Interobserver Analysis of CEUS-Derived Perfusion in Fibrotic and Inflammatory Crohn’s Disease

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Interobserver Analysis of CEUS-Derived Perfusion in Fibrotic and Inflammatory Crohn’s Disease

Interobserver-Analyse der CEUS abgeleiteten Perfusion bei fibrotischem und entzündlichem Morbus Crohn

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perfusion, contrast agents, Crohn’s disease, fibrosis, CEUS

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ABSTRACT

Aim To examine if there are perfusion differences in fibrotic versus inflammatory lesions in patients with Crohn’s disease (CD) and to assess the interobserver reliability of the analysis.

Materials and Methods 37 patients with Crohn’s disease were prospectively recruited. 20 were operated and 18 of them had fibrotic disease. 17 received and were mostly responsive to medical treatment (14/17). Each patient underwent clinical scoring and ultrasound (US) examination with high-frequency linear transducers and US contrast. The perfusion analysis was performed using exported DICOM videos with VueBox® (Bracco Suisse SA, Genève, Switzerland). The program fits the time-intensity data to a standardized curve, from which several parameters can be derived, such as amplitude-based peak enhancement (PE), total area under the curve (AUC), area under the curve during wash-in and wash-out (WiAUC and WoAUC), wash-in rate (WiR) and wash-out rate (WoR) and time-based rise time (RT), fall time (FT) and mean transit time (MTT).

Results There was a significant difference between the groups for the parameters PE (p = 0.032), WiAUC (p = 0.035) and WoR (p = 0.038). We found no significant difference for RT, MTT, FT, WiR, AUC and WoAUC. An interobserver analysis showed correlation between two observers for all the parameters (r = 0.66–0.92, p < 0.001), except MTT (r = 0.46, p = 0.129). Bland Altman analysis revealed a fixed bias for the parameters PE, WiAUC and RT.

Conclusion The amplitude-based parameters PE, WiAUC and WoR could potentially be used to separate fibrotic and inflammatory lesions in patients suffering from CD due to significant differences and low interobserver variability.

ZUSAMMENFASSUNG

Ziel Untersuchung, inwieweit bei Patienten mit Morbus Crohn (CD) Perfusionsunterschiede zwischen fibrotischen und entzündlichen Läsionen bestehen, sowie die Bewertung der Interobserver-Reliabilität der Analyse.

Material und Methoden Siebenunddreißig Patienten mit CD wurden prospektiv aufgenommen; 20 wurden operiert und 18 davon hatten eine fibrotische Erkrankung. Siebzig erhielten eine medizinische Behandlung und sprachen mehrheitlich darauf an (14/17). Jeder Patient wurde klinisch bewertet und sonografisch (US) mit hochfrequenten linearen Schallköpfen und CEUS untersucht. Die Perfusionsanalyse erfolgte mit exportierten DICOM-Videos mittels VueBox® (Bracco Suisse SA, Genève, Schweiz). Das Programm passt die Zeitintensitätsdaten an eine Standardkurve an, aus der mehrere Parameter abgeleitet werden können, z. B. amplitudenbasiertes Peak Enhancement (PE), gesamte Area Under Curve (AUC), Area Under Curve während des Wash-in und Wash-outs (WiAUC und WoAUC), Wash-in Rate (WiR) und Wash-out Rate (WoR) und zeitbasierte Rise Time (RT), Fall Time (FT) und mittlere Durchflusszeit (MTT).
Introduction

Crohn’s disease (CD) is a chronic idiopathic inflammatory disease of the gastrointestinal tract, with a relapsing-remitting nature. It is complicated by stenosis in approximately 35% of patients during the first 10 years of disease [1, 2], making differentiation between the clinical expressions of the disease important [1–3]. Currently, there is no established method to differentiate between mainly fibrotic and mainly inflammatory lesions in CD except for endoscopy with histology. If a bowel segment with significant stenosis can be identified as fibrotic without inflammation, current medical treatment will not be effective and the bowel segment should be surgically removed.

The diagnosis of CD is confirmed by clinical evaluation combined with endoscopic, histological, radiological and biochemical investigations. CT, MRI and ultrasound (US) are used to minimize patient discomfort and assess sub-epithelial and peri-intestinal pathology and there is good correlation between these imaging techniques [4, 5]. Due to the ionizing radiation of CT, it is preferable to use US and MRI, especially in young patients. US is also well suited for repeated examinations, well tolerated by patients, and can be performed bedside.

Contrast-enhanced US can be used to quantify the microvasculature [6]. Dynamic contrast-enhanced US (DCE-US), which is the analysis of contrast enhancement over time, enables the estimation of perfusion [7, 8]. Several studies have shown a correlation between DCE-US parameters and clinical activity indices, such as the Crohn’s disease activity index and the Harvey Bradshaw index, endoscopy and histology [3, 9–11]. Furthermore, DCE-US could potentially be used to differentiate between inflammatory and fibrotic lesions due to differences in contrast enhancement and other perfusion parameters measured with dedicated software [12–14].

It has previously been shown that increased angiogenic activity occurs in CD leading to increased blood flow and micro-vessel density. The quantification of micro-vessel density corresponds to the degree of inflammation [15]. In fibrotic areas, however, blood flow is decreased [12, 13]. The differences in blood flow allow the examiner to differentiate between these two clinical expressions of CD, as shown by recent work by Nylund et al. [12]. In this study a perfusion model and dedicated software were used and enabled assessment of absolute perfusion. Several commercially available solutions for such off-line analysis are now available and may improve the implementation of such methods in clinical practice.

The aim of this study was to examine whether DCE-US could be used to differentiate between mainly inflammatory lesions and mainly fibrotic lesions in CD using commercially available software and to assess the interobserver variability of the analysis.

Materials and methods

Patients

37 patients with CD were included between October 2008 and December 2011 in a case control study. The patients were prospectively recruited through the outpatient clinic or at the bed ward at the Section of Gastroenterology, Department of Medicine (n = 17), and the Division of Gastrointestinal Surgery, Department of Surgery, Haukeland University Hospital (n = 20). The patients from the group receiving medical treatment with either systemic steroid or anti-TNF medication were included due to a flare-up of CD with a Crohn’s Disease Activity Index > 150. The patients from the group receiving surgical treatment were operated either due to stenotic disease or insufficient response to medical treatment. The patients received small bowel, ileocolic or large bowel resection. Patients were excluded from the study if there were normal findings on US or if there were contraindications for the US contrast agent such as age < 18 years, pregnancy, previous allergic reaction, unstable heart disease or serious obstructive lung disease. Patients in the medical group were not included if they had received treatment with anti-TNF in the last three months before inclusion. Two patients from the surgical group were excluded from the final analysis due to a lack of significant fibrosis in the resected bowel wall. The study was approved by the Regional Ethical Committee, and all patients signed informed consent.

Ultrasound examination

All patients were examined with US less than 7 days before receiving medical or surgical treatment, using a Logiq 9 and Logiq E9 ultrasound machine (GE Healthcare, Milwaukee, USA). A curvilinear probe (C1 – 5, 1 – 6 MHz) was used for abdominal overview, details of the intestinal wall were examined with a linear transducer (ML6 – 15, 9 – 15 MHz) and a linear probe (9L, 5.5 – 9 MHz) was used for the CEUS examination.

All examinations were performed by the primary investigator (K. N.) who had performed about 500 US examinations of the bowel prior to the study. All segments of the small and large intestine were scanned systematically as described previously [16]. Bowel wall thickness > 2 mm was considered pathological if the
bowl lumen was thicker than 0.5 cm and >3 mm in the case of lumen smaller than 0.5 cm or collapsed [17]. The area occupying the thickest wall section was chosen for further examination with CEUS (Fig. 1).

**Dynamic contrast-enhanced ultrasound**

Dynamic contrast-enhanced US (DCE-US) was performed using the 9L transducer in contrast mode combined with Sonovue® (Bracco, Milan, Italy). The contrast mode was set to “General” in combination with color map 2.0 and dynamic range 60. Furthermore, the mechanical index was set as close to 0.1 as possible (0.09 – 0.12) by adjusting the power and depth, gain reduced to lower background tissue signal and focus set just behind the affected intestinal wall.

A venous catheter in the left cubital fossa was used for contrast injection, administered by a nurse instructed beforehand on the study procedure. The anterior part of the most affected bowel wall was chosen for this examination. In the medical group this area was defined as the thickest bowel wall segment, while in the surgical group the area scheduled for resection was examined. The probe was oriented in the longitudinal direction of the bowel with the focus just behind the anterior wall.

Absolute intensity values cannot be compared between patients as there are several causes of variability that makes standardization very difficult [18, 19]. To reduce variability, we scaled the perfusion data of the bowel tissue to the flow in a major artery. We chose the right iliac artery as it is frequently located close to the affected bowel and can be imaged at variable depths. Two injections of 0.4 and 4.4 ml of Sonovue® were given during each examination. For the first injection, the right iliac artery was identified in the right fossa and the probe position was adjusted so that the distance between the artery and the probe corresponded to the distance between the previously registered distance between the most affected bowel segment and the probe. Then 0.4 ml of Sonovue® was given as a bolus over 2 seconds followed by a flush of 10 ml of 0.9% NaCl given over 4 seconds. A 60-second loop of the injection was recorded. A low dose was used in this study to avoid oversaturation in the artery.

When the contrast from the first contrast injection had dissipated after 5 – 10 minutes, the thickest bowel wall section was located, a second bolus injection of 4.4 ml of Sonovue® was administered and another 60-second loop was recorded. The recorded cine loops were exported as DICOM (Digital Imaging and Communications in Medicine) for further analysis.

**Quantitative CEUS analysis**

The CEUS data was evaluated using the off-line software application VueBox® (Version 4.2, Bracco Suisse SA, Genève, Switzerland). Based on signal intensity changes over time, the program should be well suited for perfusion analysis [20]. VueBox® enables linearization of the video data, using conversion algorithms specific for each probe, color map and dynamic range [21]. To extract perfusion parameters, the linearized reconstructed echopower data, directly proportional to the concentration of the microbubbles, is fitted to a standardized time intensity curve (TIC) [20]. By using wash-in/wash-out kinetics, the software provides parameters based on signal intensity, evolution over time and a combination of signal intensity and time. The derived parameters were peak enhancement (PE), wash-in area under the curve (WiAUC), rise time (RT), mean transit time (MTT), wash-in rate (WIR), wash-out area under the curve (WoAUC), total area under the curve (AUC), fall time (FT) and wash-out rate (WoR) and their definitions are shown in Table 1. By using the perfusion recording from the right iliac artery as an internal reference, the perfusion parameters from different examinations could be compared.

The procedure consisted of uploading the DICOM file, selecting the correct probe calibration, deleting off-plane frames, choosing an area of interest and applying motion compensation. The bowel was oriented in the longitudinal direction and a region of interest (ROI) was drawn in the anterior part of the bowel wall. The time of contrast arrival was indicated in the TIC. Finally, the software analyzed the time intensity data (Fig. 2) [20]. The perfusion parameters derived by the software were then exported to an Excel sheet and normalized by dividing the amplitude-related parameters with the corresponding parameters from the right iliac artery. The time-related parameters were not normalized as they are independent of contrast concentration. The contrast data was quantified by two investigators on the same contrast recordings (K. N. and F. S.) to assess interobserver reliability. Both investigators were blinded to the choice of ROI and to the results of the analysis from the other investigator. F. S. was also blinded to the clinical data and the results from this analysis were used when comparing the two patient groups. The second observer (F.S) was a medical student with little clinical ultrasound experience who was trained in recognizing the bowel wall and using VueBox prior to the study.
Histopathological scoring

The surgical specimens and histology were prepared as previously described in [12]. The primary investigator was an observer during the surgical procedure and also discussed the specimen with the pathologist. The region examined with CEUS was identified macroscopically in the operation specimen and histological sections were taken from the same region. If several lesions were present, the primary investigator informed the pathologist which segment had been scanned. Then, fibrosis was classified due to the presence and arrangement of collagen in the bowel wall layers. In the submucosa, slight to moderate fibrosis was defined as an increase of loose connecting tissue that did not fill the whole submucosa, and often with some fatty tissue present. In the case of severe fibrosis of the submucosa, densely packed collagen fibers filled the whole layer and no fatty tissue was seen. Slight to moderate fibrosis in the muscularis propria was defined by increased deposition of collagen between the muscular bundles. In severe fibrosis the muscular bundles were partly reduced in size and the architecture of the layer was destroyed to some extent.

<table>
<thead>
<tr>
<th>parameter</th>
<th>abbreviation</th>
<th>definition</th>
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<tbody>
<tr>
<td>peak enhancement</td>
<td>PE</td>
<td>indicates the maximum intensity of the TIC</td>
</tr>
<tr>
<td>wash-in area under the curve</td>
<td>WiAUC</td>
<td>area under the TIC from time of arrival to the PE</td>
</tr>
<tr>
<td>wash-out area under the curve</td>
<td>WoAUC</td>
<td>the area under the TIC from the PE to the end of the curve</td>
</tr>
<tr>
<td>total area under the curve</td>
<td>AUC</td>
<td>the total area under the TIC</td>
</tr>
<tr>
<td>wash-in rate</td>
<td>WiR</td>
<td>the maximum slope of the TIC represented as a tangent at the ascending part of the curve</td>
</tr>
<tr>
<td>wash-out rate</td>
<td>WoR</td>
<td>the minimum slope of the curve, represented as a tangent at the descending part of the curve</td>
</tr>
<tr>
<td>mean transit time</td>
<td>MTT</td>
<td>average time for the blood to pass through the region of interest</td>
</tr>
<tr>
<td>rise time</td>
<td>RT</td>
<td>time from arrival of contrast to PE</td>
</tr>
<tr>
<td>fall time</td>
<td>FT</td>
<td>time from PE to a point on the X-axis where the minimum slope tangent crosses</td>
</tr>
</tbody>
</table>
The extent of fibrosis in the submucosa and muscularis propria was graded using a semi-quantitative system as performed in [22], where 0 was considered normal, 1 = slight to moderate fibrosis and 2 = severe fibrosis. To differentiate between fibrotic and non-fibrotic sections, a score of 0 in both wall layers or 0 in the proper muscle and 1 in the submucosa was considered non-fibrotic. All other score combinations were considered fibrotic.

Statistics

The data are presented with median, minimum and maximum values. Comparison of the medical and surgical group was performed using the Mann-Whitney U-test. A posthoc analysis of receiver operated characteristics (ROC) was performed to find possible cut-offs for separating inflammation and fibrosis. Box plots are shown with the median within the box; the box represents the 25th and 75th percentiles and the whiskers the 10th and 90th percentiles. An outlier represented as a circle is greater than 1.5 of the interquartile range. Pearson correlation was used to assess the level of agreement between the two observers. Bland Altman analysis was performed and the data was tested for a fixed and proportional bias between observers. A fixed bias means that one observer measures higher/lower than the other for all values. A proportional bias means that one observer measures higher/lower than the other for a range of values. Parameters that are not normally distributed may erroneously be found to have a proportional bias. A solution to this problem is to log convert these parameters. Parameters where the data were not normally distributed as confirmed by the Shapiro Wilks test were log10-converted before the Bland Altman analysis. The parameters were then tested for fixed and proportional bias with a one-side T-test and linear regression, respectively, and are presented as Bland-Altman plots with limits of agreement defined as the standard deviation of the difference multiplied by 1.96. The level of significance was p < 0.05. The data analysis was performed using IBM SPSS Statistics software version 23 for Windows (IMB Inc., Armonk, NY, USA).

Results

There were 8 females and 9 males in the medical group with a median age of 33 years (range: 20 – 50), and 10 females and 8 males in the surgical group with a median age of 37 years (range: 19 – 77). In these patients 11/18 had fibrosis score 2, 5/18 had fibrosis score 3 and 2/18 had fibrosis score 4. In the medical group 12/17 started with systemic prednisolone, 2/17 with adalimumab, 2/17 with infliximab and 1/17 with prednisolone and adalimumab. More patient characteristics are shown in ▶ Table 2. After a follow-up period of one year, one patient had been operated with an ileocecal resection while two patients

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Demographics for the surgical and medical groups of patients with Crohn’s disease. Data are presented as ratios or averages with standard deviation.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>surgical group n = 18</td>
</tr>
<tr>
<td>age (years)</td>
<td>38.4 ± 14.3</td>
</tr>
<tr>
<td>gender</td>
<td>10/18 females</td>
</tr>
<tr>
<td>age at debut (years)</td>
<td>26 ± 16.8</td>
</tr>
<tr>
<td>previous surgery</td>
<td>8/18</td>
</tr>
<tr>
<td>treatment at inclusion</td>
<td></td>
</tr>
<tr>
<td>• pentasa</td>
<td>2/18</td>
</tr>
<tr>
<td>• budesonide</td>
<td>6/18</td>
</tr>
<tr>
<td>• prednisolone</td>
<td>4/18</td>
</tr>
<tr>
<td>• azathioprine</td>
<td>7/18</td>
</tr>
<tr>
<td>• adalimumab</td>
<td>6/18</td>
</tr>
<tr>
<td>• infliximab</td>
<td>0/18</td>
</tr>
<tr>
<td>body mass index (kg/m²)</td>
<td>22.2 ± 0.9</td>
</tr>
<tr>
<td>location</td>
<td></td>
</tr>
<tr>
<td>ileum</td>
<td>15/18</td>
</tr>
<tr>
<td>colon</td>
<td>1/18</td>
</tr>
<tr>
<td>ileum &amp; colon</td>
<td>2/18</td>
</tr>
<tr>
<td>stenosis</td>
<td>16/18</td>
</tr>
<tr>
<td>fistula</td>
<td>2/18</td>
</tr>
<tr>
<td>bowel wall thickness (mm)*</td>
<td>7.4 ± 1.9</td>
</tr>
<tr>
<td>length of affection (cm)</td>
<td>11.2 ± 6.2</td>
</tr>
</tbody>
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were still not in clinical remission (CDAI ≥ 150). All other patients were responsive to treatment (fall in CDAI< 70) and in clinical remission (CDAI< 150).

There was a significant difference (Mann-Whitney U-test) between the groups for the amplitude-derived parameters peak enhancement (PE, p = 0.032), wash-in area under the curve (WiAUC, p = 0.035) and wash-out rate (WoR, p = 0.038). The results for the remaining amplitude-based parameters wash-in rate (WiR, p = 0.053), total area under the curve (AUC, p = 0.053) and wash-out AUC (WoAUC, p = 0.053) were not significantly different between the groups (▶ Fig. 3). There was also no significant difference regarding the time-derived parameters rise time (RT), fall time (FT) and mean transit time (MTT, ▶ Fig. 4).

In the posthoc ROC analysis, PE, WiAUC and WoR all had an area of 0.71 under the ROC curve. A relative PE ≥ 0.08 indicated inflammation with a sensitivity of 0.71 and a specificity of 0.72. A relative WiAUC ≥ 0.12 indicated inflammation with a sensitivity of 0.71 and a specificity of 0.67. The relative WoR ≥ 0.04 indicated inflammation with a sensitivity of 0.71 and a specificity of 0.61.

The interobserver analysis showed correlation with good to acceptable correlation coefficients among the two observers for almost all parameters, lying within the interval of r = 0.66 – 0.92 (p < 0.0001), while the MTT had a particularly poor interobserver agreement (r = 0.46, p = 0.129. ▶ Table 3).

All parameters are presented as Bland Altman plots with limits of agreement in ▶ Fig. 5. As the interobserver difference was not normally distributed for any of the parameters, they were consequently log10-converted before the Bland Altman analysis. A one-sided T-test showed a fixed bias between the two investigators for the perfusion parameters PE, wash-in AUC and RT, but not for the others. There was no proportional bias for any of the parameters.

Discussion

We found that CEUS combined with commercially available software could be used to differentiate between lesions with mainly fibrotic disease and mainly inflammatory disease in CD with acceptable interobserver agreement for the post-examination analysis. According to our results, the perfusion parameters PE, WiAUC and WoR were significantly lower in fibrotic lesions, and

<table>
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<th>Table 3</th>
<th>Interobserver analysis (K. N. and F. S.) of perfusion data obtained from Vuebox (Pearson correlation).</th>
</tr>
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<tbody>
<tr>
<td>parameter</td>
<td>correlation coefficient</td>
</tr>
<tr>
<td>PE</td>
<td>0.85</td>
</tr>
<tr>
<td>WiAUC</td>
<td>0.92</td>
</tr>
<tr>
<td>WiR</td>
<td>0.79</td>
</tr>
<tr>
<td>WoAUC</td>
<td>0.72</td>
</tr>
<tr>
<td>WiWoAUC</td>
<td>0.83</td>
</tr>
<tr>
<td>WoR</td>
<td>0.69</td>
</tr>
<tr>
<td>RT</td>
<td>0.66</td>
</tr>
<tr>
<td>mTT</td>
<td>0.46</td>
</tr>
<tr>
<td>FT</td>
<td>0.75</td>
</tr>
</tbody>
</table>
Fig. 5. Bland-Altman plots displaying the agreement between the two observers (K.N and F.S.) for the perfusion parameters peak enhancement A, wash-in rate B, wash-in area under the curve C, total area under the curve D, rise time E, and mean transit time F. There was a fixed bias for PE, wash-in AUC and RT.
of these WoR was the only parameter without an analytic bias. These parameters may be used to identify patients with fibrotic bowel segments not likely to profit from medical treatment.

Finding a reliable method to differentiate between fibrotic and inflammatory lesions is important since inflammation could be managed conservatively, while fibrotic lesions with significant stenosis require surgical treatment. CEUS combined with quantitative techniques could be a useful tool in this assessment [12–14]. Ripolles et al. found that relative peak enhancement was the best parameter to discriminate inflammation from fibrosis, while [14] Quaia et al. found that peak enhancement and the area under the TIC curve could both be used [13]. Nylund et al. [12] found a significant difference in blood volume, which is a parameter comparable to area under the TIC curve [12]. According to the results of this study, the total AUC was not significantly different, which may be explained by differences in disease severity or methodical reasons, as discussed later. In this study none of the time-derived parameters (RT, FT and MTT) were significantly different. Previously, time-to-peak has been found to have a negative correlation to the Harvey Bradshaw index and a histological inflammation score [3, 9]. There is conflicting evidence in the literature, however, as other studies show that time-derived parameters are not significantly different between patients with mainly fibrotic or inflammatory disease in CD [12–14].

The interobserver study showed significant correlations with correlation coefficients between 0.66 and 0.92 for all but the time-related parameter MTT, suggesting that this is not a reliable parameter. The other parameters could be promising if repeated contrast injections are equally reproducible. According to our data, it seems that the parameters RT and FT have the narrowest limits of agreement, indicating the least variation. However, these parameters do not seem relevant for the clinical situation we investigated. Of the significant parameters, WiAUC had the narrowest limits of agreement. There was a fixed bias in the measurements between the observers for PE and WiAUC, however, which could affect the final clinical diagnosis. These biases may have been caused by the subtle differences in the observers’ choice of contrast arrival time and region of interest which particularly affect PE, WiAUC and RT. Since there was a difference in the experience of the two observers, this may have added to this effect.

A recent study comparing measurements performed on different scanners [23] indicates that DCE-US and analysis of contrast enhancement do not seem to be reproducible in a manner allowing recommendation of the comparison of different US vendors in multi-center studies using VueBox®. The problem regarding reproducibility with different scanners could be due to the different detection of microbubbles, difficulties in obtaining raw data and variation in patient hemodynamics.

Patient-specific factors could also contribute to the poor cutoff we found in this study as a mixture of inflammation and fibrosis can occur in affected segments. The groups were also quite heterogeneous. Particularly, there were more patients with ileal disease in the surgical group than in the medical group. This could introduce a bias as there might be differences in the perfusion between the large and small bowel. Also, in this study the focus was on finding possible differences in perfusion between the bowel wall section with fibrosis or inflammation and not on differentiating inflammatory stenosis from fibrotic stenosis. For this more careful selection of patients is needed. Furthermore, although the object of the analysis is to estimate tissue perfusion, this calculation is influenced by the arterial input function (AIF) when using bolus tracking. The AIF is the local arterial input of the tissue, which is dependent on several factors such as inter-individual differences in the splanchnic blood flow, blood volume, bolus administration and distance from the injection site, all contributing to variability in the time-related variables. Jirik et al. [24] combined bolus injection and burst replenishment in a new model to solve this problem, thereby providing a robust AIF estimate and enabling the estimation of absolute perfusion. Recently presented data indicates that this method performs well also for repeated measurements [25].

High-frequency B-mode imaging of the gastrointestinal wall is easier to perform than estimating perfusion using DCE-US. Studies of the intestinal wall have shown an association between the wall layers visualized by B-mode US and histology [26, 27]. Increased inflammatory activity is characterized by thickened bowel wall, loss of stratification and a thickened submucosal layer, while increased wall thickness with intact stratification and thickening of the proper muscle is associated with fibrosis [12, 28]. However, the coexistence of fibrosis and inflammation in the bowel of CD patients [3, 13, 14] makes this an exceedingly complex problem which suggests that the discrimination between the two will probably rely on several parameters in future clinical practice including an assessment of microvasculature and perfusion. Only DCE-US can add this dimension to the ultrasound examination.

Three of the amplitude-related parameters were not significantly different although there was a trend towards it. This could be due to the small number of patients, leading to type 2 errors, and is a limitation of the study. Additionally, possible weaknesses in study design may have contributed to this. The CEUS recordings lasted 60 seconds, which could be an insufficient amount of time for evaluating contrast wash-out. Furthermore, the US recordings were performed with two different GE US scanners, probably causing greater variability. The contrast dose and injection technique were standardized, but administered manually. An infusion pump could reduce this variability, but an accurate AIF estimate could correct both for the variability in bolus administration and inter-individual differences of vasculature and cardiac output.

In conclusion, DCE-US is a promising method to be used for the imaging of patients with Crohn’s disease and the amplitude-based parameters peak enhancement, wash-in area under the curve and wash-out rate derived from VueBox® may be used to differentiate between fibrotic and inflammatory lesions in patients suffering from CD, due to significant differences and relatively low interobserver variation. In this study none of the time-derived parameters seemed to be useful and MTT was the least reproducible parameter.

Conflict of Interest

Odd Helge Giljø: Lecture fees GE Healthcare, Takeda AS, MEDA AS
Kim Nylund: Lecture fees MSD, MEDA AS, Ferring Pharmaceuticals
Acknowledgments

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Reference