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Detection of synovial inflammation in rheumatic diseases using superb microvascular imaging: Comparison with conventional power Doppler imaging

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\section*{ABSTRACT}
\textbf{Aim:} Superb microvascular imaging (SMI), a novel ultrasonography, is based on the sensitivity of Doppler technology. This study evaluated power Doppler (PD) ultrasound signals in patients with rheumatic disease using SMI and conventional PD imaging (cPDI) and compared the correlations of these signals to clinical assessments.

\textbf{Methods:} Thirty-nine patients with rheumatic disease (27 rheumatoid arthritis [RA] and 12 non-RA) were enrolled. We investigated SMI and cPDI signals in 26 joints using an Aplio 300. Individual scores were summed to calculate total SMI and cPDI scores.

\textbf{Results:} Total SMI scores were significantly higher than total cPDI scores in patients with RA, but not in those with the non-RA disease. Total SMI score was associated with serum levels of C-reactive protein (CRP) and matrix metalloproteinase-3; disease activity score 28-CRP and health assessment questionnaire disability index scores, and SMI were more sensitive to detect active synovitis than cPDI in RA patients. Among the joint regions, the wrists and metacarpophalangeal joints were more sensitive to the detection of synovial inflammation using SMI in patients with RA.

\textbf{Conclusion:} SMI was more sensitive in detecting synovial inflammation than cPDI in patients with RA. SMI could be a potentially useful imaging modality for accurately diagnosing and monitoring the disease activity of RA.

\section*{Introduction}
Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic and destructive inflammation of the joints. In the clinical course of RA, progressive multiple joint destruction leads to severe disability and shortening of life expectancy. Regarding clinical practice, detection of synovitis is indispensable for early and precise diagnosis, evaluation of disease activity, treatment response, and prognosis prediction [1]. Ultrasonography, a non-invasive imaging evaluation method, is highly useful and more sensitive than a clinical joint examination in detecting synovitis [2]. Conventional power Doppler (PD) imaging (cPDI) can visualize ongoing active synovitis by revealing abnormal blood flow, with a focus on vascualization and vasodilatation within synovial hypertrophy [3]. In addition, detecting active synovitis using cPDI is associated with diagnosis and enables prediction of progression of joint destruction [2–5]. Additionally, PD-detected synovitis has been correlated with the risk for clinical relapse and failed tapering of biologics therapy [6].

Superb microvascular imaging (SMI) is an innovative ultrasound (US) Doppler technology, which can visualize very small vascular structures that were previously not visible with older imaging modalities. cPDI uses a traditional wall filter to remove clutter artifacts caused by background tissue motion and examinee motion artifacts, resulting in a loss of true low-velocity blood flow. This suggests that cPDI is limited by its inability to detect slow blood flow in very small vessels. However, SMI uses a novel wall filter to distinguish true low-velocity blood flow from clutter artifacts. In addition, SMI can visualize microvasculature with low-velocity blood flow signals using high-resolution frame rates, approximately 50 frames/s, which is more than three times the frame rate of cPDI. There have been only a few reports describing diagnostic applications of SMI in the breast, thyroid, and testicular lesions [7–9]. In particular, Ma et al. [7] reported that SMI was more sensitive than cPDI for detecting blood flow signals from malignant breast tumors. Notably, SMI can further visualize microvascular blood flow and vascularization in malignant breast tumors, which is completely invisible by cPDI. However, to date, no clinical research investigating the utility of SMI for assessing individual joint synovial regions in patients with the rheumatic disease has been reported.

The present study was based on the hypothesis that SMI is more sensitive in detecting synovitis than cPDI. Accordingly, we investigated SMI and cPDI signals in each joint/joint region of patients with rheumatic diseases who...
exhibited joint symptoms and compared the correlation of these signals to clinical and laboratory assessments.

Materials and methods

Patients

Patients with musculoskeletal symptoms who visited the Department of Rheumatology and Applied Immunology, Saitama Medical University Hospital between September and December 2014, after accurate diagnosis of RA or a possible diagnosis of RA, were consecutively recruited to the study. Thirty-nine patients with rheumatic disease (27 with RA or 12 non-RA: seronegative spondyloarthropathy \(n=2\); polymyalgia rheumatica \(n=2\); osteoarthritis \(n=2\); unclassified arthritis \(n=1\); systemic lupus erythematosus \(n=1\); mixed connective tissue disease \(n=1\); adult-onset Still’s disease \(n=1\); granulomatosis with polyangiitis \(n=1\); sarcoidosis \(n=1\)) were enrolled in this study. The study was reviewed and approved by the Institutional Review Board of the Saitama Medical University Hospital.

Clinical and laboratory assessment and US examination

Clinical information was collected by medical history review, which included tender and swollen joint counts, patient global visual analog scale, serum levels of C-reactive protein (CRP) and matrix metalloproteinase-3 (MMP-3), disease activity score (DAS), and health assessment questionnaire disability index (HAQ-DI). Patient demographic, clinical, laboratory, and treatment data are summarized in Table 1. US was performed on the same day as the clinical evaluation by 2 rheumatologists (KY and TTW), who had more than 5 years of experience and expertise in musculoskeletal sonography, and were blinded to the clinical information and laboratory data. Patient recruitment, clinical evaluation, and disease diagnosis were performed by rheumatologists, who were not involved in the sonographic examination. Sonographic examination was carried out by the independent sonographers (KY and TTW), who were certified by the Japan College of Rheumatology.

SMI and cPDI signals were assessed in the joints of both hands (metacarpophalangeal [MCP], proximal interphalangeal [PIP], and interphalangeal [IP] joints), the wrists, elbows, and knees (total 26 joints) using a 9.0 or 18.0 MHz linear transducer (Apio 300, Toshiba Medical Systems Corporation, Tochigi, Japan). In detail, in the finger joint regions, the 1st to 5th MCP, 2nd to 5th PIP joints, and IP joints were scanned in the longitudinal plane over the dorsal aspect. In the wrist joint regions, the radiocarpal and intercarpal joints, and the distal ulna were scanned in the longitudinal plane over the dorsal aspect. In the elbow joint regions, the humeroradial joints were scanned in the longitudinal plane over the anterior aspect, and humeroulnar joints were scanned in the longitudinal plane over the anterior and lateral aspects. In the knee joint regions, the femorotibial joints were scanned in the longitudinal plane over the anterior, medial and lateral aspects. This study was performed in a daily practice environment. Therefore, using both SMI and cPDI to scan a large number of joints is time-consuming and would unrealistically impair feasibility. Recently, Yoshimi et al. reported that eight selected joints, including the bilateral wrist, knee, and the second and third MCP joints, are sufficient for monitoring the activity of RA in daily practice [10]. Accordingly, we assessed the bilateral wrist, knee, and MCP joints, and we added thePIP, IP, and elbow joints, which are many patients required and relatively easy to assess. SMI and cPDI were performed using a pulse repetition frequency set at 220–234 Hz and 870–966 Hz, respectively. A color-coded SMI, which shows blood flow in a color display, was used. The color gain was automatically set to 40 dB, which adequately suppressed the background color. The synovial SMI and cPDI signals were scored on a semi-quantitative scale of 0 to 3 (0: no synovial blood flow signal; 1: mild (<3 signals within the synovial hypertrophy); 2: moderate (>3 signals in less than one-half of the synovial hypertrophy); and 3: marked (signals in more than one-half of the synovial hypertrophy) [6]. Each joint/joint region was scored for synovial SMI and cPDI signals on a scale from 0 to 3 (representative imaging of each grade [0 to 3] by SMI is presented in Figure 1). A global index for the total SMI and cPDI scores (the sum of synovial SMI or cPDI signals)

| Table 1. Demographic characteristics at SMI and cPDI examinations. |
|------------------|------------------|
|                  | RA patients \((n=27)\) | Non-RA patients* \((n=12)\) |
| Sex              | Male \((n=11)\); female \((n=16)\) | Male \((n=2)\); female \((n=10)\) |
| Age, years       | 64.0 \((41–79)\) | 63.0 \((33–86)\) |
| Disease duration, years | 9.4 \((0.3–43)\) | 7.1 \((0.1–40)\) |
| Stage            | 1: 8; II: 8; III: 6, IV: 5 | – |
| Class            | 1: 1; 2: 12; 3: 8; 4: 6 | – |
| ACPA positive, n/n (%) | 15/19 \((79)\) | 0/12 \((0)\) |
| CRP, mg/dl       | 1.8 \((0.1–16.2)\) | 0.9 \((0.1–4.8)\) |
| MMP-3, ng/ml     | 221.5 \((241.6–672.9)\) | 238.0 \((41.3–774.5)\) |
| DAS28-CRP(4)     | 3.5 \((1.2–5.6)\) | – |
| HAQ-DI score     | 0.9 \((0.2–2.4)\) | – |
| Current therapy  | Treatment \((n=21)\): CS \([n=12]\), MTX \([n=8]\), biologics \([n=1]\), non-treatment \([n=6]\) | Treatment \((n=6)\): CS \([n=5]\), MTX \([n=1]\), non-treatment \([n=6]\) |

Values are mean (range).

*Seronegative spondyloarthropathy \((n=2)\); polymyalgia rheumatica \((n=2)\); osteoarthritis \((n=2)\); unclassified arthritis \((n=1)\); systemic lupus erythematosus \((n=1)\); mixed connective tissue disease \((n=1)\); adult-onset Still’s disease \((n=1)\); granulomatosis with polyangiitis \((n=1)\); sarcoidosis \((n=1)\); SM: superb microvascular imaging; cPDI: conventional power Doppler imaging; RA: rheumatoid arthritis; ACPA: anti-citrullinated protein antibody; CRP: C-reactive protein; DAS: disease activity score; MMP-3: matrix metalloproteinase-3; HAQ-DI: health assessment questionnaire disability index; CS: corticosteroid; MTX: methotrexate.
score obtained for each evaluated joint/joint region; 0 to 114) was calculated for each patient.

Interobserver agreement between sonographers was evaluated by randomly selecting SMI and cPDI signals for each joint region from stored images of baseline ultrasound examination. One hundred and ninety images (38 images/patient × 5 patients) were graded against SMI and cPDI signals by the sonographers at the end of the study period.

The validation of grading scale by SMI was evaluated by randomly selecting SMI and cPDI signals for each joint region from stored images of baseline ultrasound examination.

Statistical analysis

Statistical analysis was performed using GraphPad Prism version 5.04 (GraphPad Software Inc., 2012, La Jolla, CA). Comparison between two independent groups was analyzed using the Mann–Whitney test. The correlation between the total score obtained in each imaging session, and between the SMI score and the cPDI score were obtained using 190 images (38 images/patient × 5 patients) and calculated using the Spearman’s rank test; p < .05 was considered to be statistically significant.

Results

Comparison of total SMI and cPDI scores in patients with rheumatic disease

A total of 39 patients with rheumatic disease (27 RA and 12 non-RA) who exhibited arthritic symptoms underwent quantitative joint ultrasonography, including SMI and cPDI, under blinded conditions. The sum of the SMI and cPDI scores obtained for each evaluated joint/joint region (total 26 joints) was calculated for each patient. The intraclass correlation coefficients for interobserver agreement of SMI and cPDI was very high (0.95 and 0.86, respectively), suggesting that ultrasound data used for analyses are reliable. In addition, the correlations between the SMI score and the cPDI score were analyzed. A significant correlation was observed between the SMI score and the cPDI score (r = .48; p < .0001).

The total SMI score was significantly higher than the total cPDI score in patients with RA (SMI median 7.0 [interquartile range [IQR]: 4.0–18.0] versus cPDI median 2.0 [IQR: 0.0–5.0]; p = .0007) (Figure 2(a)). In all patients, the total SMI score was visibly higher than the total cPDI score. In contrast, there was no significant difference between the total SMI and cPDI scores in patients with non-RA disease (SMI median 1.0 [IQR: 0.0–1.0] versus cPDI median 0.0 [IQR: 0.0]; p = .10) (Figure 2(b)).

Correlation coefficient between total SMI/cPDI scores and the serum levels of CRP/MMP-3 in patients with RA

The correlations between total SMI/cPDI scores and the serum levels of CRP/MMP-3 in patients with RA were analyzed. The total SMI score was significantly correlated with serum levels of CRP and MMP-3 (CRP: r = .51, p = .006; MMP-3: r = .52, p = .006) (Figure 3(a)). In contrast, the total cPDI score did not correlate with the serum levels of CRP and MMP-3 (CRP: r = .22, p = .26; MMP-3: r = .26, p = .21) (Figure 3(b)).
Correlation coefficient between total SMI/cPDI scores and DAS28-CRP/HAQ-DI score in patients with RA

The correlations between total SMI/cPDI scores and DAS28-CRP/HAQ-DI scores in patients with RA were compared. The total SMI score showed greater correlation with DAS28-CRP compared with the total cPDI score (total SMI score versus DAS-CRP: \( r = .74, \ p < .001 \); total cPDI score versus DAS-CRP: \( r = .57, \ p = .002 \)) (Figure 4(a)). In addition, the total SMI score showed significantly stronger correlation with HAQ-DI score compared with the total cPDI score (total SMI score versus HAQ-DI score: \( r = .41, \ p = .040 \); total cPDI score versus HAQ-DI score: \( r = .21, \ p = .295 \)) (Figure 4(b)).

Prevalence of the synovial SMI and cPDI signals in each joint

Figure 5 shows the difference in the proportion of the synovial SMI and cPDI signals for each joint. In the wrists and MCP joints, the prevalence of grade 1 was significantly higher in SMI compared with that in cPDI (SMI 70.4% versus cPDI 14.8%; \( p < .0001 \); SMI 40.7% versus cPDI 18.5%, \( p = .0316 \), respectively). In contrast, the prevalence of grade 0 was significantly lower in SMI compared with cPDI. We also examined other joints, but no significant change was observed. These results demonstrated that SMI is more sensitive in detecting synovial inflammation than cPDI, especially in the wrists and
MCP joints, but not in the PIP joints, elbows, or knees in patients with RA.

Discussion

The present study was the first to evaluate SMI and cPDI in 39 rheumatic disease patients with symptomatic synovial joints using established semi-quantitative scores, and we demonstrate several findings. First, the total SMI score was significantly higher than the total cPDI score in RA patients, but not in non-RA patients. Second, the serum levels of CRP and MMP-3, and HAQ-DI score were significantly correlated with SMI score but not the total cPDI score. Among the joint regions, the wrists and MCP joints were more sensitive to the detection of synovial inflammation using SMI in patients with RA. These results suggest that SMI was more sensitive in detecting synovial inflammation compared with cPDI in patients with RA. Therefore, SMI could be a useful imaging modality in providing early diagnosis and, potentially, in monitoring the disease activity of RA.

Very recently, Li et al. [11] reported that SMI significantly improved the detection of blood flow signal within the PIP and MCP joints compared with PDUS in patients with RA. However, they did not evaluate other joints, including the wrists, elbows, and knees. Moreover, they did not compare SMI and cPDI signals in RA and non-RA patients, nor did they evaluate correlations between the SMI/cPDI signals and clinical and laboratory assessments, or disease activity in patients with RA. Therefore, demonstration of the utility of SMI in patients with RA, as we have shown here, supports previous reports that SMI offers improved sensitivity in detecting inflammatory blood flow in patients with RA.

In the present study, the total SMI score, but not the total cPDI score, was significantly correlated with the levels of serum CRP and MMP-3 (Figure 3). This suggests that the total SMI score reflects serum CRP and MMP-3 levels with more sensitivity than the total cPDI score. In general, synovial inflammation is a reflection of a systemic inflammatory reaction, which is demonstrated by significantly increased serum levels of CRP [12]. Therefore, the levels of serum CRP have been shown to mirror synovial inflammation and to correlate with radiographic progression [13]. On the other hand, MMP-3 is a proteolytic enzyme, which is produced by proliferating synovial tissues. The active form of MMP-3 is also a marker of synovial inflammation. A previous early RA cohort study reported that elevated levels of MMP-3 at baseline were significantly correlated with radiographic progression [14]. Taking this into consideration, SMI could be useful in evaluating the potential severity of synovial inflammation and facilitating prediction of radiographic progression in patients with RA.

Because SMI is an imaging technique sensitive to the degree of intra-articular vascularization, it may result in false-positives: for example, noise expression on bone surfaces was judged as abnormal blood flow; normal blood flow detected by SMI, which is not detected by cPDI, was judged to be abnormal blood flow. Accordingly, we fully fixed the
echo probe on the joints to minimize motion artifacts. In addition, we assessed a large number of joints and performed repeated measurements to distinguish between normal and abnormal blood flow.

Our study had four major limitations, the first of which was its small sample size, while the second was that there was no available standardized scoring system for SMI. Third, SMI and cPDI assessments of synovitis were both performed by the same two rheumatologists; therefore, bias may have affected the results and led to an overestimation of the sensitivity of SMI. Fourth, 24 of 27 RA patients and 6 of 12 non-RA patients were already diagnosed; consequently, bias may have affected the results and led to overestimation of the sensitivity of SMI. Therefore, our research was an exploratory pilot study and our results need to be confirmed in future (validation) studies.

In conclusion, our results suggest that SMI detects synovial inflammation with more sensitivity than cPDI in patients with RA. SMI can be helpful for visualizing synovial angiogenesis that cannot be detected using cPDI in patients with RA. Additional studies with long-term follow-up are needed to validate the role of SMI in improving diagnostic accuracy and evaluating radiographic progression.

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Conflict of interest
None.

References


