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High-resolution Visualization of Intestinal Microcirculation using Ultra-microangiography in Patients with Inflammatory Bowel Disease: A Pilot Study

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ABSTRACT

Background & Aims: Ultra-microangiography (UMA) is a novel Doppler technique with optimized wall filtering that provides high sensitivity to low-velocity blood flows and optimized visualization of microcirculation. The aim of this pilot study was to compare intestinal vascularization assessed by color Doppler signals (CDS) and UMA.

Methods: We investigated intestinal vascularization using UMA and CDS in 13 patients with confirmed inflammatory bowel disease (IBD). A cohort of 28 patients without structural bowel disease served as the control.

Results: Microcirculation and dysregulated microcirculation in patients without and with inflammatory bowel disease can be visualized and quantified using UMA. In 83 % of IBD patients and 76% of non-IBD patients, a high resolution of intestinal perfusion could be achieved using UMA.

Conclusions: To the best of our knowledge, this is the first study to investigate intestinal vascularization using UMA in patients with and without structural bowel disease. Quantification and visualization of intestinal vascularization should be further investigated in prospective studies and could help guide our therapy of patients with IBD.

Key words: ultrasound – color Doppler ultrasound – ultra-microangiography – intestinal ultrasound – IBD.

Abbreviations: CDS: color Doppler ultrasound; CEUS: contrast-enhanced ultrasonography; CPP: color pixel percentage; CT: computed tomography; IBD: inflammatory bowel disease; MRI: magnetic resonance imaging; SES-CD: Simple Endoscopic Score for Crohn´s Disease; UMA: ultra-microangiography; cUMA: color-UMA, pUMA: power-UMA: sUMA: subtraction-UMA.

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INTRODUCTION

The importance of ultrasound in assessing intestinal morphology has gained importance in the diagnosis, prediction, and follow-up of patients with inflammatory bowel disease (IBD) [1-3]. Various ultrasound techniques and criteria have been used to evaluate intestinal inflammation [4]. Most evidence exists for the thickness of the intestinal wall and increased perfusion as a reflection of the inflammatory burden [1, 5, 6]. Bernd Limberg pioneered the definition of a semiquantitative assessment of intestinal vascularization as an expression of inflammation in IBD [7]. The Limberg score is now commonly used to assess vascularization, and a Limberg score of 2 or higher is considered abnormal. The advantage of this classification is its ease of its clinical implementation [1]. The main disadvantage is the high interobserver heterogeneity [8, 9], and until now, there have been no clear criteria for the quantification of microcirculation in the intestine by ultrasound.

Microcirculation contributes to local inflammation and responds to inflammatory insults. A larger diameter of afferent blood vessels, increased flow in these vessels, and an overall higher number of vessels contribute to the inflammatory response [10, 11]. Neoangiogenesis fueled and maintained by inflammatory activity and microvascular remodeling appears to be one of the driving factors in the pathogenesis of IBD [12].

To date, color Doppler signals (CDS) have been a piece of the puzzle in the assessment of intestinal inflammation in a variety of studies [13-17], and vascularization has been shown to play a major role in the complex inflammatory process of

IBD [18]. Changes in microcirculation precede structural changes in the intestinal wall [19]. Accordingly, an accurate, quantitative assessment of intestinal microcirculation could be a crucial parameter for assessing a short-term response to therapy in IBD. Therefore, high-end devices with optimal spatial resolution are required.

Through the implementation of contrast-enhanced ultrasonography (CEUS) in routine diagnostics, clinicians have tried to bridge the gap between conventional ultrasound and computer tomography (CT) imaging or magnetic resonance imaging (MRI). CEUS uses stabilized microbubbles with gaseous content, which are injected intravenously and allow the visualization of blood flow within the intestine, thus addressing the shortcomings of ultrasonography imaging, yielding a much better understanding of microcirculation compared to CDS [20]. A significant correlation has been shown between CEUS and MRI or CT-imaging in the evaluation of disease activity in IBD [21]. In addition, recent studies were able to demonstrate, how CEUS was capable of predicting treatment response and outcome in patients with Crohn´s disease undergoing immunomodulatory treatment [22]. However, CEUS is not widely used in routine diagnostics due to lack of expertise among physicians in application and evaluation, as well as the high costs of individual injection solutions. Although side effects are rare and only mild, allergic reactions, including anaphylactic shock, have been reported following the injection of contrast enhancing agents [23].

Ultra-microangiography (UMA) is a novel Doppler technique designed to improve the detection rate of vessels and to assess microcirculation using ultrasound without the need for contrast enhancing agents. UMA uses an effective wall filtering algorithm that can distinguish signals of slow tissue movement from those of the blood flow and therefore achieves a higher sensitivity to low-velocity blood flow. UMA captures high-quality raw ultrasound signals through the ultrasound plane wave/divergence wave (hereafter referred to as plane wave) with high efficiency and uses an advanced tissue suppression algorithm to intelligently remove tissue interference from the raw signals. The high sensitivity and spatial resolution of UMA are based on two key technological innovations: a high frame rate imaging technique for plane waves and an adaptive spatiotemporal tissue-rejection filtering technique [24-26].

In this study, we applied the ultra-microangiography technique in patients with increased intestinal inflammation and in those with presumed physiological intestinal integrity. The focus of our investigation was the qualitative and quantitative assessment of intestinal blood flow and the evaluation of ultra-microangiography parameters as potential biomarkers of inflammatory burden in inflammatory bowel disease.

METHODS

Patients

We included patients with a confirmed diagnosis of IBD and delineated the varying severity of inflammation based on bowel wall thickness and multimodality imaging of vascularization. The control group consisted of patients without IBD. This group had a wide spectrum of concomitant diseases and no clinical or morphological evidence of structural bowel disease.

Bowel wall thickness was measured in the bowel segment where the most prominent bowel pathology was noted. Clinical, sonographic, endoscopic, and histological parameters were integrated in the assessment of disease activity. Our IBD cohort comprised patients from our outpatient department. The ultrasound examination was performed on the day of presentation, alongside the assessment of laboratory values and stool samples. The following data on disease activity was obtained through endoscopic and histological assessments and originates from longitudinal follow-up examinations within our department, ensuring a maximum temporal offset of three months.

To assess disease activity, standardized endoscopic scoring systems, such as the Simple Endoscopic Score for Crohn´s Disease (SES-CD) [27] and Mayo Clinic Score (Mayo Score) [28] were applied. The classification of patients into subgroups of remission, partial remission or exacerbation was determined by an experienced physician in the treatment of IBD patients. This decision was based on a comprehensive review of all findings along with the clinical symptoms and history of the patient.

Ultrasound Examination and Technique

All examinations were performed by an experienced examiner (who performs more than 3,000 examinations/year). The RESONA R9 device (Mindray Bio-Medical Electronics Co., Ltd) was used. The examinations were validated in a blinded manner by 2 experienced examiners.

The structured bowel ultrasound examination was based on the systematics by the "International Bowel Ultrasound Group" (IBUS) according to a fixed protocol, starting with the examination of the colon followed by the examination of the small intestine using a multifrequency linear sector transducer (2-9 MHz, Mindray, Resona R9).

The bowel was first examined for segmental or generalized thickening of the bowel wall > 3 mm with accompanying mural edema with or without accompanying free fluid, lymphadenopathy, hyperemia, and enlargement of the bowel fat. For conventional Doppler imaging, flow parameters were adapted to low venous flow, scale < 10 cm/s, wall filter < 100 dB, and color gain at high level, but without artifacts. In patients without intestinal pathologies, the sigmoid colon was examined by UMA. In patients with IBD, the bowel section with the most widened bowel wall and the strongest CDS was examined by UMA. The patients were first examined using CDS followed by UMA to evaluate intestinal perfusion.

The UMA setting consists of three sub-modalities, being color-UMA (cUMA), power-UMA (pUMA), and subtraction-UMA (sUMA). Whereas cUMA assesses the velocity, magnitude, and direction of blood flow, pUMA demonstrates the power intensity and direction of blood flow. Subtraction UMA enhances the features of pUMA and provides the option to manually adjust the background signal [29].

Ultrasound Imaging Analysis

To further investigate whether UMA adds additional value to the visualization of the intestinal microcirculation, two

experienced examiners evaluated the digital video sequences of CDS and UMA for vascularization in terms of overall flow detection and vascular branching detail. Differences were scored from 1 (worst) to 5 (best). Grading refers to the extent to which the course of the vessels could be assessed. The maximum score was given, if the entire course of the vessels could be visualized. If the score was 1, the vessel sections were not visualized using any method (CDS or UMA). With a value of 1, vessels with a diameter of 2-3 mm were imaged and a point value of 2, vessels with a diameter of 1 mm were visualized. A point value of 3 implies that smaller capillaries were imaged, but not the entire course of the vessel. A point value of 4 indicates that most capillaries were imaged with only small gaps. Grades 4 and 5 on the visual scale indicate that the intestinal vascular course can be seen over a long distance and are considered high resolution.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics (2022), version 28.0. Because of the explorative nature of the study, data analysis was mostly based on descriptive statistics. Continuous variables are presented as mean ± standard deviation (SD) and minimum to maximum ranges. Categorical variables are presented as frequency (percentage). CDS and UMA scores were compared using the chi-square test.

RESULTS

We studied 13 patients with a confirmed diagnosis of IBD and delineated the varying severity of inflammation on the basis of bowel wall thickness and multimodality imaging of vascularization (Table I/Table II). As a control group, we examined 28 patients without IBD (Supplementary file).

Table I. Demographics and characteristics of IBD patients (n=13)

Median age, years	42
Mean age, years (± SD)	40.9 (± 14.0)
Gender	
Male, n (%)	7 (53.8)
Crohn's disease, n (%)	8 (61.5)
Exacerbation	4
Partial Remission	3
Remission	1
Ulcerative colitis (%)	5 (38.4)
Exacerbation	3
Remission	2
Intestinal wall thickness (B-Mode[1])	
0	1
1	8
2	1
3	1
Undetermined	2

[1]B-Mode/Intestinal wall thickness: 0 (3–4 mm, normal), 1 (5–6 mm, little), 2 (7–8 mm, moderate), 3 (>8 mm, severe).

In our study cohort of 13 IBD patients, the majority (7 patients) suffered from acute exacerbation at the time of the ultrasound examination. In another 3 patients some form of inflammatory activity (either through elevated levels of fecal calprotectin, symptoms, or endoscopic findings) could

Table IIa. Characteristics of patients with Crohn´s disease enrolled in the current study

Age (years)	52	42	24	26	64	57	51	30
Gender	F	M	F	M	F	F	M	M
CRP (mg/l)	< 5	24.0	6.2	13.0	15.0	< 5	8.2	< 5
Previous surgery	ICR	ICR Sigmoid resection Appendectomy	None	None	None	ICR	ICR	ICR
Activity[1]	Partial remission	Exacerbation	Exacerbation	Exacerbation	Exacerbation	Remission	Partial remission	Partial remission
Intestinal findings on US	Hyperaemia	Distention hyperaemia stenosis	Moderate irritation	Stenosis hyperaemia	Mild hyperaemia	Stricture	Mild hyperaemia	NA
IWT (B-Mode[2])	1	1	NA	3	0-1	0-1	1	1
Current IBD therapy	Ustekinumab	Ustekinumab	Mesalazine	Azathioprine, prednisolone	Vedolizumab	Methotrexate	Ustekinumab	Infliximab
Previous complications	Stenosis	Stenosis anal abscess fistulae	None	Terminal ileitis	None	Fistulae anal stenosis	Perforation ileostomy	Fistulae ileostomy
Faecal calprotectin (mg/kg)	NA	270	174	962,9	108	78	131	110
Endoscopic findings	SES-CD score 1	SES-CD score 3						
	NA	SES-CD score 10	NA	NA	SES-CD score 2	NA		

ICR: ileocoecal resection; IBD: inflammatory bowel disease; IWT: intestinal wall thickness; [1]: disease activity assed via established clinical and endoscopic indices; [2]Intestinal wall thickness measured at max. width; 3:B-Mode/bowel wall thickness: 0 (3–4 mm, normal), 1 (5–6 mm, little), 2 (7–8 mm, moderate), 3 (>8 mm, severe).

Table IIb. Characteristics of patients with ulcerative colitis enrolled in the current study

Age (years)	50	51	23	33	29
Gender	M	F	M	M	F
CRP (mg/l)	< 5	< 5	< 5	28.6	< 5
Previous surgery	None	Colonostomy	None	None	None
Activity[1]	Exacerbation	Exacerbation	Remission	Exacerbation	Exacerbation
Intestinal findings on US	Hyperaemia stricture	Moderate hyperaemia	None	Strong hyperaemia	Moderate hyperaemia
IWT (B-Mode[2])	1	1	0	2	0
Current IBD therapy	Mesalazine	Infliximab	Azathioprine		
Vedolizumab	Upadacitinib	Mesalazine			
Previous complications	None	Stenosis	None	None	None
Faecal calprotectin (mg/kg)	25.3	99.5	138.6	1015.7	141
Endoscopic findings	NA	MAYO score 2	MAYO score 0	MAYO score 3	Proctitis

For abbreviations see Table IIa.

be detected, which led to their classification into the partial-remission group. Only 3 of the observed patients, one patient with Crohn´s disease and two patients with ulcerative colitis, showed signs of full remission. In the ultrasound examination of the patient with Crohn´s disease and one of the patients with ulcerative colitis, there was no evidence of hyperemia in the intestinal wall. Marked increased intestinal wall thickness, another parameter of inflammation, could not be detected in any of those three patients.

The only pathological finding in the patient with Crohn´s disease was a stricture, detected in B-Mode ultrasound examination in the anastomotic region after ileocecal resection. For the evaluation of strictures and distinction of inflammatory strictures from scarred strictures, our established elastography was used.

A characterization of patients without evidence of chronic inflammatory bowel disease, serving as control group, can be found in Table III of the supplementary materials. The main focus of examination in this group was to collect data on microcirculation of the intestinal wall in individuals not affected by chronic inflammation, in order to achieve visual reference points. Nevertheless, some alterations of intestinal micro-perfusion were found in patients with liver cirrhosis, infection, and diverticulitis. Whether there are different patterns of altered microcirculation differentiating IBD patients from individuals with other forms of altered perfusion has yet to be investigated.

Table III shows a comparison of the visual scaling of CDS and UMA in the group of patients with IBD. The average score for assessing the visualization of intestinal perfusion by CDS was 1.9 (±0.66 standard deviation (SD)). In direct comparison, the average score for the visualization of intestinal perfusion by UMA was 3.9 (±0.51 SD).

Table IV shows the comparison of the visual scaling of CDS and UMA in the non-IBD group. The average score for assessing the visualization of intestinal perfusion by CDS was 1.6 (±0.74). In direct comparison, the mean score for assessment of visualization of intestinal perfusion by UMA was 3.8 (±0.64).

In 83% of IBD patients and 76% of non-IBD patients, a high resolution of intestinal perfusion could be achieved using UMA.

Details of different ultrasound modalities in IBD patients are illustrated in Figs. 1-5.

DISCUSSION

To date, intestinal vascularization has been measured using ultrasound with scores such as the Limberg score. These scores are subject to interobserver heterogeneity [8, 9].

Table III. Visual scaling CDS vs. UMA in patients with IBD

CDS, IBD, n=13				
1	2	3	4	5
N = 3	N = 7	N = 2	N = 0	N = 0
N = 1 not evaluable because of insufficient image quality				
UMA, IBD, n=13				
1	2	3	4	5
N = 0	N = 0	N = 2	N = 9	N = 1
Not significant	< 0.05	Not significant	< 0.05	Not significant
N = 1 not evaluable because of insufficient image quality				

Number of patients with a color Doppler score (CDS) or ultra-microangiography (UMA) score of 1 to 5. The number of patients with an equal CDS and UMA score was compared using the chi-square test.

Table IV. Visual scaling of CDS vs. UMA in non-IBD patients

CDS, Non IBD, n=28				
1	2	3	4	5
N = 11	N = 12	N = 1	N = 1	N = 0
UMA, Non IBD, n=28				
1	2	3	4	5
N = 0	N = 1	N = 5	N = 17	N = 2
< 0.01	< 0.05	Not significant	< 0.005	Not significant
N = 3 not evaluable because of insufficient image quality				

Number of patients with a color Doppler score (CDS) or ultra-microangiography (UMA) score of 1 to 5. The number of patients with an equal CDS and UMA score was compared using the chi-square test.

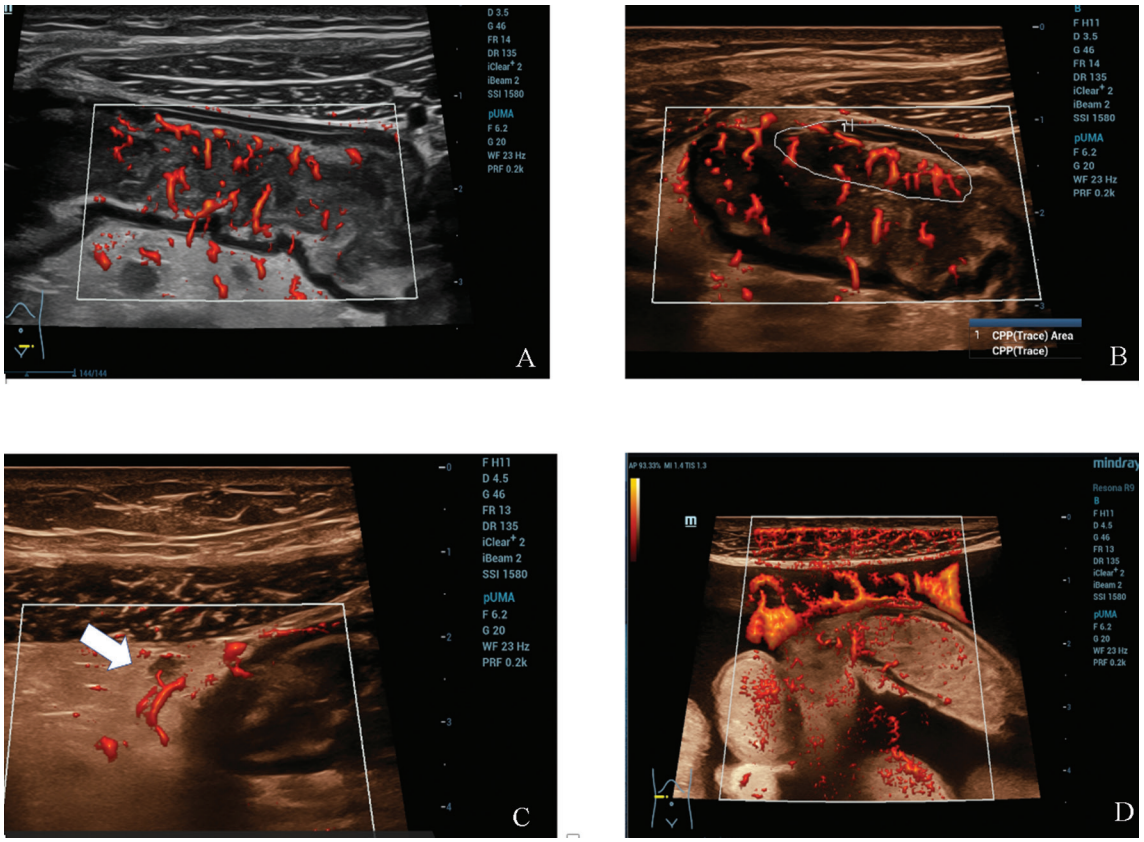

Fig. 1. A-D using Power ultra-microangiography (UMA). A+B: Power UMA in the sigmoid colon in a 32-year-old patient with severe pancolitis. C: Paraintestinal lymphadenopathy (marked with the white arrow) with visualized microcirculation in a severe acute relapse of ulcerative colitis. D: A 57-year-old patient with ascites and marked reactive intestinal hyperemia.

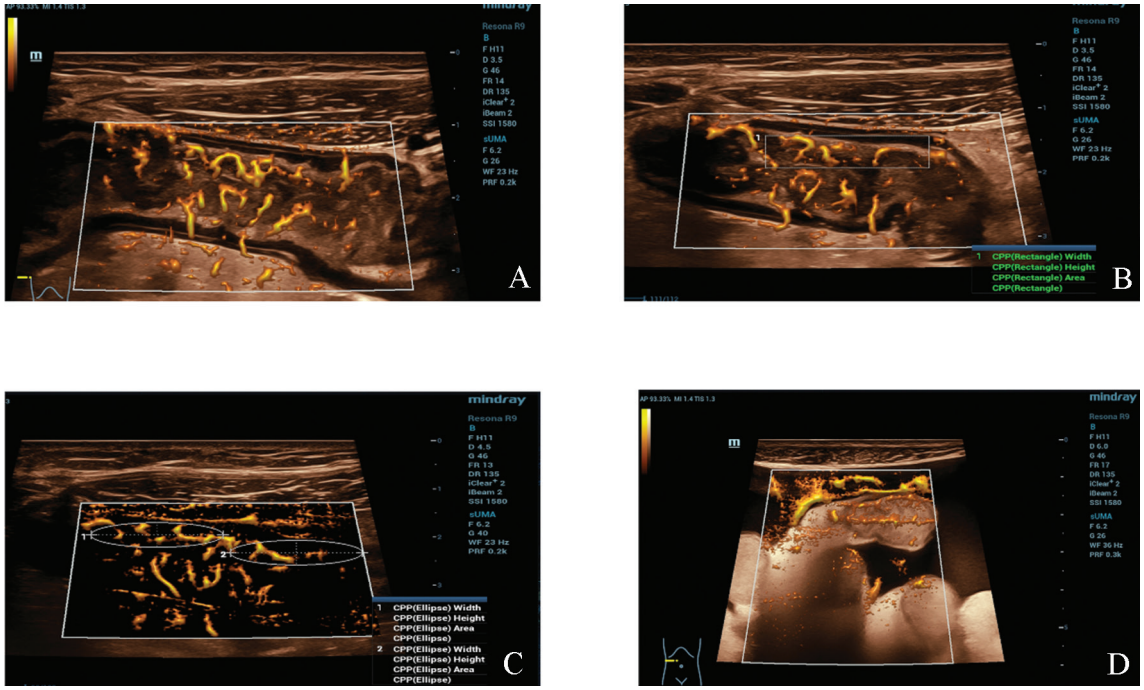

Fig. 2. A-D using subtraction ultra-microangiography (sUMA) A-C: Power UMA in the sigmoid colon in a 32-year-old patient with severe pancolitis. B: Within the rectangular window, quantitative measurement of the color pixel percentage (CPP) within the intestinal wall is performed. C: Within the ellipse, quantitative measurement of the CPP within the intestinal wall is performed. D: 57-year-old patient with ascites and marked reactive intestinal hyperemia.

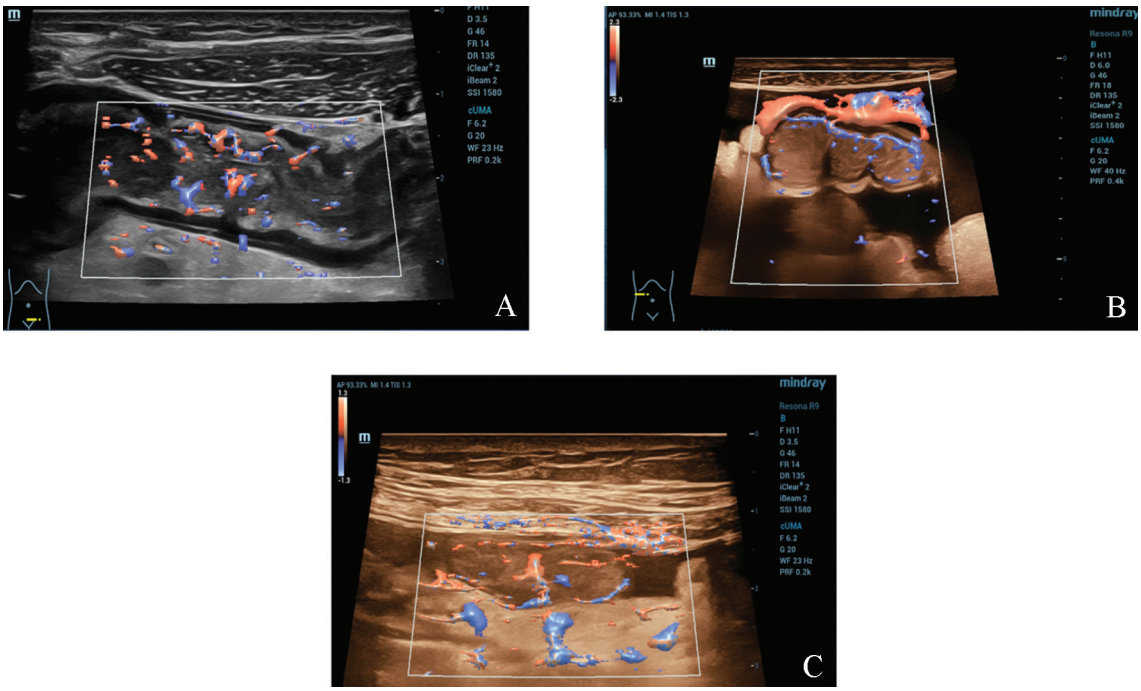

Fig. 3. A-C using color ultra-microangiography (UMA) A: Color UMA in the sigmoid colon in a 32-year-old patient with severe pancolitis. B: 57-year-old patient with ascites and marked reactive intestinal hyperemia. C: Increased perfusion in the jejunum in a 56-year-old patient with active Crohn 's disease.

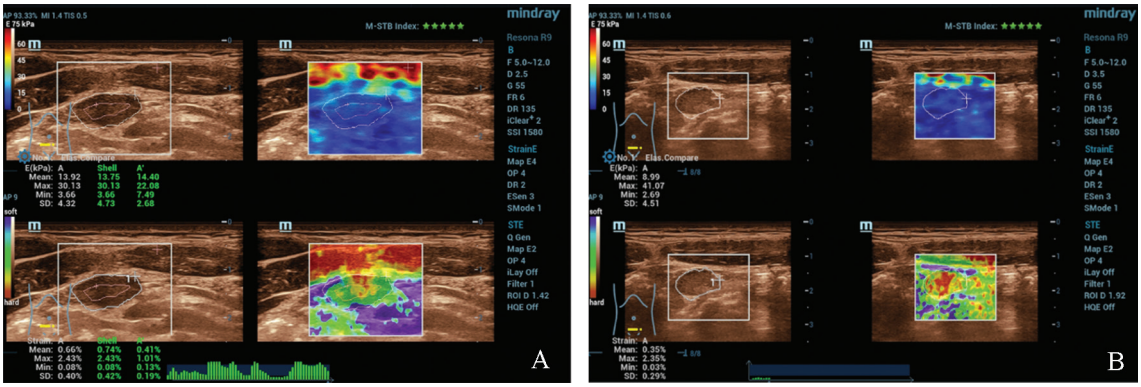

Fig. 4. A+B: 36-year-old patient with undulating upper abdominal pain with irritable bowel syndrome. Two different measuring points in the area of the small intestine Synchronous elastography measurements using strain elastography and shear wave elastography (SWE). Predominant soft tissue in the small intestine wall. The measurement field within the intestinal wall was manually set.

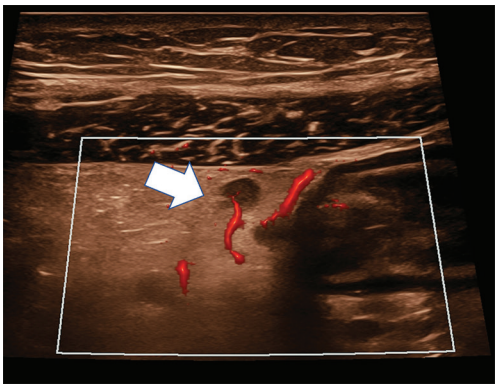

Fig. 5. Feeding vessel to an enlarged paraintestinal lymph node visualized using power ultra-microangiography (pUMA) and marked with white arrow.

The current Stride II (Selecting Therapeutic Targets in Inflammatory Bowel Disease) criteria have defined desirable treatment goals for patients with IBD, one of them being mucosal healing [30]. Until now, assessment of mucosal inflammation has been performed by endoscopy, but there is growing evidence that sonographic assessment of mucosal inflammation could yield comparable results to guide therapy [31]. In this study, we showed that UMA, a novel ultrasound technique, could enhance the quality and accuracy of ultrasound as a diagnostic tool. Compared with endoscopy, the advantages of bedside bowel ultrasound are its noninvasive nature and rapid availability. Disadvantages include the lack of dysplasia monitoring and associated infection diagnosis (e.g. cytomegalovirus) [32]. Another advantage of endoscopy is its direct macroscopic assessment of the intestinal mucosa and histological verification of the inflammatory burden.

To the best of our knowledge, this work is the first to investigate UMA for visualization of intestinal microvascularization. In 83% of IBD patients and 76% of non-IBD patients, a high resolution of intestinal perfusion could be achieved using UMA. The extent of blood flow was more clearly visible, and the enhanced image provided better spatial resolution by suppressing background noise. This enabled a precise examination of the vascular supply in the different layers of the intestine. In our series, we could demonstrate that UMA offers the possibility to better visualize and quantify microcirculation in the small and large bowel. Using the color pixel percentage (CPP) score, vascularization can be objectified and quantified. In addition, the new UMA technique has the advantage that the measurement areas can be defined with rounded, angular, and individually tailored regions.

We found that UMA flow imaging allows the detection of mural microvasculature of the intestinal wall vessels and hyperemia to the surrounding mesentery with much higher detailed resolution and can provide angiography-like images in the subtraction technique. With the additional integration of strain and shear wave elastography, UMA allows for an augmented differentiation between inflammatory and fibrous stenosis. One patient in the IBD cohort presented with a stenosis of the intestinal anastomosis following ileocoecal resection, which could be correctly identified in the ultrasound examination with UMA enhancement and was later confirmed by endoscopy.

Nevertheless, UMA remains dependent on the examination conditions and is limited to a maximum depth of up to 6 cm using linear probes. To obtain perfusion kinetics of the intestinal wall comparable to MRI, CEUS may be required in addition [33].

Several studies have investigated the significance of CEUS in inflammatory bowel diseases. They were able to show that a successful visualization of the microcirculation in the intestinal wall can provide crucial information in the evaluation of disease activity and even predict therapeutic response and outcome [22]. Research on penetration changes of the intestinal wall and the detection thereof using CEUS, has been particularly successful in graft-versus-host disease (GVHD) and COVID-19-associated intestinal involvement [33, 34].

Whether the quality of visualization yielded by UMA can produce similar results comparable to CEUS has to be the subject of future investigations.

Possible advantages include the omission of an additional agent and simplified interpretability, including objective measurements using the CPP score.

Another advantage of UMA is the examination of a larger number of lesions, whereas with CEUS, the examiner must concentrate on one target lesion. The extent to which UMA ultrasound can complement or even replace other diagnostic and monitoring tools such as CT/MRI or endoscopy needs to be further investigated.

Our control group comprised twenty-eight patients without IBD. In these patients, the difference in image quality and vascular visualization was even more significant. Using conventional CDS Doppler ultrasound, we were able to achieve an average score of 1.6 regarding image quality, whereas using UMA ultrasound, an average score of 3.8 was achieved.

It is apparent that the differences between UMA and conventional ultrasound Doppler were more pronounced in patients with less prominent hypervascularization and therefore smaller vessels with lower blood flow velocities. In patients with prominent signs of inflammation, especially hypervascularization, regular Doppler ultrasound may be able to accurately produce a visual image that corresponds to the inflammatory activity in the patient. Nevertheless, the threshold for adequate visualization is much lower with UMA and thus enables the attending physician to also detect inflammation in a less pronounced state.

Thus, UMA may be particularly useful for guiding therapy and evaluating therapeutic response, paving the way for closer, noninvasive patient surveillance and more personalized care.

Our results agree with the findings of Zhao et al. [24] and Chen et al. [25], who studied patients with rheumatoid arthritis and keloids. Both groups demonstrated a high sensitivity and good resolution in small vessels with low blood flow for UMA. Furthermore, both studies demonstrated UMA to be superior to color Doppler signals in the visualization of small capillaries and microcirculation [24, 25].

However, the UMA technology also has various limitations. Technically, high-resolution linear samples are necessary for intestinal ultrasound. This Doppler technique provides only semiquantitative results, and the signal strength significantly depends on factors such as depth, tissue density, substances that hinder penetration (such as water or fat), and whether the probe is applied with force. In addition, the smallest capillary level can only be visualized with CEUS. On the other hand, using UMA, in our experience, the visualization of the number and course of intestinal vessels is significantly improved compared with conventional Doppler sonography. The increase in resolution quality is also due to significantly increased artifact reduction and a three-dimensional representation.

Interventional multicenter studies have begun to define intestinal ultrasound parameters to allow early detection of mucosal and transmural responses with a higher sensitivity compared with endoscopy. We have the assessment that for an early evaluation of a therapy response, intestinal vascularization is a crucial parameter and can be deduced before mucosal changes.

We envision the future of UMA technology in the long-term observation and therapy monitoring of IBD patients. Due to the often relatively young age of onset of the disease, these individuals stand to benefit from less invasive and radiation-sparing diagnostic tools.

Ultra-microangiography allows visualization and quantification of intestinal microcirculation, and therefore represents a directional advancement in intestinal bowel ultrasound.

CONCLUSIONS

Ultra-microangiography visualizes intestinal inflammation very sensitively and displays vascularization down to the small capillaries. This technical innovation offers great opportunities for the diagnosis, prediction, and monitoring of inflammatory bowel diseases. Future studies should investigate the role of UMA in the imaging of intestinal perfusion in relation to disease activity and treatment response in patients with IBD.

Conflicts of interest: None to declare.

Authors' contributions: S.A.F., E.M.J., H.C.T., A.K., M.M. conceived and designed the study. S.A.F, E.M.J., H.C.T. collected the data. S.A.F., E.M.J., H.C.T., C.B. performed the statistical analysis. S.A.F, E.M.J., H.C.T., A.K., M.M., C.B., K.G., S.K. interpreted the different ultrasound modalities findings. S.A.F, E.M.J., H.C.T analyzed the data and drafted the manuscript. All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

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Supplementary material: To access the supplementary material visit the online version of the *J Gastrointestin Liver Dis* at http://dx.doi.org/10.15403/jgld-5495

REFERENCES

1. Ilvemark JFKF, Hansen T, Goodsall TM, et al. Defining Transabdominal Intestinal Ultrasound Treatment Response and Remission in Inflammatory Bowel Disease: Systematic Review and Expert Consensus Statement. J Crohns Colitis 2022;16:554–580. doi:10.1093/ecco-jcc/jjab173
2. Allocca M, Furfaro F, Fiorino G, Peyrin-Biroulet L, Danese S. Point-of-Care Ultrasound in Inflammatory Bowel Disease. J Crohns Colitis 2021;15:143–151. doi:10.1093/ecco-jcc/jjaa151
3. Al-Ani AH, Vaughan R, Christensen B, Bryant RV, Novak KL. Treat to transmural healing: how to incorporate intestinal ultrasound into the treatment of inflammatory bowel disease. Br J Radiol 2022;95:20211174. doi:10.1259/bjr.20211174
4. Goodsall TM, Nguyen TM, Parker CE, et al. Systematic Review: Gastrointestinal Ultrasound Scoring Indices for Inflammatory Bowel Disease. J Crohns Colitis 2021;15:125–142. doi:10.1093/ecco-jcc/jjaa129
5. Stojkovic Lalosevic M, Sokic Milutinovic A, Matovic Zaric V, et al. Intestinal Ultrasonography as a Tool for Monitoring Disease Activity in Patients with Ulcerative Colitis. Int J Clin Pract 2022;2022:3339866. doi:10.1155/2022/3339866
6. Sævik F, Eriksen R, Eide GE, Gilja OH, Nylund K. Development and Validation of a Simple Ultrasound Activity Score for Crohn's Disease. J Crohns Colitis 2021;15:115–124. doi:10.1093/ecco-jcc/jjaa112
7. Limberg B. Diagnosis of chronic inflammatory bowel disease by ultrasonography. Z Gastroenterol 1999;37:495–508.
8. Sasaki T, Kunisaki R, Kinoshita H, et al. Use of color Doppler ultrasonography for evaluating vascularity of small intestinal lesions in Crohn's disease: correlation with endoscopic and surgical macroscopic findings. Scand J Gastroenterol 2014;49:295–301. doi:10.3109/00365521.2013.871744
9. Wu S, Zeng L, Li W, et al. The value of multi-modes of ultrasound in evaluating segmental mucosal healing in patients with Crohn's disease. Dig Liver Dis 2022;54:763–770. doi:10.1016/j.dld.2021.12.009
10. Papa A, Scaldaferri F, Danese S, et al. Vascular involvement in inflammatory bowel disease: pathogenesis and clinical aspects. Dig Dis 2008;26:149–155. doi:10.1159/000116773
11. Danese S, Deban L. Does the mucosal microcirculation play a role in IBD? Inflamm Bowel Dis 2008;14 Suppl 2:S125-S126. doi:10.1002/ibd.20716
12. Pousa ID, Maté J, Gisbert JP. Angiogenesis in inflammatory bowel disease. Eur J Clin Invest 2008;38:73–81. doi:10.1111/j.1365-2362.2007.01914.x
13. Helwig U, Fischer I, Hammer L, et al. Transmural Response and Transmural Healing Defined by Intestinal Ultrasound: New Potential Therapeutic Targets? J Crohns Colitis 2022;16:57–67. doi:10.1093/ecco-jcc/jjab106
14. Maaser C, Petersen F, Helwig U, et al. Intestinal ultrasound for monitoring therapeutic response in patients with ulcerative colitis: results from the TRUST&UC study. Gut 2020;69:1629–1636. doi:10.1136/gutjnl-2019-319451
15. Parente F, Molteni M, Marino B, et al. Are colonoscopy and bowel ultrasound useful for assessing response to short-term therapy and predicting disease outcome of moderate-to-severe forms of ulcerative colitis?: a prospective study. Am J Gastroenterol 2010;105:1150–1157. doi:10.1038/ajg.2009.672
16. Ripollés T, Martínez MJ, Barrachina MM. Crohn's disease and color Doppler sonography: response to treatment and its relationship with long-term prognosis. J Clin Ultrasound 2008;36:267–272. doi:10.1002/jcu.20423
17. Ahmed R, Debian H, Fawzi M, et al. Diagnosis of Inflammatory Bowel Disease by Abdominal Ultrasound and Color Doppler Techniques. Curr Med Imaging 2021;17:1085–1093. doi:10.2174/1573405616666210104114536
18. Guan Q. A Comprehensive Review and Update on the Pathogenesis of Inflammatory Bowel Disease. J Immunol Res 2019;2019:7247238. doi:10.1155/2019/7247238
19. Dickson K, Malitan H, Lehmann C. Imaging of the Intestinal Microcirculation during Acute and Chronic Inflammation. Biology (Basel) 2020;9:418. doi:10.3390/biology9120418
20. Puca P, Del Vecchio LE, Ainora ME, Gasbarrini A, Scaldaferri F, Zocco MA. Role of Multiparametric Intestinal Ultrasound in the Evaluation of Response to Biologic Therapy in Adults with Crohn's Disease. Diagnostics (Basel) 2022;12:1991. doi:10.3390/diagnostics12081991
21. Pecere S, Holleran G, Ainora ME, et al. Usefulness of contrast-enhanced ultrasound (CEUS) in Inflammatory Bowel Disease (IBD). Dig Liver Dis 2018;50:761-767. doi:10.1016/j.dld.2018.03.023
22. Laterza L, Ainora ME, Garcovich M, et al. Bowel contrast-enhanced ultrasound perfusion imaging in the evaluation of Crohn's disease patients undergoing anti-TNFα therapy. Dig Liver Dis 2021;53:729-737. doi:10.1016/j.dld.2020.08.005
23. Hu C, Feng Y, Huang P, Jin J. Adverse reactions after the use of SonoVue contrast agent: Characteristics and nursing care experience. Medicine (Baltimore) 2019;98:e17745. doi:10.1097/MD.0000000000017745
24. Zhao C, Wang Q, Wang M, et al. Ultra-microangiography in evaluating the disease activity of rheumatoid arthritis and enhancing the efficacy of ultrasonography: A preliminary study. Eur J Radiol 2021;137:109567. doi:10.1016/j.ejrad.2021.109567
25. Chen C, Liu S, Zhao C, et al. Activity of keloids evaluated by multimodal photoacoustic/ultrasonic imaging system. Photoacoustics 2021;24:100302. doi:10.1016/j.pacs.2021.100302
26. Montaldo G, Tanter M, Bercoff J, Benech N, Fink M. Coherent plane-wave compounding for very high frame rate ultrasonography and transient elastography. IEEE Trans Ultrason Ferroelectr Freq Control 2009;56:489–506. doi:10.1109/TUFFC.2009.1067

27. Koutroumpakis E, Katsanos KH. Implementation of the simple endoscopic sctivity score in crohn´s disease. Saudi J Gastroenterol 2016;22:183-191. doi:10.4103/1319-3767.182455
28. Paine ER. Colonoscopic evaluation in ulcerative colitis, Gastroenterol Rep (Oxf) 2014;2:161-168. doi:10.1093/gastro/gou028
29. Xiaoguo Song NX. Technical White Paper, Ultra Micro Angiography. 2022.
30. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. Gastroenterology 2021;160:1570–1583. doi:10.1053/j.gastro.2020.12.031
31. Allocca M, Fiorino G, Bonovas S, et al. Accuracy of Humanitas Ultrasound Criteria in Assessing Disease Activity and Severity in Ulcerative Colitis: A Prospective Study. J Crohns Colitis 2018;12:1385–1391. doi:10.1093/ecco-jcc/jjy107
32. Christian M, Giovanni M, Torsten K, Mariangela A. Ultrasonography in inflammatory bowel disease - So far we are? United European Gastroenterol J 2022;10:225–232. doi:10.1002/ueg2.12196
33. Tews HC, Kandulski A, Schmid S, et al. Contrast enhanced ultrasonography (CEUS) a novel tool to detect intestinal epithelial barrier dysfunction in severe COVID-19 disease. Clin Hemorheol Microcirc 2022;81:177-190. doi:10.3233/CH-221407
34. Pausch AM, Kammerer S, Weber F, et al. Parametric Imaging of Contrast-Enhanced Ultrasound (CEUS) for the Evaluation of Acute Gastrointestinal Graft-Versus-Host Disease. Cells 2021;10:1092. doi:10.3390/cells10051092