A comparison of clinical vs ultrasound determined synovitis in rheumatoid arthritis utilizing gray-scale, power Doppler and the intravenous microbubble contrast agent ‘Sono-Vue’®

J. D. Rees, J. Pilcher¹, C. Heron¹ and P. D. W. Kiely

Objectives. Synovitis in rheumatoid arthritis (RA) is assessed clinically by the presence of joint tenderness and swelling. Synovial thickening and increased vascularity may also be detected by high-resolution ultrasonography (US) and power Doppler (PD). This study investigated the relationship between clinical and sonographic features of synovial disease utilizing US, PD and the contrast agent Sono-Vue®.

Methods. Forty RA patients were recruited. One proximal inter-phalangeal or metacarpophalangeal joint was selected per patient, as being unambiguously either: swollen and tender, just swollen, just tender or neither swollen nor tender (Nil). Ten joints were selected per clinical group. On US, the mean synovial thickness was measured and synovial hypertrophy and erosions were graded subjectively. Synovial vascularity demonstrated by PD was scored subjectively pre- and post-contrast.

Results. All grades of synovial vascularity were found in each clinical group including the Nil group. There were significant differences between the four clinical groups for both synovial hypertrophy ($P = 0.024$ and PD scores pre- ($P = 0.022$) and post- ($P = 0.039$) contrast. Tender-only joints showed significantly less vascularity than other groups. Post-contrast, the median PD scores increased in all but the Nil group, in some cases from the normal to abnormal range.

Conclusion. Synovitis demonstrated by US and PD is not predicted by patterns of disease as described by joint swelling and tenderness despite unambiguous selection of joints. Synovial vascularity was the least in tender-only joints and was heterogeneous in all other groups, including Nil joints. These findings question the reliability of traditional clinical signs in RA synovitis assessment.

KEY WORDS: Rheumatoid arthritis, Synovitis, Ultrasound, Power Doppler, Sono-Vue, Joint tenderness, Joint swelling.

Introduction

In rheumatoid arthritis (RA), the clinical examination of synovial joints focuses on the presence of tenderness and soft tissue swelling to determine whether active inflammation is present. The relative importance of these two clinical signs is unclear, yet the presence of either or both is central to the assessment of overall RA disease activity, and to informing the treatment decision process.

The composite 28 joint RA disease activity score (DAS 28) has been widely adopted in UK practice [1] and with respect to treatment with anti-tumour necrosis factor-$\alpha$ (TNF-$\alpha$) agents, its use is mandatory [2, 3]. The DAS 28 is calculated from the 28 tender and swollen joint count, a patient global assessment and the erythrocyte sedimentation rate (ESR). In this calculation, the tender joint count is weighted more heavily than the swollen joint count by a factor of two, implying that the presence of tenderness is more significant than swelling, with respect to the disease activity. Similarly, other clinical scores imply the same hierarchy of importance, in that a swollen but non-tender joint is classified as not inflamed or inactive [4].

In practice, the DAS 28 is subject to both intra- and inter-observer variability, particularly in the assessment of joint tenderness. This is likely to have a significant effect on the final score given the high weighting placed on the tenderness component [5]. Furthermore, soft tissue swelling within a joint may be due to actively inflamed synovium (synovitis) or inactive non-vascular soft tissue. Nevertheless, all swollen joints are included in the final DAS 28 calculation even though the cause of soft tissue swelling in any single swollen RA joint may not necessarily be due to active rheumatoid synovitis.

High-resolution ultrasonography (US) is being applied increasingly to musculoskeletal medicine, including RA [6–9]. In particular, the use of Doppler ultrasound, in the form of power Doppler (PD) or colour Doppler imaging (CDI), allows an assessment of synovial vascularity and hence a distinction between inflamed and non-vascular synovial swelling. In RA, PD imaging of knee synovial vascularity correlates well with histological factor VIII expression [10], and both PD and CDI data correlate well with gadolinium (static and dynamic)-enhanced MRI images of synovitis [11, 12]. A recent refinement of CDI or PD ultrasound is the additional information gained following the administration of an intravenous microbubble contrast agent. This provides a suspension of relatively uniformly, highly reflective, stabilized gas-filled spheres, which significantly enhance the Doppler signal, improving the sensitivity of detecting low-velocity blood flow through small vessels. Ultrasound contrast agents have been reported to be of use in non-musculoskeletal ultrasound imaging, particularly of the liver [13], and their application to RA has been reported using both PD [14] and CDI [15].

Progression of bone damage in RA, and hence disability, is directly related to the presence of synovitis in any one joint [16].

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and to serum concentrations of the proangiogenic cytokine vascular endothelial growth factor [17]. Given the close correlation of PD data with both histological and MRI assessments of synovial inflammation [10–12] and the sensitivity with which PD detects increased blood flow, it follows that US may be a suitable bedside tool in the routine assessment of synovitis and hence in the management of RA. Serial measurements of the extent of PD signal are reported to correlate well with changes in clinical and laboratory markers of the disease activity following treatment [18–20]. Furthermore, the baseline metacarpophalangeal (MCP) joint synovial thickness and vascularity, measured either by MRI or PD, intriguingly appear to predict erosive progression in RA patients treated with methotrexate [16, 20].

As synovitis appears to be the best predictive marker of future damage in an individual RA joint [16, 17], the aim of this prospective study is to compare the traditional clinical signs of synovitis, joint swelling and tenderness, with the US features of synovial disease, using PD data with and without microbubble contrast enhancement, using the agent Sono-Vue® [21].

Patients and methods

Patients and clinical assessment

In this prospective comparative study, 40 patients fulfilling the 1987 ACR criteria for RA [22] were recruited from the Rheumatology department of St George’s Hospital. The Wandsworth Research Ethics Committee approved the study, and written consent was obtained. The patients’ median age was 59 yrs (range 34–84), 29 were female, the median RA duration was 6 yrs (range 1–29) and 28 were positive for rheumatoid factor. Twenty-eight patients had erosive disease on plain radiographs, though not necessarily in the joint selected for the study. An experienced rheumatologist examined each patient’s hands according to standard criteria [23] and selected one MCP or proximal interphalangeal (PIP) joint per patient. The selected joint was chosen carefully as being unambiguously either:

(i) both swollen and tender (S + T),
(ii) swollen only (S-only),
(iii) tender only (T-only) or
(iv) neither swollen nor tender (Nil).

Joint swelling was defined as soft tissue swelling, and bony swelling was excluded. A total of 10 joints per clinical group was selected (Table 1).

Immediately after clinical examination, the selected joint was assessed by US and PD pre- and post-Sono-Vue® by an experienced ultrasonographer, unaware of the clinical allocation of the joint. Blinding was maintained until US data collection and analysis for all patients in the study was complete.

US protocol

Selected joints were scanned using a Philips HDI 5000 (Philips Medical Systems, Andover, MA, USA) with a C7-15MHz ‘hockey-stick’ transducer. For the PD studies, the Doppler settings were optimized to ‘low flow’, with a medium wall filter and a pulse repetition frequency (PRF) of 700 Hz. The colour gain was then adjusted so that it was just below noise floor and remained at this level throughout the scanning protocol.

Pre-contrast protocol

Each selected joint was held in 20 degrees of palmar flexion and scanned from the dorsal surface, with sagittal (LS) and transverse (TS) images of the joint being stored to the hard drive. From a TS image through the joint, the synovial thickness was measured (in millimetres) at three points (radial, mid-dorsal and ulnar). Any erosions or additional observations (e.g. joint subluxation) were also recorded. PD studies were performed in both TS and LS and were stored as cine clips. Each study was also recorded on S-VHS for subsequent review.

Post-contrast protocol

For each contrast study, 2.4 ml of Sono-Vue® was administered, according to manufacturer’s recommendations, as a fast intravenous bolus through a cannula sited in the contralateral upper limb, followed immediately by a 10 ml normal saline flush. Contrast studies of each target joint were performed twice (once each in TS and LS), from the start of the bolus injection until the PD signal was felt to have returned to baseline level. Each study was recorded on S-VHS and cine clips stored during peak enhancement.

US scores

Two experienced musculoskeletal ultrasonographers scored the selected joints by consensus based upon the stored images, cine clips and the video-recorded study. An erosion was defined as a break in the cortex visible in both transverse and longitudinal planes measuring 2 mm or more [24]. A graded scale was used in which an absence of erosions scored 0, 1–2 erosions scored 1, more than two erosions scored 2 and any large erosions (areas of regional bone destruction) scored 3 [24].

Two separate gray-scale synovial scores were recorded, one objective and one subjective. The objective score was taken from gray-scale TS images, measured at three sites (radial, mid-dorsal and ulnar) in millimetres and the mean of these was used as the final score. The subjective score was classified in a standard manner [20, 25–27] and was graded on a scale from 0 to 3 on the basis of the overall appearances of synovium (thickness and distribution) from gray-scale TS and LS images (Table 2). An absence of synovial hypertrophy (< 1 mm) in any plane scored 0; a small degree, 1; moderate, 2 and marked hypertrophy, 3.

The PD images were scored subjectively on a graded scale in a standard manner [15, 18, 19, 25, 27] from 0 to 3 on the basis of the appearances on TS and LS images, both pre- and post-contrast (Table 2). An absence of the PD signal scored 0, single vessel dots scored 1, confluent vessel dots over less than half the area of synovium scored 2 and over greater than half the area of synovium scored 3 (Fig. 1). A score of 0 or 1 was considered normal, and 2 or 3 indicative of active inflammation.

<table>
<thead>
<tr>
<th>Table 1. Distribution of joints selected for US assessment per clinical group</th>
<th>MCP 1</th>
<th>MCP 2</th>
<th>MCP 3</th>
<th>PIP 2</th>
<th>PIP 3</th>
<th>PIP 4</th>
<th>PIP 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>S + T</td>
<td>n = 10</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>S-only</td>
<td>n = 10</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>T-only</td>
<td>n = 10</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Nil</td>
<td>n = 10</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

S + T, both swollen and tender; S-only, swollen only; T-only, tender only; Nil, neither swollen nor tender; MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint.
Statistical analysis

All statistical tests were performed using SPSS software (SPSS 12.0 for Windows rel. 12.0, Sep 2003 SPSS Inc.).

Results

Within each of the clinical groups, a wide range of scores was recorded for each of the US measures of synovial disease. The degree of overlap was such that none of the clinical groups could be easily distinguished from the others on the basis of US scores, nor did any particular PD appearance clearly distinguish a specific pattern of clinical signs. Clinically detectable synovial swelling was always detected by US but this was not necessarily reflected in the PD scores, where some S-only or S+T joints scored 0 or 1 pre- and post-contrast.

Comparison of US scores between clinical groups

Median scores (and ranges) for each of the five outcome variables per clinical group are shown in Table 3. The Kruskal–Wallis test was used to compare the differences between multiple groups. This demonstrated significant differences between the four clinical groups for the subjective synovial score on gray-scale images, and the PD scores both pre- and post-contrast. The objective synovial thickness score and the erosion score were not significantly different between the four clinical groups (Table 3).

The Mann–Whitney U-test was used to assess differences between the clinical groups pair wise, for the three significant Kruskal–Wallis outcome variables.

Gray-scale subjective synovial score

The individual subjective synovial scores per clinical group are shown in Fig. 2. The mean score for the S-only group was

<table>
<thead>
<tr>
<th>Variables</th>
<th>Nil</th>
<th>T-only</th>
<th>S-only</th>
<th>S+T</th>
<th>K-W P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjective synovial score (0–3)</td>
<td>2 (0–3)</td>
<td>1.5 (0–3)</td>
<td>3 (2–3)</td>
<td>2 (1–3)</td>
<td>0.024</td>
</tr>
<tr>
<td>Objective synovial score: thickness (mm)</td>
<td>13.5 (6–24)</td>
<td>11.5 (4–47)</td>
<td>20.5 (13–45)</td>
<td>22.5 (5–47)</td>
<td>0.063</td>
</tr>
<tr>
<td>PD score pre-contrast (0–3)</td>
<td>1 (0–2)</td>
<td>0 (0–1)</td>
<td>1 (0–2)</td>
<td>1.5 (0–2)</td>
<td>0.022</td>
</tr>
<tr>
<td>PD score post-contrast (0–3)</td>
<td>1 (0–3)</td>
<td>0.5 (0–2)</td>
<td>2 (0–3)</td>
<td>2 (0–3)</td>
<td>0.039</td>
</tr>
<tr>
<td>Erosion score (0–3)</td>
<td>1 (0–3)</td>
<td>1.5 (1–3)</td>
<td>2 (1–3)</td>
<td>1.5 (0–3)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

S+T, both swollen and tender; S-only, swollen only; T-only, tender only; Nil, neither swollen nor tender; K-W P, Kruskal–Wallis P-value.
significantly higher than those for the T-only ($P=0.023$) and the Nil groups ($P=0.011$). The individual scores were as high as 3 in both the T-only (two MCP joints) and the Nil groups (one MCP joint) despite being carefully selected as unambiguously not swollen (Fig. 2), and these two groups and all the other between-group comparisons were statistically indistinguishable.

**Pre-contrast PD score**

The individual pre-contrast PD scores per clinical group are shown in Fig. 3. All of the scores in the T-only group were either 0 or 1 (considered normal) whereas in the Nil group in four joints (two PIP and two MCP) the score was 2, i.e. indicative of active inflammation, despite these joints being carefully selected as unambiguously neither swollen nor tender. With the exception of the T-only group, grades of vascularity from normal to abnormal (0–2) were found in all of the other clinical groups. The mean scores for the T-only group were significantly lower than those for the S + T ($P=0.007$), S-only ($P=0.035$) and Nil ($P=0.052$) groups. All the other between-group comparisons were statistically indistinguishable.

**Post-contrast PD score**

No adverse events were experienced following the administration of Sono-Vue®. Following contrast injection, the mean duration of visible enhancement of the PD signal was 156 sec.

The individual post-contrast PD scores per clinical group are shown in Fig. 4.

Both normal (score 0 or 1) and abnormal (score 2 or 3) grades of vascularity were found in all the four clinical groups and, in particular, within the Nil group, the PD post-contrast scores extended to 2 for three joints (two PIP and one MCP) and to 3 for one joint (MCP), despite the joints being carefully selected as unambiguously neither swollen nor tender. The mean score for the S + T group was significantly higher than those for the T-only ($P=0.023$) and Nil ($P=0.052$) groups. All the other between-group comparisons were statistically indistinguishable.

**The effect of contrast on PD scores**

The Wilcoxon signed-rank test was used to assess the effect of Sono-Vue® on the PD signal in a paired manner per joint within each clinical group. The number of joints per group scoring 0 or 1 (normal synovial vascularity) and 2 or 3 (abnormally increased vascularity) both pre- and post-contrast is shown in Figs 3 and 4. The median PD score rose in all but the Nil group following contrast (Table 3), and the mean absolute gain was greatest for the S + T group (0.7), followed by that for S-only (0.6) and then, T-only (0.5) groups. The rise in PD scores post contrast reached significance for the S + T ($P=0.02$) and the S-only groups ($P=0.01$), but was not significant for the T-only or the Nil group.

In a total of 10 joints, the PD score rose from either 0 or 1 (normal synovial vascularity) pre-contrast to 2 or 3 (abnormally increased vascularity) post-contrast. This effect was seen in no joints of the Nil, four of the T-only (three MCP and one PIP), three of the S-only (all PIP) and three of the S + T (all PIP) groups.
Discussion

This is the first study to analyse the relation between traditional clinical signs of synovitis, namely joint tenderness and swelling, both separately and together, and synovial disease as determined by US, using gray-scale synovial hypertrophy and PD scores, both pre- and post-contrast. In general, the results demonstrate that the information provided by US and PD bears little relation to the patterns of disease as described by the traditional clinical signs of joint swelling and tenderness.

Data from the Nil group demonstrate that an apparently normal joint may have synovial hypertrophy and increased vascularity undetectable on clinical assessment. Thus, the individual pre- and post-contrast PD scores were either 2 or 3 (unequivocally abnormal) in four of the 10 selected Nil joints, two each from the PIP and MCP regions (Figs 3 and 4). These findings are in accordance with the previously published data from RA wrist, MCP and PIP joints using PD and CDI [9, 11, 12, 15, 25]. Indeed, it has been suggested that synovitis undetected clinically (but detectable by US) may be responsible for continuing erosive damage in patients with clinically controlled RA [25].

Data from the T-only group demonstrate that this clinical sign, on its own, does not appear to be indicative of the underlying synovial disease in RA. First, there was no difference in the gray-scale synovial hypertrophy score between the T-only group and the Nil group, as might be predicted from the absence of clinical swelling. Second, the individual pre-contrast PD scores were all normal in this group (Fig. 3). Finally, as a group there was no significant change in PD scores following the contrast. The implication for clinicians is that tenderness on its own in RA does not appear to be a sign of increased vascularity and, by implication, synovitis.

Factors that might explain this observation include the subjective nature and variability in the threshold for reporting tenderness, and the variety of alternative non-synovial structures from which tenderness might emanate, including damaged bone and periarticular tissues. These findings are supported by two other studies in RA. Naredo et al. [25] reported that tenderness counts did not correlate with ultrasound-detected joint effusion, synovitis or PD signal, in contrast to the swollen joint counts that did. Wakefield et al. [28] reported in early oloaarthritis that the proportion of patients with US-determined synovial hypertrophy in a ‘painful only’ (equivalent to our T-only) group was much lower (33%) than that in a clinically determined synovitis group (79%).

Data from the S-only group demonstrate that soft tissue swelling in a rheumatoid joint may or may not be associated with increased synovial vascularity and, by implication, synovitis. Pre-contrast, four out of 10 joints in the S-only group demonstrated abnormally increased vascularity, whereas the post-contrast number rose to seven (Figs 3 and 4). The relative importance of abnormal vascularity only demonstrable following the contrast is unclear, but the overall conclusion that an S-only joint may or may not be actively inflamed has important implications for the interpretation that clinicians place on this clinical sign. Other studies (and a widely used articular index) have taken the view that an S-only joint is not inflamed, and classified the joints in this category as ‘inactive’ [4, 9, 14, 15]. Our data suggest that this is inappropriate. Indeed, the inclusion of S-only joints in the ‘inactive’ category in one study [9] may explain why the mean vessel index in that group was higher than that seen in healthy controls.

Joints that are both swollen and tender appear the most likely to be inflamed, demonstrated by the significantly higher PD scores in the S+T group compared with the T-only and Nil joints, and the significant increase in PD signal following contrast within this group. However, it was notable that five of the 10 joints in this group scored only 0 or 1 on the pre-contrast PD score (Fig. 3), though this fell to two joints post-contrast (Fig. 4).

In keeping with our findings, a previous study of 43 RA wrist, MCP or PIP joints found to be both swollen and tender, reported that 26 (60%) had increased vascularity on CDI [12].

The use of microbubble contrast agents, such as Sono-Vue®, as an adjunct to PD is limited by the burden of expense, the requirement for intravenous access and additional time to acquire the data. It is therefore important to determine prospectively whether the additional information provided by contrast agents will outweigh these factors. As the addition of contrast improves the detection of low-velocity flow through small vessels, by increasing the power within the Doppler signal, an apparent increase in perfusion, even in normal synovium, would be expected in the post-contrast study. A recent report of colour Doppler activity in normal MCP joints (from healthy volunteers) following the injection of two different contrast agents demonstrates this [29]. However, interestingly in our study, in 10 joints (all of which were either T-only, S-only or S+T) a change from normal (PD grade 0–1) to abnormally increased perfusion indicative of active inflammation (PD grade 2 or 3) was seen following the contrast. Whilst these scores represent a marked increase in perfusion post contrast, the significance remains unclear, particularly with respect to the development of bone damage.

A weakness of this study may be the subjective nature of the synovial and PDS scoring systems. This may seem simplistic, but was chosen because it is easy to replicate between individuals and centres, has been widely adopted and may be easily applied to routine clinical practice [30]. Furthermore, such scores have been found to demonstrate close concordance with one fully quantitative score [31].

Although this study was sufficiently powerful to detect statistical differences between some of the clinical groups in three of the five US scores of synovial disease, these differences are insufficiently systematic (with the exception of the T-only pre-contrast PD scores) to be applied to the assessment of individual joints. Thus, the overriding conclusion of this study is that there is wide heterogeneity in the US synovial appearances within each clinical group, with the groups becoming homogenous to the extent that the patterns of the disease described by traditional clinical signs bear little relation to the US appearances of synovial disease in RA.

In particular:

(i) Whilst a joint that is both swollen and tender is the most likely to show US features of increased vascularity, only 50% of this group were abnormal on pre-contrast PD images, though this rose to 80% on post-contrast PD images.

(ii) A joint that is just swollen is indeterminate in that it may or may not have increased synovial vascularity; an observation that is at variance with a widely used articular index which places such joints into an ‘inactive’ group [4, 9, 14, 15].

(iii) A joint that is just tender is the least likely to have synovial abnormalities on US, and this contrasts with the apparent importance attributed to tenderness in the calculation of the widely used DAS 28.

(iv) A neither swollen nor tender joint may contain US features of synovial disease, both hypertrophy and increased vascularity, as has been described previously [9, 11, 12, 15, 25, 26, 28].

The link between synovial vascularity and ultimate joint damage [16, 17] makes the differentiation between inactive and actively inflamed synovium in the rheumatoid joint one of the most important challenges in clinical practice. Our observations suggest that traditional clinical signs, and hence composite scores of disease activity which use them, do not appear to give information that relates closely to synovial features detected by US with PD. It is now important to confirm the apparent predictive ability of PD with respect to joint damage [20] and to demonstrate whether US and PD data can provide alternative...
disease activity scores [30, 31], which may be applied with greater precision to treatment escalation algorithms. If so, it is likely that the safety and relative ease with which US and PD may be applied to the clinical setting will place this modality of assessment at the centre of the management process for RA.

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