Disentangling the Medusa in Synovitis: TRICKS DCE Peak Fusion Images in the Assessment of Inflammatory Arthritis

Angela Atinga[1], **miny.walker1**[2], **Anish Raithatha**[3], **mdelahozpolo**[4], **ynyr**[5], **a.kinderlerer**[6], **Dimitri Amiras**[7], **and sawsan.abuflayeh1**[8]

[1]Affiliation not available
[2]Imaging Department, Imperial College Healthcare NHS Trust
[3]Imaging Department, Imperial College Healthcare NHS Trust
[4]Affiliation not available
[5]Affiliation not available
[6]Rheumatology Department, Imperial College Healthcare NHS Trust
[7]Imaging Department, Imperial College Healthcare NHS Trust
[8]Affiliation not available

ABSTRACT

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Keywords

1. Magnetic Resonance Angiography
2. Synovitis
3. Rheumatoid
4. Metacarpophalangeal Joint

Introduction/background

The inflammatory arthritides are systemic disorders that can result in long-term deformity and disability. The occurrence of severe long term sequelae in affected patients has reduced, which is attributable to earlier detection of disease and advances in treatment, with increased use of disease modifying anti-rheumatic drugs (DMARDs) and biologic agents.

Synovitis is well understood as the hallmark of rheumatoid arthritis (RA) and responsible for joint destruction.[1] Synovial angiogenesis has been proposed as one of the earliest markers of inflammatory arthritis and a critical early stage in the progression of synovitis and joint destruction.[2,3] In addition to nurturing the hyperplastic synovium, angiogenesis promotes persistence of synovial inflammation through the influx of inflammatory cells to create the disease-specific microenvironment in RA[4].[5] Some effector molecules such as tumour necrosis factor-alpha (TNF-α), vascular endothelial growth factor (VEGF) and angiopoietin 1 (Ang-1) have been identified as key elements in the development of new blood vessel formation. Inhibition of these angiogenic factors could reduce the progression of synovial hyperplasia and joint destruction.[6] Therefore, imaging identification of angiogenesis would allow early therapeutic intervention as a means of preventing joint destruction and improve the course of the disease.[7]

Magnetic Resonance Imaging (MRI) is highly sensitive in detecting the classic features of inflammatory arthritis, specifically synovitis and tendon related disease, erosions and Bone Marrow Oedema (BMO) as a precursor of erosive change.[Østergaard2005?] It is also sensitive for detection of enthesitis, one of the three key criteria (apart from dactylitis and peripheral arthritis) required to diagnose seronegative peripheral inflammatory disease.[1] Contrast enhanced MRI is routinely used in our practice for early detection of disease and in diagnostically challenging cases. It is particularly useful in the small subgroup of patients that are in clinical remission but demonstrate radiological evidence of disease[Østergaard2005].[8] Early treatment in this group confers a better outcome for patients and underpins the therapeutic strategy in inflammatory arthritides.

The synovial enhancement rate in contrast enhanced MRI has been shown to correlate with synovial volume, erosion, vascularity, capillary permeability and metabolic activity, and has been a classical marker of active disease.[9] Magnetic Resonance Angiography (MRA) sequences, such as Time-resolved Imaging of Contrast KineticS (TRICKS, GEHC, Milwaukee, WI, USA), allow detection of newly recruited vessels in the early phase of disease, prior to diffuse synovial enhancement.[3] Dynamic contrast enhancement also allows analysis of perfusion parameters, specifically, the peak or maximum enhancement. This measure has been shown to correlate with patient rated pain and the degree of synovitis on histology.[äumen2014?] When fused to a structural volumetric T1 sequence, this can provide a pictorial representation of areas of synovitis.

Utilising these techniques can prove difficult in a clinical environment, particularly as there is an increased amount of imaging for the radiographers and interpreting radiologists to process and analyse. Therefore, the utility and practicality when compared to post-contrast imaging must be evaluated. This pilot study describes our initial experience and evaluates the benefit of TRICKS magnetic resonance angiographic (MRA) imaging and peak enhancement fusion images in the assessment of synovitis at the metacarpophalangeal joints.

Methods and materials

Patient selection:

We retrospectively collected data from consecutive patients who had local institutional MR imaging to assess for synovitis over a period of 1 year (August 2015 to August 2016). Patients who did not have complete TRICKS sequences where excluded.

MRI Imaging:

Patients were positioned with the hand of interest elevated above the head on the scanning table with a small field of view coil (knee coil) applied. All imaging was acquired on a GE 3T Discovery 750 MR scanner (GEHC, Milwaukee, WI, USA).

The standard protocol included: axial and coronal T1, T2 fat-saturated (FS) and post-contrast T1 FS sequences. Dynamic contrast enhanced MRA images were acquired at the same time using the TRICKS sequence . Only a single injection of 10ml of MR contrast, Gadavist (Bayer Healthcare Pharmaceuticals Inc, Wayne NJ, USA) was required. Although a standard field of view for the TRICKS sequence was specified, this was altered in some patients due to subject size differences.

TRICKS MRI PARAMETERS	VALUE
Scan length	3 minutes 30 seconds
Field of View (FOV)	21cm
Frequency	416
Phase	256
Slice thickness	1.8mm
Repetition Time (TR)	4.6ms
Echo Time (TE)	Approximately 2ms (minimum)
Slices	40
Number of Excitations (NEX)	0.75
Bandwidth	83.33
Temporal phases	40
Flip angle	30°
Imaging options	3D, TRICKS, ZIP56, Asset

Figure 1. Summary of MR imaging parameters for the TRICKS sequence

Post-processing:

Post-processing was performed using OLEA SPHERE software (ver 2.2) as part of Vitrea 6.81 (Vital Images Inc., Minnesota, USA). The workflow was semi-automated using the OLEA workflow with a step-by-step guide in a locally designed handbook. Automated sequence identification, motion correction and automatic arterial input function steps were used. Adjustments to these steps, including manual arterial input function, were made if required.

The volumetric T1 weighted pre-contrast TRICKS images and subtracted MRA sequences were used in post processing. Image representation of the peak enhancement[10] was fused in colour with the TRICKS volumetric T1-weighted sequence and reconstructed in the coronal plane, which was the plane of acquisition. In cases where the volumetric T1 images were not available, the peak enhancement data was fused onto the standard T1 coronal image. The coronal fused reconstructions were exported back to the local PACS viewer for interpretation with the enhancement curve as a qualitative indicator of the sufficiency of each study.

Example images

Radiologist interpretation:

3 consultant MSK radiologists (with at least 10 years' experience each) reviewed each anonymised study for synovitis and erosions, as per a modified OMERACT RAMRIS scoring method.[11] Scoring was performed on separate occasions on the standard and fusion images in the absence of a previous report or clinical findings.

	MCP Joints																			
	Synovitis				Bone Erosion								Bone Oedema							
					Proximal				Distal				Proximal				Distal			
Case Number	2	3	4	5	2	3	4	5	2	3	4	5	2	3	4	5	2	3	4	5
1	2	2	2	2	0	0	1	4	0	0	0	1	0	0	0	0	0	0	0	1
2	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7	1	3	0	1	0	2	0	0	0	2	0	0	0	2	0	0	1	2	0	0
8	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	0	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10	1	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11	2	0	3	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Figure 2. Example of the score sheet used, adapted from the EULAR-OMERACT RAMRIS scoring method. Each parameter - synovitis, bone erosion and bone marrow oedema - was graded from 0 to 3 (traditional OMERACT scoring sheet measured bone marrow oedema in a scale up to 10).

Clinical interpretation:

A consultant rheumatologist (with greater than 10 years' experience) retrospectively reviewed each clinical case, focusing on the clinical presentation, blood tests, provisional diagnosis and medication history. The aim was to group diagnoses together where possible, give a semi-quantitative degree of diagnostic confidence, and assess for any correlation with the MRI findings.

The clinical grading system is outlined below:

Statistical analysis:

We collected qualitative analysis from each reader regarding the value of the fusion sequences in each case.

We also compared the OMERACT scores obtained from the standard imaging with those obtained from the TRICKS MRA fusions images to assess for intra-observer and inter-observer variability, using interclass correlation (ICC) and a paired student's T-test. All calculations were performed using SPSS software (ver ***).

Example Images / Fusion Images

Example Fused PEAK images

Example 4th + 5th Metacarphophalangeal Joints Synovitis

Results

20 patients were included in the final analysis. 4 of these patients had complete TRICKS imaging but the volumetric pre-contrast T1 images were not available, therefore the peak enhancement data was fused to the standard T1 coronal images.

**demographic data

The patients tolerated the study well and the TRICKS images were of diagnostic quality. The total study time was 40 min to acquire the standard post contrast images. Acquisition of the TRICKS sequence took approximately 8 minutes and was completed prior to the final images in the standard sequence.

The post-processing was semi-automated and could be performed easily by a novice user with the aid of our guidebook.

The interpreting radiologists reported a high level of confidence in reading the MRA and fusion sequences following a brief period of training.

Each radiologist assessed 4 joints per patient in twenty patients, giving a total of 80 joints in the standard and fusion groups in the final analysis.

We used an intraclass coefficient correlation to assess the consistency of the mean scores of the raters for the standard post contrast images and for the fusion images.

Insert fusion and post contrast ICC tables

This demonstrates better inter-rater agreeability with fusion imaging (0.851, 95% CI 0.784 -0.900) when compared to the standard post contrast imaging (0.64, 95% CI 0.376-0.780). Of particular note, there was a very large spread in scores using the post-contrast imaging as reflected by the wide confidence interval. This was based on a two-way random model where the same radiologists read all the same cases and were treated as a representative sample of radiologists as a whole.

We then compared the scores of patients who received treatment with biologic agents or DMARDs and those who did not. This was done for each reader and for the fusion and post contrast scores separately. We first employed a Levene's test to assess for equality of variance and then performed a T-test between the two scores after. If there was no significant difference between the two groups on the Levene's test (Sig. >0.05), then we interpreted the first line of the t-test. If there was a significant difference between the two groups (Sig <0.05), then we assessed the second row of the t-test.

Insert table

Reader 1: Significant difference in the OMERACT scores obtained between the two patient groups with fusion imaging ($t = -2.22$, $p<0.04$). No significant difference in the OMERACT scores obtained between the two groups with the post-contrast imaging.

Reader 2 found no significant difference between the OMERACT scores in the two patient groups on both the fusion and post-contrast images.

Reader 3 found no significant difference between the OMERACT scores in the two patient groups on both the fusion and post-contrast images.

Two of the three readers felt that fused DCE images provided additional benefit and our results show that they minimize inter-rater variability in image interpretation in this study. However, when comparing this against clinical outcome, only one reader demonstrated a significant difference in OMERACT scores with the fusion images between patient groups who ended up on treatment versus those who did not. Of note, there was no significant difference between these two patient groups on the current standard imaging.

Conclusion

Limitations:

1) Patients were not strictly anonymised. A degree of blinding was achieved by temporal separation between original image interpretation and this retrospective analysis. The most recent imaging was performed at least 8 months prior to image review.

2) The sample size of patients was small.

3) The field of view was altered for some studies for clinical reasons. These were kept in the study as reviewers felt it reflected a real world environment

4) The DIPs and PIPs and flexor tendon sheaths were not assessed on this occasion and can be assessed with further studies

5) Assessment of the fusion images was performed only in the coronal plane due to technical factors, but the standard images were reviewed in two orthogonal planes. This can be addressed by further studies

6) There was no assessment for motion artefact.

7) This study focused primarily on features of synovitis and did not assess features such as enthesitis and tenosynovitis.

8) Clinical review was performed by a single clinician and the criteria was not predefined

9) While a descriptive parameters of dynamic contrast enhancement characteristics such as the peak enhancement is easily understood, these are specific to the scanner used and field strength, which limits comparison.[12]

Benefits

We have shown that the fusion of peak enhancement DCE is possible and reduced levels of inter-observer variability in the assessment for synovitis. This also correlated with the confident clinical diagnosis of an inflammatory arthritis for one reader.

Time resolved MRA is useful sequence in the assessment of synovitis. This does not significantly add to scanning time for post contrast imaging and is technically feasible. Automating the processing has generated reproducible images that are achievable within a clinical setting and time frame.

Replacing standard pre and post contrast imaging with a TRICKS MRA sequence and post processed peak enhancement fusion images could significantly reduce scanning time for patients (by up to a quarter at our institution), potentially increasing throughput and reducing waiting times. Further assessment with a larger sample size with clinical correlation is needed to assess this further.

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