (b) Color Doppler US shows the hypervascular pattern of the bowel wall. (c) Cadence Contrast Pulse Sequencing. Diffuse transparietal contrast enhancement (arrows) after sulfur hexafluoride-filled microbubble injection.

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Fig. 3: Figure 3a, b 35-years old man with ileal Crohn’s disease. (a) Unenhanced gray-scale ultrasound. Stratified echo pattern (arrows) of the involved ileal loop. (b) Cadence Contrast Pulse Sequencing. Submucosal contrast enhancement (arrows) after sulfur hexafluoride-filled microbubble injection.

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Fig. 4: Figure 4a, b. Results of quantitative analysis. The different morphology of a time-intensity curve obtained in an inflammatory (a) and fibrotic (b) ileal stenosis. The fibrotic ileal loop presents a lower area under curve and a longer time to peak intensity.

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**Fig. 5:** Figure 5a, b. Results of quantitative analysis. The different morphology of a time-intensity curve obtained in an inflammatory (a) and fibrotic (b) ileal stenosis. The fibrotic ileal loop presents a lower area under curva and a longer time to peak intensity.

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Conclusion

Bowel wall vascularity quantitation on contrast-enhanced US may differentiate inflammatory from fibrotic stenoses in patients with CD based on the area under the time-intensity curve curve.
References


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