Assessing synovitis based on dynamic gadolinium-enhanced MRI and EULAR-OMERACT scores of the wrist in patients with rheumatoid arthritis

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Abstract

Objective

The objective of this study was to correlate dynamic contrast-enhanced MRI (DCE-MRI) perfusion parameters and conventional MRI scored with RAMRIS acquired from the wrists of patients with rheumatoid arthritis (RA).

Methods

Fifty-nine RA patients had conventional and DCE-MRI of the wrist using a low-field 0.2T ESAOTE extremity scanner. Synovitis, bone oedema and bone erosions were assessed using RAMRIS. DCE-MRI data were analysed using dedicated software Dynamika resulting in a set of perfusion parameters.

Results

RAMRIS synovitis score and the number of enhancing pixels in DCE-MRI images have shown significant correlation. In this study, the parameters reflecting the dynamics of MRI signal enhancement (maximum enhancement, initial enhancement rate and the time of onset of enhancement) did not correlate with RAMRIS synovitis score, with bone oedema and with bone erosions scores.

Conclusion

One-way analysis of variance leads to conclusions consistent with the correlation analysis. There were cases of inflammation seen in axial images of a 3D T1-weighed gradient echo sequence not reflected in the perfusion data.

Key words

MRI, dynamic contrast-enhanced MRI (DCE-MRI), RAMRIS, synovitis, wrist

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Introduction

The early diagnosis of rheumatoid arthritis (RA) and accurate monitoring of disease activity are essential for efficient anti-arthritic therapy. Among affected joints, hand is one of the earliest sites to be involved in RA. Among traditional methods for assessment of RA are radiography, Doppler ultrasonography and clinical examination. The potential of each one of these methods is limited to some extent. For example, the diagnosis of early symptoms of RA *e.g.* synovitis or bone oedema is not possible with radiography, while there is no consensus of the type and number of joints to examine with Doppler ultrasonography.

In numerous studies magnetic resonance imaging (MRI) was used to examine wrist joints in RA. These studies have proved a predictive value of MRI findings (synovitis, bone oedema, and bone erosions) in the wrist joint with respect to destructive bone damage. Recently much effort has been made by OMERACT group to develop an MRI-based RA scoring system (RAMRIS) (1). Since its recommendation it has been shown that RAMRIS is reproducible and relatively sensitive to changes due to therapy or disease progress (2). Although RAMRIS certainly outperforms other common methods of assessing RA, some of its limitations are being recognised. Currently RAMRIS scoring is not supported by any dedicated computer-aided diagnosis applications. For this reason RAMRIS scoring is time-consuming since it involves retrieving from picture databases and examining a few different MRI sequences. More-over it requires analysing and quantifying multiple, frequently small details in three dimensions (*e.g.* erosions and bone oedema in 15 bones). Further, RAMRIS is in fact a semi-quantitative scoring system (*e.g.* the actual volumes of erosions or oedema are not reported), which can be a source of a substantial inter-operator variability (2). Some grade ranges (*e.g.* synovitis score) may also seem too rigid, especially for quantifying early changes.

Recently there have been some efforts to develop quantitative methods of assessing RA-related changes and comparing them with RAMRIS outcomes. In a study of Crowlay *et al.* (3) MRI images of the wrist were acquired on a 3T scanner. Bone erosions and oedema were outlined interactively in slices of 3D MRI images. Then the volume of erosions and oedema was calculated and compared with RAMRIS scores. The authors reported good correlation between RAMRIS and manual erosion measures and mild correlation between RAMRIS and manual oedema measures.

Dynamic contrast enhancement MRI (DCE-MRI) has been proposed for assessment of the inflamed synovium (4, 5). The core of DCE-MRI is sequential acquisition of rapid MRI sequences before and during the injection of a contrast agent. Then, the acquired data are analysed to classify the perfusion patterns of image voxels. The potential of DCE-MRI for quantifying synovitis was assessed in a study of Cimmino *et al.* (6). In this study MRI was performed with a low-field (0.2T), extremity-dedicated scanner. After an injection of a contrast agent, 20 consecutive fast spin-echo images of 3 slices of the wrist were obtained every 18 seconds. Based on the analysis of the signal enhancement curves, the authors have introduced a few parameters, which were shown to discriminate between active and inactive RA patients. The argument for using low-field scanners in RA diagnosis are the relatively low cost of the device, low cost of an MRI examination and higher patient's' comfort. Although the dedicated extremity MRI images are characterised by a lower signal-to-noise ratio and consequently a lower image quality, while the acquisition time is longer, it appears that RA scores based on high- and low-field MRI scanners are correlated (7).

In an attempt to support and standardise the assessment of synovitis inflammation based on DCE-MRI data acquired with low-field strength extremity MRI scanners, a dedicated software (Dynamika, http://www.imageanalysis.org.uk/) has been recently developed (8). In a study of Boesen *et al.* (9) the outcome of Dynamika and RAMRIS were compared. It was reported that RAM-

RIS synovitis and bone oedema scores significantly correlate with parameters derived from the perfusion data. Although it was concluded in the study that the proposed approach is promising, further research was recommended to identify the sources of possible discrepancies between RAMRIS and DCE-MRI based analysis.

For this purpose the present study compares assessment of RA based on DCE-MRI and conventional MRI. We observed significant correlation between RAMRIS synovitis grades and the number of enhancing pixels extracted from the perfusion data in accordance with findings reported in Boesen *et al*. (9). However, there are several parameters where the correlation was poor. In the present study, in contrast to the study of Boesen *et al*. (9), bone oedema scores did not correlate with the perfusion parameters. Several possible improvements of the DCE-MRI-based assessment of RA are suggested.

Materials and methods

Materials

Forty-six consecutive RA patients of the Department of Rheumatology, Cracow University Hospital participated in the study. All patients had pain in at least one wrist and were imaged with DCE-MRI as a part of the diagnostic procedure. None of the patients had contraindications for the contrast-enhanced MRI. The age of the patients was in the range from 23 to 74 years: the mean (standard deviation) of the age was 47 (13) years. All patients had MRI of at least one wrist. If pain was reported in both wrists, MRI of both wrists was performed in two different days. Static and dynamic MRI were performed in all 46 patients, using a 0.2T musculoskeletal extremity E-scanner (ESAOTE Ltd, Genova, Italy). Totally 59 study cases were collected. The patients were examined in supine position in accordance with the recommendations of the manufacturer. Prior to the contrast injection, the following MRI sequences were acquired: gradient echo scout, coronal short tau inversion recovery (STIR) (pixel spacing 0.7mm and slice thickness 3.5 mm) and a coronal turbo 3D T1-weighted gradient echo (pixel spacing 0.75mm and slice thickness 0.7 mm). Then, the gadolinium contrast was injected intravenously of 0.1mmol/kg body weight (Magnevist, Bayer Schering Pharma AG, Germany) and 30 consecutive acquisitions of three pre-positioned 5-mm coronal T1-weighted gradient echo dynamic MRI images (TR/TE 60/6, FOV 180x180mm, reconstruction matrix 256x256 pixels) were performed every 10 seconds. The three coronal 5-mm DCE-MRI slices were positioned tangentially to the long axis of the radius and covered the central part of the wrist in the axial plane. Finally, the coronal 3D T1-weighted gradient echo sequence was acquired. All captured sequences were transferred to a professional DICOM viewer and further analysed.

Methods

The STIR and pre-/post-contrast T1-weighted gradient echo images were used for RAMRIS scoring of bone erosions, bone marrow oedema and synovitis. DYNAMIKA software (www.imageanalysis.org.uk, UK) was used to analyse the DCE-MRI data. Using this software, the enhancement pattern of each pixel was recognised and assigned to one of the four classes: no enhancement, persistent enhancement, plateau and wash-out, as described in detail in (8). Additional parameters such as initial rate of enhancement (IRE), maximum enhancement (ME) and time of onset of enhancement (Tonset) were also extracted from the data. Note that the signal enhancement in the dynamic MRI examination, analysed in detail in DYNAMIKA, is expected to occur primarily in the inflamed synovium regions.

Among other parameters, DYNAMIKA reports the number of enhancing pixels in the field of view (FOV). On the other hand, RAMRIS synovitis is scored in three separate regions (the distal radioulnar joint - DRUJ, radiocarpal joint - RCJ and intercarpal-carpometacarpal joint - IC-CMCJ). Thus, the RAMRIS synovitis scores of each patient were summed to form a single number in the range from 0 to 9 with unit step, referred to as total synovitis score (TSS) and correlated with the outcome of DYNAMIKA. Similar approach was adopted to define a total oedema score (TOS) and a total bone erosion score (TBES). The three parameters, TSS, TOS and TBES were correlated with the perfusion parameters returned by DYNAMIKA.

Results

The RAMRIS synovitis scores found for the group of all examined patients are summarised in Table I for the three analysed regions (DRUJ, RCJ, IC-CMCJ). The RAMRIS bone oedema and bone erosions scores are summarised in Table II and Table III, respectively for all examined bones. The results presented in the tables demonstrate the diversity of the group and the observed pathological changes. The histograms of the TSS, TOS and TBES are shown in Fig. 1. The values of the Pearson's coefficients of correlation r between perfusion parameters and TSS, TOS and TBES are shown in Table IV. In the table the coefficients of correlation, which are significant at 0.1% level are only shown. There is no correlation between RAMRIS parameters and maximal enhancement, Tonset, IRE and persistent pixels count. TBES does not correlate with any of the perfusion parameters. The strongest correlations are observed between TSS and the plateau pixels count (r=0.73). TSS is plotted against the plateau pixels count in Figure 2a. Mild linear correlation between TOS and the plateau pixels count (r=0.63) is observed mainly because

Table I. The total number of RAMRIS synovitis scores.

Region	RAMRIS synovitis scores			
	0	1	2	3
DRUJ	25	26	5	3
RCJ	16	28	11	4
IC-CMCJ	17	31	7	4

Table II. The total number of RAMRIS bone oedema scores.

Region	RAMRIS bone oedema scores			
	0	1	2	3
Base MCP total	285	5	5	-
Trapezium	52	3	2	3
Trapezoid	56	3	-	2
Capitate	55	2	3	1
Hamate	55	2	2	2
Scaphoid	47	8	1	4
Lunate	45	6	3	6
Triquetrum	53	5	1	2
Pisiform	60	-	-	1
Distal radius	57	2	1	1
Distal ulna	58	3	-	-

Table III. The total number of RAMRIS bone erosion scores.

Region	RAMRIS bone erosion scores										
	0	1	2	3	4	5	6	7	8	9	10
Base MCP total	261	32	2	-	-	-	-	-	-	-	-
Trapezium	48	5	2	1	3	-	-	-	-	-	-
Trapezoid	49	7	-	3	-	-	-	-	-	-	-
Capitate	25	25	4	5	-	-	-	-	-	-	-
Hamate	41	13	3	1	-	-	1	-	-	-	-
Scaphoid	37	12	5	3	1	-	-	1	-	-	-
Lunate	18	28	5	2	3	1	-	1	1	-	-
Triquetrum	29	28	-	2	-	-	-	-	-	-	-
Pisiform	55	2	1	1	-	-	-	-	-	-	-
Distal radius	51	4	3	1	-	-	-	-	-	-	-
Distal ulna	53	4	1	1	-	-	-	-	-	-	-

Table IV. The values of the coefficient of correlation between perfusion and RAMRIS parameters - FOV and ROI analysis.

	RAMRIS	Total pixel count	Persistent pixels count	Plateau pixels count	Washout pixels count	Maximum enhancement	IRE	Tonset
FOV	TSS	0.67	ns	0.73	0.45	ns	ns	ns
	TOS	0.52	ns	0.63	ns	ns	ns	ns
	TBES	ns	ns	ns	ns	ns	ns	ns
ROI	TSS	0.75	ns	0.77	0.62	ns	ns	ns
	TOS	0.59	ns	0.65	ns	ns	ns	ns
	TBES	0.42	ns	0.47	ns	ns	ns	ns

ns: correlation not significant (p-value >0.1%).

Table V. Mean (standard deviations) of perfusion parameters in groups characterised by different values of TSS.

TSS	0	1	2	3	≥4
Number of cases	8	9	14	13	15
ME	1.44 (0.07)	1.41 (0.14)	1.41 (0.11)	1.48 (0.22)	1.5 (0.21)
IRE	0.017 (0.008)	0.013 (0.009)	0.014 (0.007)	0.016 (0.01)	0.012 (0.007)
Tonset	153 (95)	160 (99)	159 (185)	140 (92)	104 (103)
Persistent	39 (26)	45 (26)	44 (39)	49 (32)	42 (34)
Washout	65 (60)	54 (44)	102 (64)	93 (59)	241 (156)
Plateau	68 (67)	78 (78)	126 (110)	133 (129)	546 (365)

there are a few extremely large values of TOS in the dataset (Fig. 2b). After removing the three largest TOS values the correlation between TOS and the plateau pixels count drops down to 0.25 and becomes insignificant.

It has been suggested (9) that the quality of the RA diagnosis, based on the perfusion data, supported by DYNAMIKA software can be improved if the analysis is restricted only to the regions in which synovitis is expected to occur. For this purpose a ROI tool of the DYNAMIKA software was used to manually select the regions of the analysis. A single ROI, surrounding DRUJ, RCJ and IC-CMCJ regions was selected for one of the three analysed slices in which the strongest enhancement was observed. Then, the perfusion parameters were calculated for the selected ROI and correlated with the RAMRIS-based parameters. The results of the correlation analysis are shown in Table IV. Comparing FOV and ROI-based results it can be seen that restricting perfusion analysis to a manually selected ROI increases the values of the correlation coefficient. This increase is not statistically significant in any case. The results of ROI analysis are qualitatively the same as in the case of the FOV analysis. TSS and TOS are plotted against the ROI-based plateau pixels count in Figures 2c and 2d, respectively.

Because it can be argued that RAMRIS scoring of synovitis is semi-quantitative (*i.e.* depending on the volume of enhancing synovium tissue at a given location patients are classified into classes with different RAMRIS grades assigned), TSS can be eventually considered a categorical predictor in which case ANOVA analysis can be applicable. To explore this possibility, a group of all examined patients was divided into five subgroups characterised by TSS values equal to 0, 1, 2, 3 and greater than or equal to 4. The mean and standard deviations of perfusion parameters in the groups are shown in Table V. Next, the one-way analysis of variance was conducted to test whether there are significant differences between perfusion parameters in these groups. It was found that there was no significant difference between ME, IRE, Tonset and the persistent pixels count (p-values equal to 0.48, 0.69, 0.75 and 0.97, respectively) in all groups. The hypothesis that washout and plateau pixels counts are the same in all groups was rejected (p-values less than 0.0001 in both cases). The

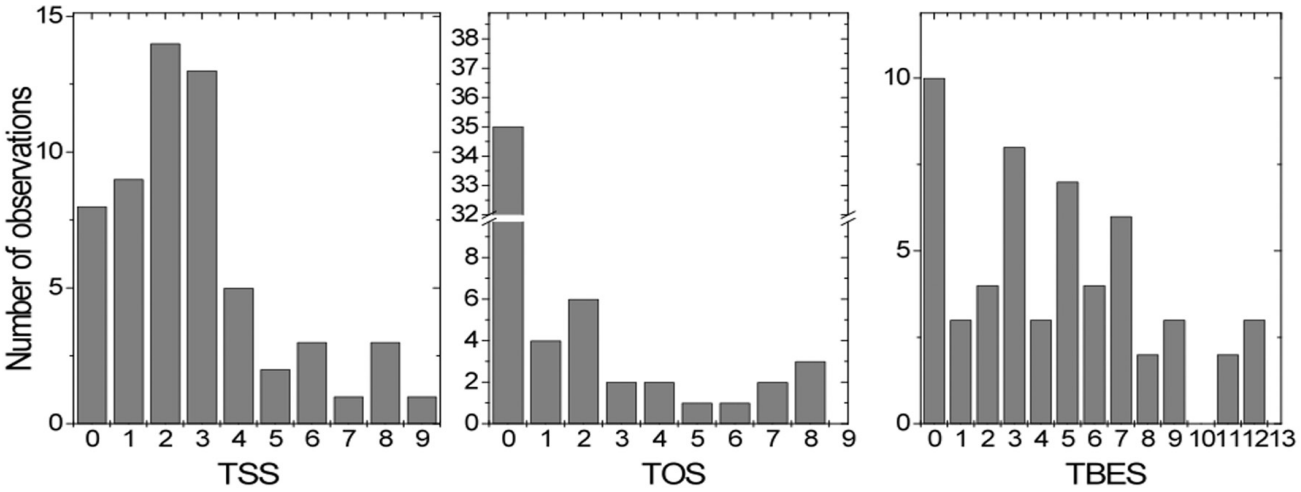

Fig. 1. The histograms of TSS (total synovitis score - left panel), TOS (total oedema score - middle panel) and TBES (total bone erosions score - right panel) values.

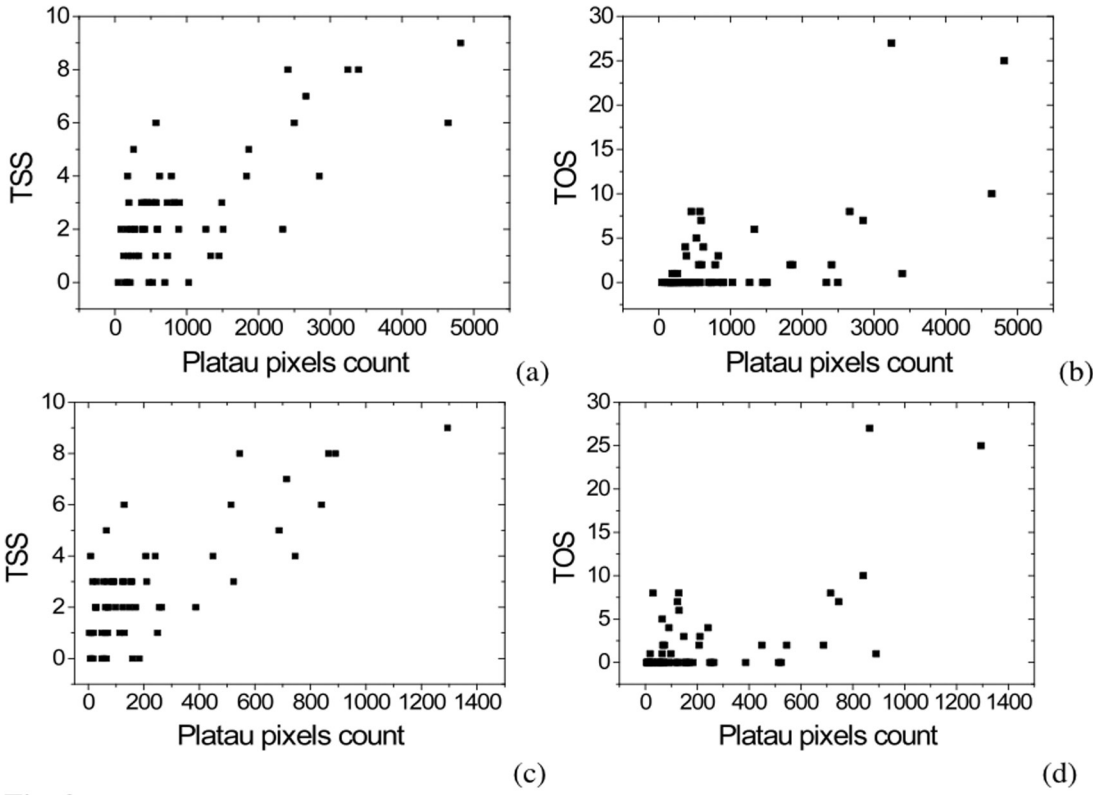

Fig. 2.
(**a**) TSS plotted against the plateau pixels count - FOV analysis.
(**b**) TOS plotted against the plateau pixels count - FOV analysis.
(**c**) TSS plotted against the plateau pixels count - ROI analysis.
(**d**) TOS plotted against the plateau pixels count - ROI analysis.

post-hoc Tuckey HSD test indicated that the washout pixels count in the group with TSS≥4 was significantly higher than in the other groups and there were no significant differences between any other pairs of groups. Similarly, the plateau pixels count in the group with TSS≥4 was significantly higher than in the other groups and there were no significant differences of the plateau pixels count between any other pairs of groups.

Discussion

This study compares the results of two methods of assessing rheumatoid arthritis: a semi-quantitative method based on RAMRIS-OMERACT recommendation and a quantitative method based on the analysis of the perfusion data. Since quite strong correlation was observed between the total synovitis score and the number of enhancing "plateau" pixels, it can be concluded that the DCE-MRI is a promising tool for assessing synovitis. Unfortunately, the results of our study indicate that the perfusion analysis does not support diagnosis of bone oedema and bone erosions. The significant correlation between the total bone oedema score and the number of enhancing pixels can be an artefact, which follows from the fact that bone oedema can be associated with synovitis.

The correlation between TSS and the enhancing pixels count is significant,

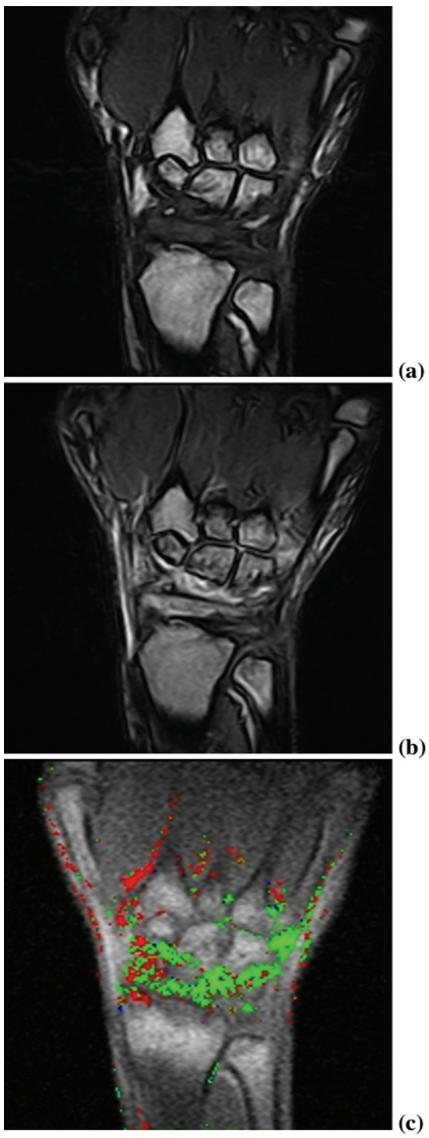

Fig. 3. Sample coronal slices of a 3D T1-weighted gradient echo sequence before (**a**) and after (**b**) contrast injection. (**c**) Enhancing regions of a DCE-MRI slice (red, green and blue pixels, depending on the enhancing pattern) showing correspond to regions of enhanced signal in (**b**).

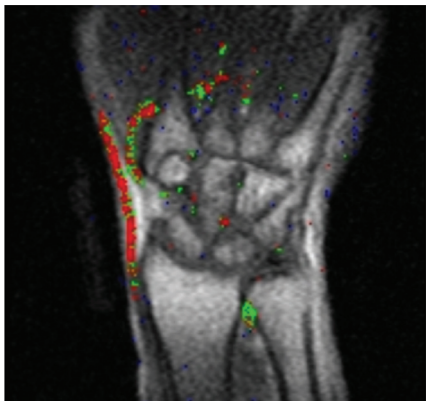

Fig. 4. Typical artefacts in perfusion images: enhancing vessels (left side - elongated structure) and noise (scattered small blue clusters).

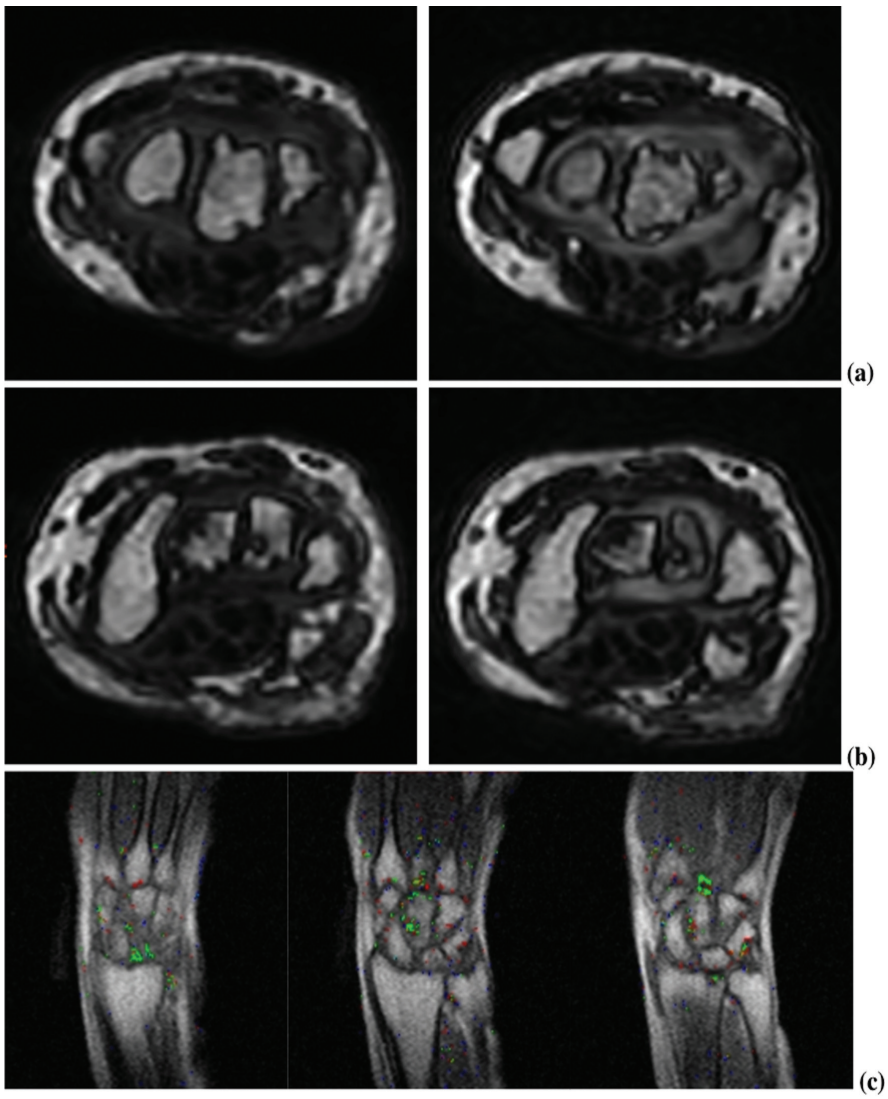

Fig. 5. (**a**), (**b**) Axial slices of a 3D T1-weighted gradient echo sequence, demonstrating relatively strong enhancement not seen in the perfusion data (**c**). Enhancement in the perfusion data is observed only in pixels marked with red, green or blue colours.

However, based on the data, it can not be concluded that the two methods of assessing synovitis are equivalent, which is expected given the conceptual differences of the methods.

In most cases the enhancement regions seen in the slices of the coronal 3D T1-weighted gradient echo sequence coincided well with the enhancement regions in the DCE-MRI slices (Fig. 3). In some cases the number of enhancing pixels was quite high, compared to low TSS value. In many of these cases the field of view contained blood vessels. Because the enhancement pattern of pixels corresponding to vessels and to inflamed synovium was the same, the number of enhancing pixels was overestimated (Fig. 3). To correct for this effect it was typically sufficient to restrict the perfusion analysis to a manually placed region of interest. An important feature of perfusion data analysis software is the possibility to correct the data for possible movements of the examined wrist between the successive acquisitions of the consecutive DCE-MRI series. Because the quality of the perfusion data images acquired with a low-field MRI scanner is inherently poor, the correction of the movement was not always optimal leading to artificially enhancing regions localised at the edges of the cross-section images of a hand. This error can be also corrected by proper selection of a region of interest. Low signal to noise ratio of the DCE-MRI

images resulted in yet another artefact - a numerous small clusters of enhancing pixels scattered over the field of view (Fig. 4). Correction of this effect is not possible without a dedicated tool. We have noticed that the scattered clusters are most frequently marked as pixels with persistent signal enhancement, which indicates an artefact. Because these pixels are likely noise artefacts, this explains the lack of correlation of the persistent pixels count with RAMRIS-related parameters. The overall effect of the artefacts seen in the DCE-MRI data is low sensitivity of the perfusion analysis to early synovitis. As demonstrated by the ANOVA results, significant changes in the number of enhancing plateau or washout pixels is seen after TSS grows over 3.

Figure 2 demonstrates several cases of high TSS and low number of enhancing pixels. The image data for such cases is presented in Figure 5. Inspection of the axial slices (Fig. 5a, b) shows that the volume of inflamed synovium is large. However, only marginal enhancement, presumably noise, is seen in coronal DCE-MRI slices (Fig. 5c). Axial slices of the 3D T1-weighted gradient echo sequence, recommended by OMERACT-RAMRIS provide the data of sufficient quality to unambiguously recognise inflamed synovial regions. On the other hand, it is difficult to detect signal enhancement when enhancing structures are overlaid on other anatomic structures and the signal to noise ratio is poor. Because only slices with the same orientation can be directly compared, the fact that different cross-section planes were used to evaluate RAMRIS scores and perfusion parameters certainly is a source of discrepancies between both methods.

To conclude, given the results of correlation analysis it appears that the perfusion analysis is a promising tool to diagnose synovitis in RA patients. This study shows that application of DCE-MRI is currently restricted due to the limited quality of imaging data obtained with low field scanners, although these data is perceived to be of sufficient quality to conduct RAMRIS based diagnosis. Among perfusion parameters only the number of enhancing pixels correlated with RAMRIS parameters. It was found that analysis based on user-selected region of interest was apparently necessary to limit the influence of artefacts on the perfusion parameters but, ultimately, no significant improvement of the correlation with RAMRIS scores was achieved. Perfusion analysis based on the entire field of view cannot be recommended without dedicated tools removing noise and movement artefacts and enhancing structures which are not related to synovitis. Because of poor quality of low-field MRI the potential of the perfusion analysis should be rather explored based on data acquired with high-field MRI scanners.

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