

Original Article

Superb Micro-Vascular Imaging improving inflammatory flow blood sensitivity in patients with rheumatoid arthritis

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Abstract: Synovial hyperplasia is a typical feature of rheumatoid arthritis. Power Doppler ultrasound has good sensitivity in detection of vascularization within synovial proliferation, however, it is still limited to detect slow flow and flow in small vessels of neo-angiogenesis. In this study, we compare the assessment of joint vascularity by using a SQS grading for both PDUS and Superb Microvascular Imaging. Two hundred and twenty-five proximal interphalangeal joints and metacarpophalangeal joints of patients (48 women, 27 men) were evaluated by PDUS and SMI. The color grading 0-3 was used in PDUS and SMI image respectively. Excellent interobserver reliability could be achieved (ICC = 0.812). Synovial blood flow signals were detected in 179 of 225 joints (79.6%) with SMI and in 144 (64.0%) of 225 joints with PDUS. Compared with PDUS, SMI increased 18.5% vascularization within active RA patients, and increased 60.0% vascularization within inactive RA patients. A substantial agreement was found between PDUS and SMI score (Kappa = 0.615, $P < 0.001$). However, SMI significantly improved the detection of color flow signals. With the use of SMI, 43.2% power flow signals increased from Grade 0 to 1 or higher, 25.5% increased from Grade 1 to 2, 2.8% increased from Grade 2 to 3. We conclude that SMI significantly improves the detection of blood-flow signal within the PIP and MCP joints compared to PDUS.

Keywords: Superb Microvascular Imaging, blood flow, ultrasonography, rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disorder that primarily affects the small joints. Synovial hyperplasia is a typical feature of RA. Active synovitis is closely related to the diagnosis, treatment response, and prognosis of a patient with RA. Being more sensitive than clinical examination in detecting joint inflammation, power Doppler ultrasound (PDUS) has become the modality of imaging for visualizing joints and soft tissues in patients with RA [1]. The role of ultrasonography in the diagnosis and management of RA has significantly evolved in recent years. Ultrasound can be used to improve the certainty of a diagnosis of RA above clinical criteria alone [1]. PDUS in detection of vascularization within synovial proliferation is important for early diagnosis of inflamed joints and for monitoring disease progression [1]. It has been shown that inflammation detected by the presence of color flow signal is asso-

ciated with structural deterioration in rheumatoid arthritis [2, 3]. The presence of color flow signal has also been correlated with the risk of clinical relapse [3-5].

Several different Doppler scoring systems have been proposed for synovitis activity. Most frequently used scoring system is the semi-quantitative scoring system (SQS) grading the Doppler information from 0-3 with increasing amounts of color in the synovium [6]. The decreased level change of SQS is one of the important features of imaging remission of inflammation. Therefore, the sensitivity in detecting joint inflammation by ultrasound is crucial in the patients with RA.

Although the PDUS has good sensitivity for low velocity blood flow, however, it is still limited with respect to the detection of slow flow and flow in small vessels of neo-angiogenesis [6-8]. Recently, a new Doppler technology, Superb

Table 1. Clinical characteristics of patients with RA (n = 75)

	Active patients (n = 51)	Inactive patients (n = 24)	P
Age at inclusion, years*	57.8 (± 10.7)	56.0 (± 8.9)	0.753
Female, n	32	16	0.709
BMI, kg/m ² *	26.3 (± 4.1)	27.6 (± 5.8)	0.814
Symptom duration, months [#]	21 (3~38)	32 (3~45)	0.865
ESR, mm/h [#]	31.3 (11~85)	11.4 (2~48)	0.005
CRP, mg/l [#]	27.7 (2.13~78.9)	2.6 (0.17~30.6)	<0.001

Note: *Mean (± SD). [#]Median (range). CRP, C-reactive protein, ESR, erythrocyte sedimentation rate.

Microvascular Imaging (SMI) technology has been applied to provide outstanding depiction of flow in very small vessels and at lower velocities to visualize even the smallest vessels.

Because of the significance of sensitivity for blood flow in RA, the aim of this prospective study is to compare the assessment of joint vascularity by using a SQS grading for both PDUS and SMI.

Patients and methods

This study was approved by the ethics committee of the Peking University People's Hospital, and written informed consent was obtained from all participants. Patients, fulfilling the 1987 ACR revised classification criteria for RA [9], were selected for the study from our rheumatology clinic. Disease activity was assessed by calculation of DAS28 for each patient. Furthermore, we examined 80 finger joints (digits II and III of each hand) in 10 healthy volunteers without any history of RA (7 women, 3 men) who were in the same age range as the patients.

The proximal interphalangeal (PIP) joints and metacarpophalangeal (MCP) joints of each patient were evaluated by PDUS and SMI using an Aplio 500 TUS-A500 (Toshiba Medical Systems Corporation, Tochigi, Japan) with 18 MHz broad band linear array transducer. Ultrasound was performed and interpreted in consensus by two radiologists (J.A and Z) and they had 14 and 3 years of experience in musculoskeletal ultrasound respectively. PDUS settings were optimized for detection of synovial blood flow to the level just below random noise by adjusting color gain, pulse repetition frequency, wall filter and Doppler frequency. Once

maximum color flow signals was found, the transducer was held in the same scan position to observe color flow signals by SMI technique. The color grading 0-3 was used in PDUS and SMI image respectively [6]: Grade 0: no color in the synovium; Grade 1: single color signal in the synovium; Grade 2: confluent color signals in less than half of the area of the synovium; Grade

3: more than 50% of the synovium covered by color signals. The spectral Doppler ultrasound was performed to confirm that the color flow signals represented true blood flow.

All statistical analyses were performed using SPSS 16.0, considering values of $P < 0.05$ as statistically significant. Quantitative data were expressed as the mean ± standard deviation, and qualitative data were expressed as percentages. Chi square test (Fisher's Exact Test and Pearson Chi-Square when <25% cells have expected count less than 5) was performed to assess the difference between SMI and PDUS. The agreement between SMI and PDUS was assessed using Kappa statistics. A kappa of 0~0.20 indicates poor agreement; 0.21~0.40 fair agreement; 0.41~0.60 moderate agreement; 0.61~0.80 substantial agreement; and 0.81~1 excellent agreement. Interobserver variation coefficients for color flow grading were estimated using calculation of interclass correlation coefficients (ICC).

Results

Two hundred and twenty-five finger joints of patients (48 females and 27 males; mean age, 57.2 ± 10.2 years; BMI, 27.6 ± 7.9) with RA were examined by PDUS and SMI. **Table 1** showed the clinical characteristics of the RA patients involved in the study, divided by disease activity. There were no statistically significant differences in age, BMI, and symptom duration between the two groups.

The finger joints (PIP and MCP) were identified in all patients. Excellent interobserver reliability could be achieved (ICC = 0.812). Synovial blood flow signals were detected in 179 of 225 joints (79.6%) with SMI and in 144 (64.0%) of 225 joints with PDUS. Detection of intra-articular

Superb Micro-Vascular Imaging in rheumatoid arthritis

Table 2. Comparison of US evaluation with clinical activity

		Clinical activity		Kappa	P
		+	-		
SMI	+	147	32	0.599	<0.001
	-	4	42		
PDUS	+	124	20	0.538	<0.001
	-	27	54		

Table 3. Comparison of PDUS with SMI

Grade	SMI				Total
	0	1	2	3	
PDUS 0	46	29	6	0	81
1	0	70	24	0	94
2	0	0	35	1	36
3	0	0	0	14	14
Total	46	99	65	15	225

vascularization was significantly improved by SMI ($P < 0.01$).

Table 2 showed the results of the US evaluation versus clinical activity assessment. PDUS detected intra-articular vascularization in 124 (82.1%) of 151 active joints, in 20 (27.0%) of 74 inactive joints. Kappa agreement between clinical activity and PDUS was 0.538. However, SMI detected intra-articular vascularization in 147 (97.4%) of 151 active joints, in 32 (43.2%) of 74 inactive joints. Kappa agreement between clinical activity and SMI was 0.599. Compared with PDUS, SMI increased 18.5% vascularization within active RA patients, and increased 60.0% vascularization within inactive RA patients.

Table 3 showed the comparison of the grades obtained by PDUS with SMI. A substantial agreement was found between PDUS and SMI score (Kappa = 0.615, $P < 0.001$). However, SMI significantly improved the detection of color flow signals. With the use of SMI, 43.2% power flow signals increased from Grade 0 to 1 or higher, 25.5% increased from Grade 1 to 2, 2.8% increased from Grade 2 to 3 (**Figure 1**).

Discussion

SMI is an innovative ultrasound Doppler technique employing a unique algorithm that allows visualization of minute vessels with slow velocity but without the use of a contrast agent. The capability of detection of low-velocity blood flow

by SMI is due to the following technical specifications: both blood flow and tissue motion can produce ultrasonic Doppler signals. The strong clutter signals overlap the low-velocity blood flow components. Conventional Doppler imaging applies a wall filter to remove clutter and motion artifacts in a loss of low-velocity blood flow. SMI analyzes clutter motion and uses a new adaptive algorithm to identify and remove tissue motion and reveal true blood flow. Since sensitive imaging of the degree of the intra-articular vascularization might be of major importance of diagnosis and treatment planning in patient with RA, SMI is of great value in RA.

PDUS is routinely used in clinical practice for detection of vascularity in joint of patient with RA. Presentation of vascularized synovium gives information with respect to disease activity and can add information regarding disease course aggressiveness [1, 10]. The PDUS technique, however, is limited by the incapacity to detect slow flow in very small vessels [6-8, 11, 12]. In our study, PDUS detected intra-articular vascularization in 144 of 225 joints (64.0%), in 124 of 151 active joints (82.1%), and in 20 of 74 inactive joints (27.0%). Compared with PDUS, SMI increased 60.0% vascularization within inactive RA patients, and the total rate of detection in abnormal vascularization improved 24.3%.

PDUS is used to monitor treatment strategy for efficacy in patients with RA and it is of interest in rheumatology practice and in research to score the changes overtime [13, 14]. In this study, we compared the vascularization of joint by using a SQS grading for both PDUS and SMI. A significant increase in synovial vascularity in the number of patients examined by SMI comparing with the ones examined by PDUS ($P < 0.001$). The detection of vascularization at every grade increased by using SMI, especially at Grade 2.

One of the limitations of this study is that we do not compare the results to contrast-enhanced ultrasonography. Ultrasound contrast agents significantly enhance the signal in vessels. Some reports of contrast-enhanced ultrasonography suggested it has drastically increased the diagnostic sensitivity of PDUS in inflammatory arthritis [6, 10, 15]. Klauser et al. found that using sonographic contrast on the finger joints with active RA patients revealed synovitis

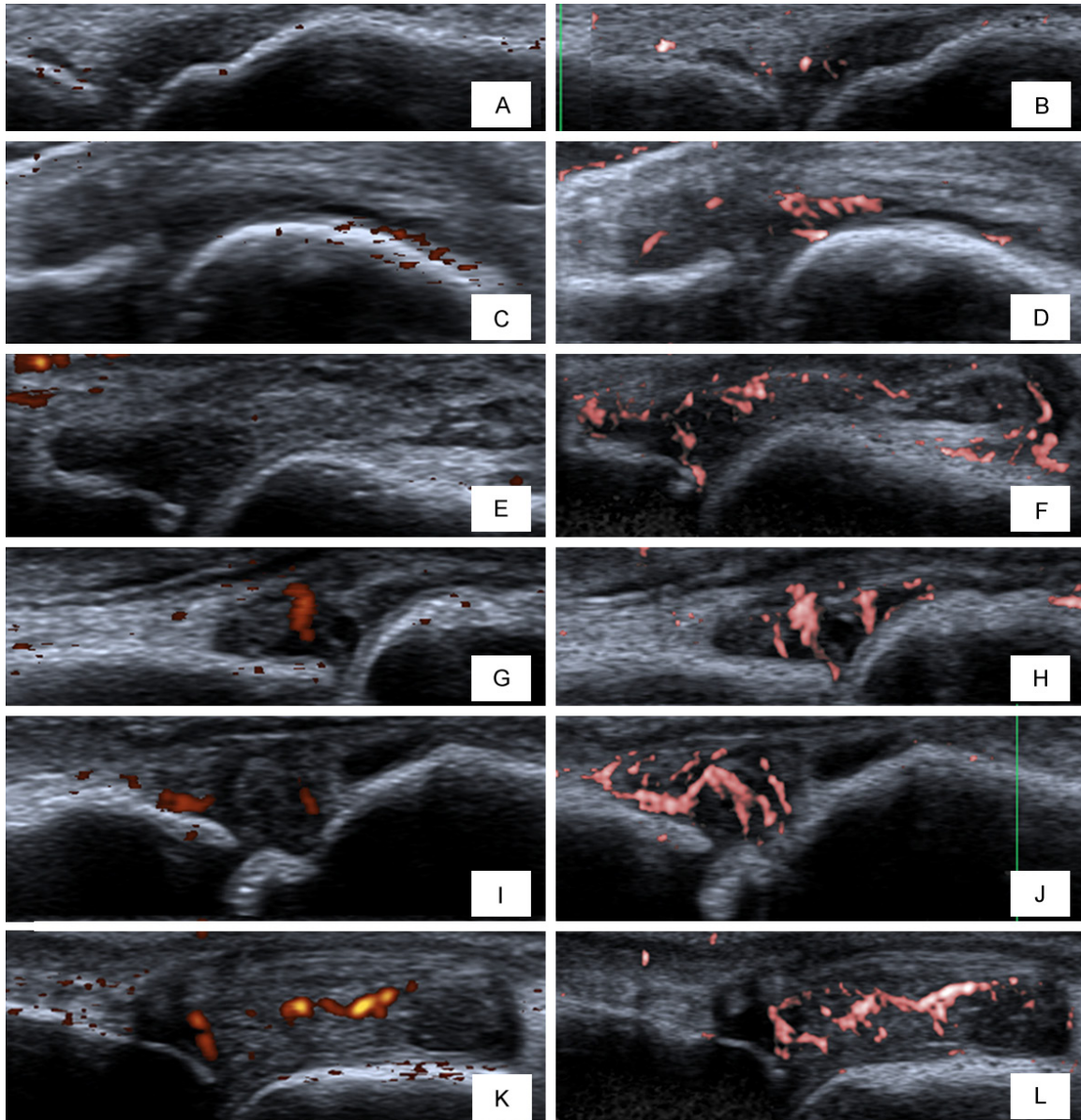


Figure 1. The flow signals in PDUS and SMI. A and B: Longitudinal sonograms of the right second metacarpophalangeal joint. A: Grade 0 in PDUS, B: Grade 1 in SMI. C and D: Longitudinal sonograms of the right third metacarpophalangeal joint. C: Grade 0 in PDUS, D: Grade 2 in SMI. E and F: Longitudinal sonograms of the left second metacarpophalangeal joint. E: Grade 0 in PDUS, F: Grade 3 in SMI. G and H: Longitudinal sonograms of the right third metacarpophalangeal joint. G: Grade 1 in PDUS, H: Grade 2 in SMI. I and J: Longitudinal sonograms of the right second metacarpophalangeal joint. I: Grade 1 in PDUS, J: Grade 3 in SMI. K and L: Longitudinal sonograms of the right second metacarpophalangeal joint. K: Grade 2 in PDUS, L: Grade 3 in SMI.

in 99% of symptomatic joints [6]. SMI detected intra-articular vascularization in 147 of 151 joints (97.4%) with active RA in our study, which was similar to recent studies of contrast-enhanced ultrasonography for the detection of joint vascularity [6, 10, 15]. On the other hand, contrast-enhanced ultrasonography is not a routine examination for RA patients, which also has several drawbacks such as the high costs,

invasiveness, prolongation of the examination and interpretation time. Because PDUS is most popular reference modality of imaging for visualizing blood flow in joints, we compared the results to PDUS. Further studies are needed to overcome these limitations. The other limitation is that we cannot obtain the pathological findings of the synovial membrane, which need to be resolved in future animal experiments.

Superb Micro-Vascular Imaging in rheumatoid arthritis

Based on our preliminary results, we conclude that SMI significantly improves the detection of blood-flow signal within the PIP and MCP joints compared to PDUS. Therefore, this technique can sensitively evaluate the inflammatory activity in patients with RA. We believe it can make up the shortage of current PDUS. It may play an important role in the field of Rheumatology.

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Disclosure of conflict of interest

None.

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