

# STEADY-STATE GADOFOSVESET-ENHANCED DARK LUMEN MR-ENTEROGRAPHY

## MR-ENTEROGRAFIE S VYUŽITÍM USTÁLENÉ FÁZE INTRAVASKULÁRNÍ DISTRIBUCE GADOFOSFESETU

original article

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### SUMMARY

Ferda J, Mirka H, Koželuhová J, Kastner J, Baxa J, Ferdová E, Daum O, Třeška V, Kreuzberg B. Steady-state gadofosveset-enhanced dark lumen MR-enterography

**Aim.** To evaluate the feasibility dark lumen MR enterography (MRE) employing the gadofosveset-enhanced steady-state phase in the assessments of Crohn's disease (CD) activity.

**Method.** 50 patients with proved CD (28 pt. with CD activity index 150 and more) underwent MRE after intravenous administration of the blood-pool agent gadofosveset. MRE was performed after oral bowel preparation with 2.5% mannitol. Gradient echo T1 weighted images were obtained without intravenous contrast application, than in first-pass dynamic phase after application of gadofosveset in arterial, early-portal and late-portal phases. Additional images were performed after ten minutes after actual beginning of the intravenous injection during blood-pool steady-state distribution of gadofosveset. If the bowel wall enhancement was occurred, the lasting and the changes of the enhancement pattern through all phases were evaluated.

**Results.** Lasting 10 minutes and more, the layered retained enhancement was detected in 26 of 28 patients. Only in 2 of cases with CDAI more than 150, homogeneous bowel wall enhancement was present on delayed images. The sensitivity of the layered retained enhancement as a sign of CD activity was 92.9% (26/28); specificity was 95.5% (21/22) respectively.

**Conclusion.** Thanks to its blood-pool distribution, gadofosveset could be used as the targeting contrast agent of the hypervascularized inflammatory tissue in patients with

### SOUHRN

Ferda J, Mirka H, Koželuhová J, Kastner J, Baxa J, Ferdová E, Daum O, Třeška V, Kreuzberg B. MR-enterografie s využitím ustálené fáze intravaskulární distribuce gadofosfesetu

**Cíl.** Zhodnotit využití ustálené fáze distribuce gadofosvesetu v zobrazení activity Crohnovy nemoci při MR-enterografii.

**Metoda.** Padesát nemocných s ověřenou Crohnovou nemocí (28 nemocných s aktivní nemocí CDAI 150 a více) podstoupilo MR-enterografii (MRE) s aplikací intravaskulární kontrastní látky gadofosvesetu intravenózně. MRE byla provedena po perorální přípravě 2,5% manitolem. Bylo provedeno zobrazení pomocí T1 vážených obrazů gradientního echa bez podání kontrastní látky, poté po intravenózní aplikaci gadofosvesetu v arteriální, časně portální a pozdní portální fázi. Další série zobrazení byla provedena s odstupem 10 minut od aktuálního začátku aplikace gadofosvesetu. Pokud byla přítomna opacifikace střevní stěny, bylo posuzování trvání a změny vzorce nasycení střevní stěny v průběhu fází zobrazení.

**Výsledky.** U 26 z 28 nemocných s aktivní Crohnovou nemocí přetrvávalo vrstvené syčení kontrastní látkou I po 10 minutách od aktuálního začátku aplikace kontrastní látky, jen u dvou nemocných a aktivní Crohnovou nemocí bylo syčení stěny homogenní. Sensitivita vrstveného syčení přetrvávající 10 minut byla pro určení aktivity Crohnovy nemoci 92.9% (26/28); specifita 95.5% (21/22).

**Závěr.** Díky své intravaskulární distribuci může být gadofosveset využit jako látka cíleně zobrazující hypervaskularizovanou zánetlivou tkáň u Crohnovy nemoci. Vrstvené nasycení stěny střevní trvající 10 a více minut

active Crohn disease. Layered bowel wall enhancement remained more than 10 minutes was well correlated with clinical sign of the CD activity

**Key words:** MR-enterography, Crohn's disease, blood-pool contrast agent, gadofosveset.

dobře koreluje se známkami aktivity Crohnovy nemoci.

**Klíčová slova:** MR-enterografie, Crohnova nemoc, blood-pool kontrastní látka, gadofosveset.

## INTRODUCTION

The last decade has seen important advances in imaging of the bowel, with the advent of assessments using multidetector-row computed tomography (MDCT) and magnetic resonance imaging (MRI) (1–4). The advances in MRI have been driven by the development of new fast imaging sequences and oral bowel preparation. MR-enterography is an emerging technique for small bowel imaging and it was introduced to overcome the individual limitations with duodenum intubation using an oral preparation (5–8). Crohn's disease (CD) has become one of the most frequent indications of small bowel imaging using MRI. Since the evaluation of Crohn's disease activity might have a major influence on therapy strategies, recently used imaging methods were introduced into routine clinical practice. The enhancement of the granulomatous tissue in an affected bowel wall was considered to be an important finding in patients with active CD (9, 10). Being retained within the blood vessels, the new blood-pool contrast agent gadofosveset is being introduced as a new agent usable during contrast enhanced MR-angiography in the dynamic and also in the delayed blood-pool specific phases (11–13). The aim of our study was to assess feasibility of gadofosveset in imaging of hypervascularized granulomatous tissue specific for CD. This paper reviews one center's initial experience with gadofosveset-enhanced MR-enterography in patients with Crohn's disease. The efficacy and safety of the gadofosveset-enhanced MR-angiography has been confirmed by multicentric studies (14), but no reports about its use in bowel imaging are known to the authors.

## MATERIAL AND METHODS

### Subjects

The study protocol was approved by the local ethic committee; all patients gave their written informed consent. MR-enterography with intravenous application of the gadofosveset was performed in 50 consecutive patients (28 males, 22 females, mean age 34.5 years) with known Crohn's disease. Patients

had been referred for MRE between November 2006 and June 2007. 12 patients underwent previous ileocaecal resection. Patients were referred to our department from one gastroenterologist specializing in Crohn's disease. All patients had previously undergone detailed clinical examination including evaluation of the Crohn's disease activity index (CDAI).

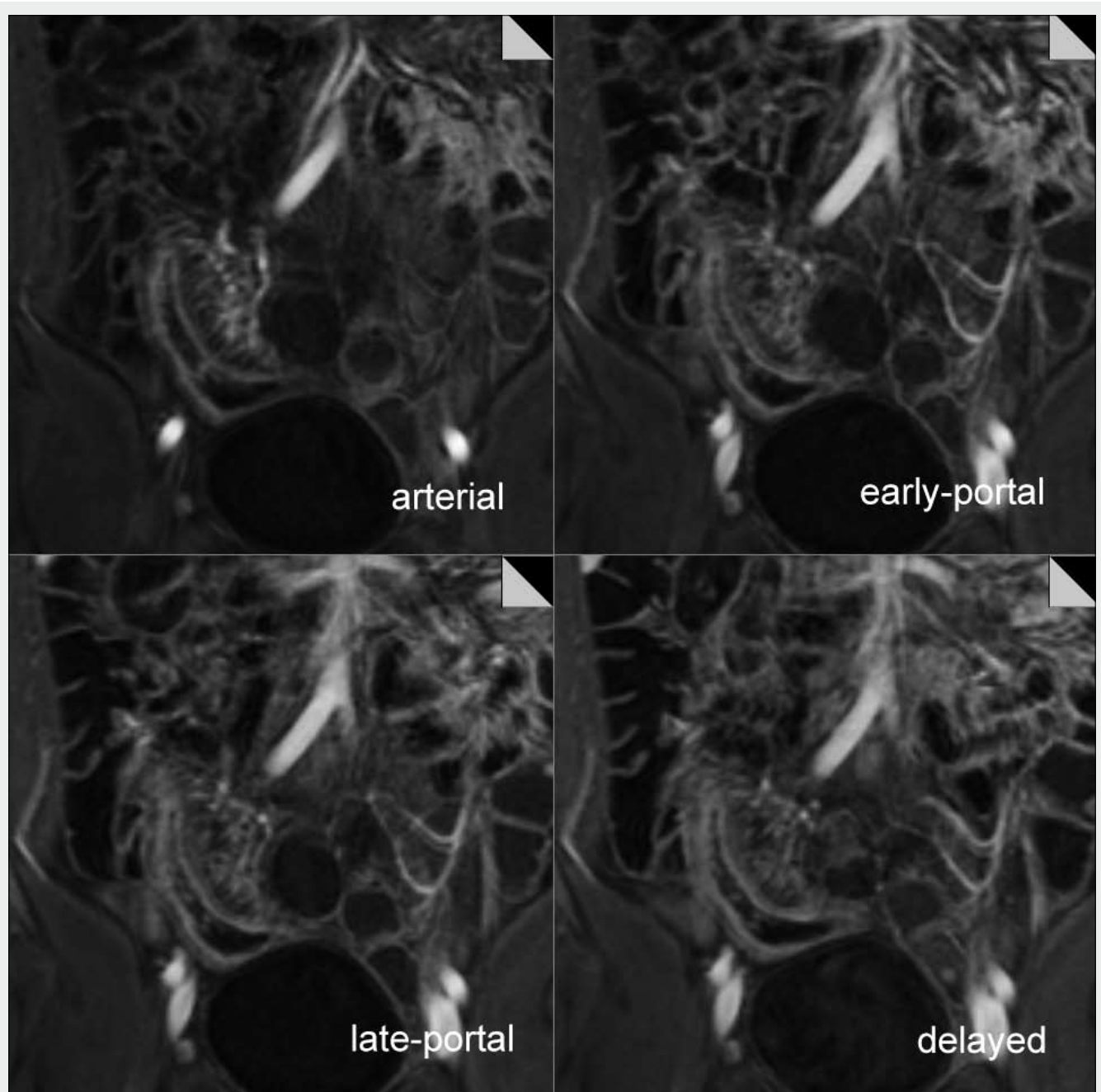
### Patient preparation

Patients fasted the night before the examination. The bowel preparation was given by slow, fractional drinking of a 1500–2000 ml of 2.5% mannitol water solution within 60–90 minutes. This preparation distended bowel loops and filled the whole extension of small loops and also the large bowel in most of cases. Immediately before data acquisition, the antecubital vein was cannulated and 20 mg of hyoscine butylbromid (Buscopan, Boehringer Ingelheim, Germany) was administered intravenously to reduce peristaltic motion of the bowel and to facilitate the distension of loops.

### Imaging protocol

All examinations were performed with 1.5 T equipment (Magnetom Avanto TIM 76 × 18, Siemens, Erlangen, Germany). An abdominal phase array six-element-coil was used in all patients. The patient was positioned in the magnet in head first supine position. Initial bright lumen images were made while the breath was held in coronal and sagittal orientation using steady-state free precession sequences (trueFISP, TR 5.1 ms; TE 2.6 ms; TA 1.28 s per image, matrix 312 × 512; PAT accelerating factor 2, adapted number of images). Then first non-enhanced dark lumen images were performed in coronal orientation, 3D spoiled gradient echo images (FLASH – fast low angle single shot in modification VIBE – volume interpolation breath hold examination: TR 3.3 ms; TE 1.4 ms; acquisition time 22.08 s; FA 26 gr.; matrix 231 × 256; PAT accelerating factor 2; 72 images) with spectral fat suppression were used.

After non-enhanced images, triple acquisition of the first-pass dynamic contrast enhanced images was performed in



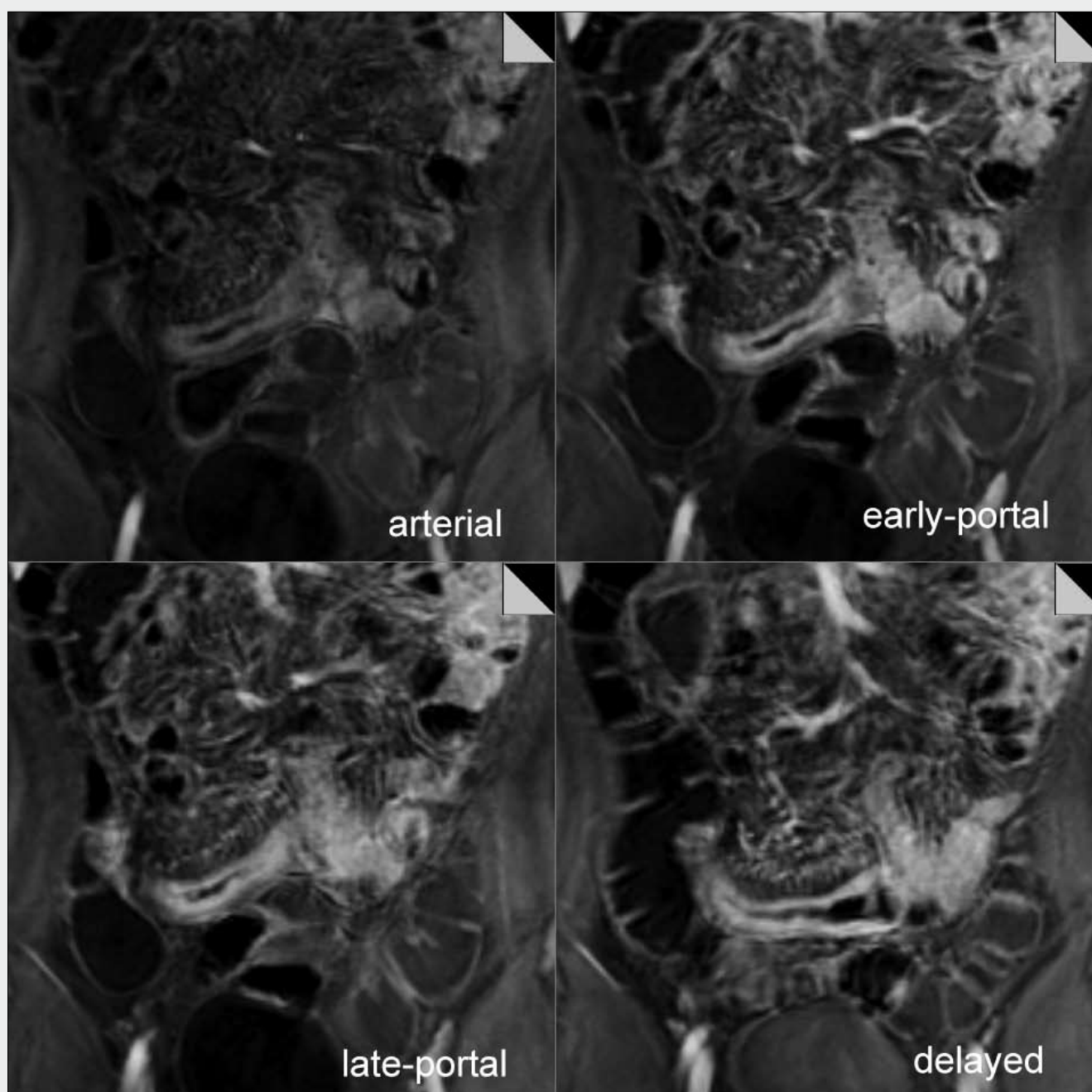
▲ Obr. 1

**Fig. 1. Comparison of the first-pass dynamic imaging in arterial, early-portal, late-portal and delayed (gadofosveset-steady-state) phases of the terminal ileum affected by active Crohn's disease. The stratification of the thin enhanced layer of the mucosa and edematous sub-mucosa lasted during all phases.**

**Obr. 1. Porovnání dynamického zobrazení v arteriální, časně portální a pozdní portální fáze s pozdní fází (gadofosveset-steady-state) fáze v oblasti terminální kličky ilea postiženého aktivní Crohnovou nemocí. Vrstvení nasycené mukózní vrstvy a submukózního edému přetrvává přes všechny fáze zobrazení.**

coronal orientation with the same parameters as mentioned above. The gadofosveset trisodium (Vasovist, Bayer Schering Pharma, Berlin, Germany) was administered with the dose 0.12 ml/kg with flow rate 2 ml/s using a power injector. The injection was finished by a saline flush of 50 ml. The timing of the acquisition was 20 s after the actual beginning of the contrast application in the arterial phase, followed by the early- and late-portal images, each with a delay of 10 s after the end of the previous acquisition. Dynamic data acquisition

in coronal orientation was followed by the transversal images covering the whole abdominal cavity in two data acquisitions; parameters of the sequence were the same as in coronal images. The last image data set was performed 10 minutes after the end of dynamic phase data acquisition in the same orientation as during the dynamic phase. The whole imaging protocol took 20 minutes. The presence of nausea, vomiting or severe diarrhea was recorded to evaluate the tolerance of the procedure.



▲ Obr. 2

**Fig. 2. Comparison of the first-pass dynamic imaging in arterial, early-portal, late-portal and delayed (gadofosveset-steady-state) phases of the terminal ileum affected by active Crohn's disease – the same patient as shown in figure 1 six months later during a new relapse of Crohn's disease activity. The stratification of the enhanced layer reaches mucosa and sub-mucosa; only a discrete hair-like layer of the edema is present. The differentiation of the layers is enabled during all phases.**

**Obr. 2. Porovnání dynamického zobrazení v arteriální, časně portální a pozdní portální fázi s pozdní fází (gadofosveset-steady-state) fáze v oblasti terminální kličky ilea postiženého aktivní Crohnovou nemocí – stejný nemocný jako na obrázku 1 o šest měsíců později v dalším relapsu aktivity Crohnovy nemoci. Vrstvení nasycené mukózní vrstvy a submukózní vrstvy, jen vlasovitá vrstvička edému je patrna, diferenciace vrstev přetrvává přes všechny fáze zobrazení.**

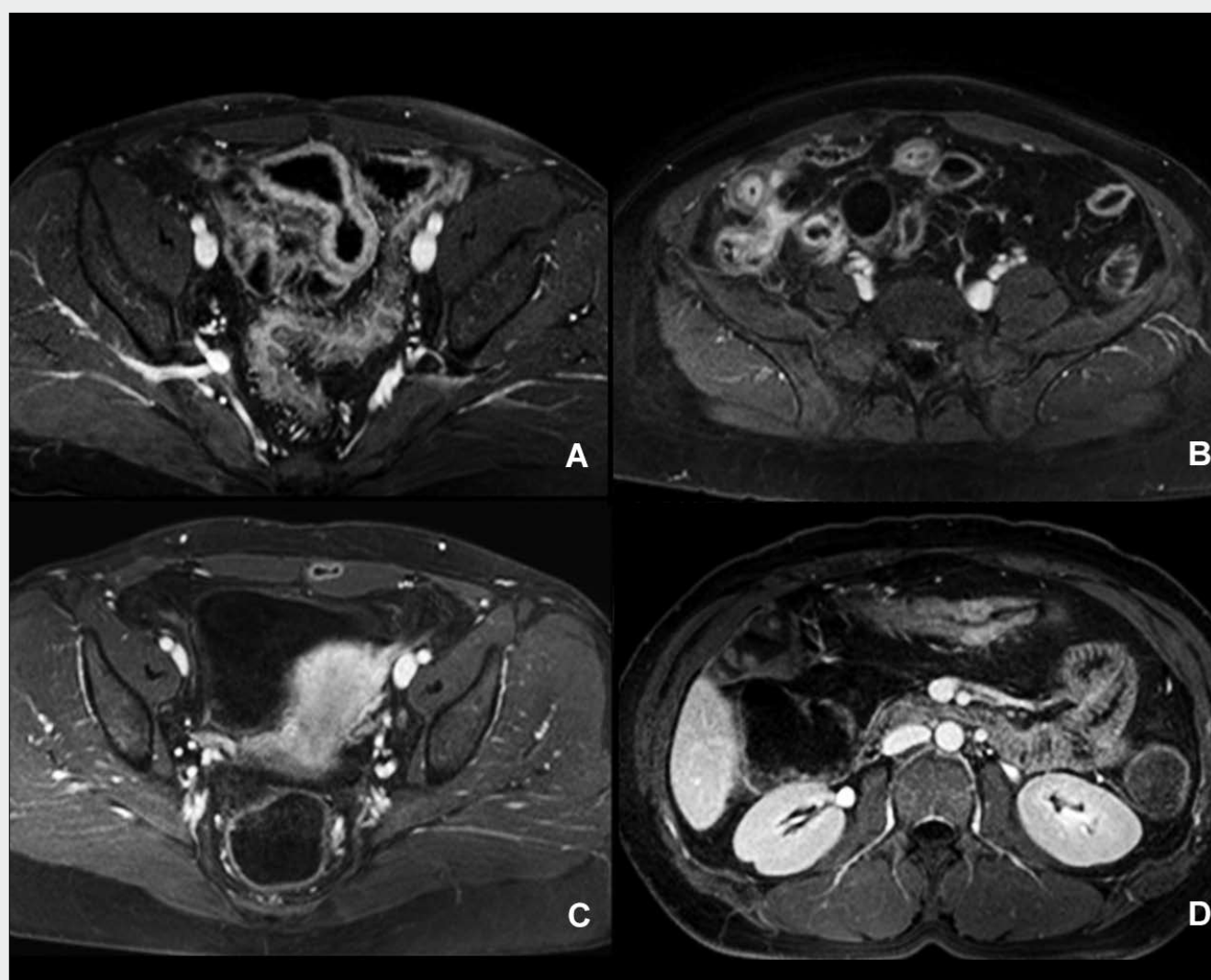
## Image analysis

The four image sets (arterial, early-portal, late-portal and delayed) were compared and the presence of the retained enhancement was evaluated. The enhancement in delayed images was compared with clinical assessment of the CD activity using the Crohn's disease activity index (CDAI) according to the criteria of Best et al. (15); values above 150 signal active disease.

## RESULTS

MRE examination was well tolerated by all patients; no undesirable effects were noted. No clinically significant side effects occurred during the examination, only nausea in two patients during oral preparation. Retained in the affected bowel during the delayed phase, sub-mucosal or mucosal enhancement combined with a hypo-intense layer of the mural edema





▲ Obr. 3

**Fig. 3. Different findings of active Crohn's disease during the delayed (gadofosveset-steady-state) phase.** A – cobblestoning in the ileum, enhanced mucosa with edematous sub-mucosa in sigmoid; B – multiple affected loops with enhanced entero-enteral fistulae; C – enhanced wall of the fistula in the left straight abdominal muscle; D – trans-mural micro-fistulae of the transverse colon; note the normal enhancement of the jejunum mucosa.

**Obr. 3. Různé nálezy aktivní Crohnovy nemoci v pozdní fázi (gadofosveset-steady-state) MR-enterografie.** A – reliéf dlažebních kostek v ileu, nasycení mukózy edém submukózy sigmatu; B – mnohočetné postižení kliček se sytícími se entero-enterálními píštělemi; C – nasycení stěny píštěle v přímém svalu břišním; D – transmurální mikrofistule příčného tračníku, za povšimnutí stojí normální syčení mukózy jejunu

was found in 26 patients with CDAI 150 and more, additional finding of the enhancement in the wall of the fistulae or in the abscess membrane in 9 of these 26 patients. Slightly increased homogeneous intensity of the whole bowel wall was found in 2 patients with CDAI more than 150. No bowel enhancement was found in 21 patients with clinically non-active disease; only one case of the layered enhancement occurred among the non-active patients. The sensitivity of the layered retained enhancement as a sign of CD activity was 92.9% (26/28); specificity was 95.5% (21/22) respectively.

## DISCUSSION

Gadofosveset trisodium (Vasovist, Bayer Schering Pharma, Berlin, Germany) originally named MS-325 (11–20) was introduced during 2006 in clinical use in European Union

countries, but it is still not approved in the United States. The potential of gadofosveset advanced the contrast enhanced MRA (12, 16). Retained within the blood-pool compartment (11), gadofosveset allows imaging of the vessels during the equilibrium phase at high resolution without the constraints of timing (11, 12, 16). Due to its superior relaxivity (12, 16, 17), gadofosveset offers improved first-pass imaging.

All dynamic techniques using spoiled gradient echo sequences during holding of the breath, including MRE, exploited the first-pass approach (2–4, 9, 10). If the conventional extracellular agent is used, the agent escapes within a few minutes into the extracellular extravascular space and occupies it (11). The important changes, such as enhanced hypervascularized layer, in the bowel wall could disappear (10). The conventional contrast could be accumulated in edematous tissue and also during the delayed phase could enhance fibrous tissue by the same principle as in scar imaging of the

myocardial infarction. These facts rule the primary role in the problems of hypervascularized tissue imaging several minutes after the actual beginning of the conventional extracellular contrast injection.

After contrast administration, a steady-state in gadofosveset kinetics is reached after about three minutes (11, 12, 17). Due to the slow clearance from the intravascular pool, imaging of the steady state is enabled for about one hour after contrast injection (16). The prolongation of the gadofosveset intravascular retention is the consequence of reversible binding to plasma albumin. The same binding also leads to increased relaxivity of the albumin-bound complex in comparison to the unbound state (17). The T1 shortening achieved with gadofosveset is highly effective during first-pass dynamic imaging and also makes it possible to reduce the gadolinium dosage by two to three times lower than that of conventional gadolinium contrast agents (11–17).

Contrast enhanced dark lumen MRE is typically based on three-dimensional radiofrequency spoiled gradient echo sequences (1–10). Multiple studies have suggested that the layered patterns of the enhancement on T1-weighted images after intravenous gadolinium contrast application are specific for active Crohn's disease (9, 10). With conventional contrast agents, the contrast achievable resolution is limited by the time that is available for imaging as the concentration in the vessels of the hypervascularized granulation tissue declines within a few minutes. First-pass imaging during the arterial, early-portal and late-portal phases could be performed in a manner similar to that used with conventional contrast materials. A higher flip angle than the Ernst angle, about 35°, is recommended by more studies, but in our institution we use only a slightly increased angle of 26°. The value of a flip angle was selected according to our own experience with image quality of performed gadofosveset-enhanced MR-angiographies (16). MRE with gadofosveset offers the possibility of obtaining steady-state images up to 1 hour after contrast injection, which allows for acquisition of high-resolution images, especially in the affected regions in proper planes.

The following imaging problems could occur during gadofosveset delayed enhanced MRE: problems with decreased intensity of the images in the steady-state phase and theoretically problems with reduced albumin-binding in protein loss in patients with pronounced symptoms of active CD. The reduction of the signal intensity of the steady state imaging with gadofosveset is explained by the decrease of the albumin-bound complex concentration (11, 12, 16). The problem of the false positive layered enhancement in non-active disease could occur if the fatty tissue is present in the middle bowel wall layer (10).

The inflammatory changes were studied using gadofosveset. Gadofosveset enhanced MRI appeared to be a sensitive tool for detection of renal and vascular-wall inflammation in an animal model of systemic lupus erythematosus (18). Other possible novel indications could be in the assessment of the hyper-vascular tumors or in the assessment of the metastatic involved lymph nodes (19) or myocardial perfusion and viability evaluation (20). The first reports about these new appli-

cations were performed. Our own experience with gadofosveset-enhanced MRE confirmed the ability of the inflammatory granulomatous-tissue specific imaging with this substance.

Recently, the use of CT-enteroclysis or CT-enterography is of interest for the evaluation of patients with small-bowel diseases. However the disadvantages of the CT methods are exposure of ionizing radiation and disability of functional imaging (3).

Recent studies have reported that magnetic resonance imaging is not able to detect aphthoid ulcers in comparison to the conventional enteroclysis; this limitation is not overcome using blood-pool contrast agent (6). But due to the trapped contrast material in hypervascularized tissue in the bowel, fistulae, abscess membranes and affected lymph nodes, and also in hypertrophic vessels (vasa recta) in the mesentery, the imaging with blood-pool contrast might have multiple advantages in restaging of CD activity in chronic patients. The advantages of the spoiled gradient echo images over steady-state free precession sequences were proved and pronounce the effectiveness of the gadofosveset-enhanced images, especially when high resolution images are used.

Stenosis of the small intestine occurs frequently in CD and results from the inflammatory changes, edema, fibrosis and spastic contraction (9, 10). The differential diagnosis between fibrotic strictures and stenosis due to the active inflammation is essential in treatment planning. Edematous changes designate patients for medical therapy, but the presence of the fibrous stricture indicates treatment by surgical resection. Delayed phase images might help to determine patients suitable for conservative or surgical therapy.

The similar appearance of fibrotic changes in the mesentery and hypertrophy of the vasa recta so-called "comb sign" is a limitation of the steady-state free precession sequences and also delayed images after application of the conventional gadolinium extracellular contrast agents (4–6). Blood-pool agents might overcome these limitations. Uptake of the contrast agent in lymph nodes allowing detection of the smallest nodes is observed also during the blood-pool specific phase of the gadofosveset.

There are some limitations to our study. The behavior of the conventional contrast was not assessed in the same patients; previously used protocols didn't contain the delayed coronal images in our institution, but the observation that contrast enhancement was disappearing and made weaker was the reason for using the blood-pool agent.

## CONCLUSION

Gadofosveset might have potential as a contrast agent targeting the hypervascularized inflammatory tissue in CD activity assessments. The lasting enhancement of the hypervascularized tissue of the bowel wall enables prolonging the period of effective scanning in CD. The enlarged acquisition window makes it possible to obtain high resolution images of the affected region.

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