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ORIGINAL ARTICLE

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Power Doppler sonography for detection of intraarticular vascularization in knee joints of patients with rheumatoid arthritis

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Abstract A series of 47 knee joints in 24 patients with rheumatoid arthritis were examined for intraarticular vascularization by power Doppler sonography. The intensity of vascularization was compared with the synovial effusion and proliferation evaluated by gray-scale sonography and the clinical findings in the patients. Vascularization was graded from 0 to 3 by counting the number of color-flow signals: grade 0, no signals; grade one, 1–4 signals; grade two, 5–8 signals; grade three, 9 or more signals. The grade of vascularization correlated with the grade of synovial effusion ($P < 0.01$), the grade of synovial proliferation ($P < 0.05$), and the serum levels of C-reactive protein ($P < 0.05$). It correlated inversely with disease duration ($P < 0.01$). Consistent with improvement of articular inflammation, a decrease in the number of color-flow signals was observed in two patients. Power Doppler sonography is suitable for evaluating the intensity of synovitis and for monitoring the clinical activity of rheumatoid patients.

Key words Knee joint synovitis · Power Doppler sonography (PDS) · Response to treatment · Rheumatoid arthritis (RA) · Synovial effusion

Introduction

Ultrasonography has been used successfully to evaluate synovial effusion, synovial proliferation, and bone erosions in joints of patients with rheumatoid arthritis (RA)[1–8] and to monitor the therapeutic response of joint inflammation in RA patients.[9,10] Power Doppler sonography has recently been used to visualize intraarticular vascularization and to evaluate synovitis in joints[11–17] as well as to monitor the therapeutic response of arthritis in RA patients.[18,19] In the present study, we evaluated the usefulness of power Doppler sonography for detecting vascularization in inflammatory knee joints and evaluating clinical activity of RA patients.

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Patients and methods

Patients

The subjects were 24 patients (20 women, 4 men) with rheumatoid arthritis; 47 knee joints were examined (1 knee joint was excluded because it was an artificial joint). The mean patient age was 61 years (range 33–86 years), and the mean disease duration was 6.7 years (range 0.5–25 years). The diagnosis of RA was based on the 1987 revised criteria of the American College of Rheumatology (ACR).[20] Using the modified indices of synovitis activity proposed by Thompson et al.,[21] the clinical activity of joint inflammation was classified as active (swollen, warm, and tender: grade 2), moderately active (swollen and tender: grade 1), or inactive (only swollen or neither swollen, warm, nor tender: grade 0). C-reactive protein (CRP), the erythrocyte sedimentation rate (ESR), and rheumatoid factor (RF) were evaluated as inflammatory markers tested during a period starting 2 weeks before and ending 2 weeks after the power Doppler sonography examination.

Gray-scale sonography and power Doppler sonography

Gray-scale sonography and power Doppler sonography were performed using a Toshiba Aplio-80 system. A multidimensional linear scanner (PLT-704 AT) was used as the transducer, at 11–5 MHz. The B-mode frequency was 11.0 MHz, and the color mode frequency was 5.3 MHz. The

suprapatellar region of the knee was scanned longitudinally and transversely. The intensities of the synovial effusion and synovial proliferation were evaluated semiquantitatively by gray-scale sonography using the grades established by Rubaltelli et al.[1]: grade 0, thickness of ≤1 mm; grade 1, thickness of 2–4 mm; grade 2, thickness of 5–7 mm; grade 3, thickness of ≥8 mm.

Vascularization was defined as the color-flow signals in the intraarticular soft tissue between the high echogenic cortical surface of the femur and the moderately echogenic articular capsule. Standard machine settings (transmission power <500 mW/cm^2; low pass wall filter No. 3; medium persistence) were used and remained fixed throughout the study. These setting were chosen to maximize sensitivity to low-velocity and low-volume blood flow. The power Doppler gain was optimized by increasing gain until noise appeared and then reducing it just enough to suppress the noise (usually about 60%–70% gain). Standard power Doppler settings were used, with a pulse repetition frequency (PRF) of 11.7–12.2 KHz. The window (color region of interest) was restricted in the vascular area studied. After visualization of color-flow signals, pulsed-wave spectral Doppler imaging was performed using the lowest filter setting (125 Hz) and the smallest scale available that would display the Doppler waveforms as large as possible without aliasing. A spectral Doppler tracing was obtained to confirm that the power Doppler signals represented true arterial or venous flow.

The intensity of vascularization in the intraarticular space was evaluated using a modified version of the method proposed by Klauser et al.[22] to count color-flow signals in the chosen area (window), as follows: grade 0, no intraarticular color-flow signals; grade one, 1–4 signals (1–5 in Klauser and associates' method); grade two, 5–8 signals (6–10 in Klauser and associates' method); grade three, 9 or more signals (11 or more according to Klauser et al.). The results of power Doppler sonography were evaluated independently by two examiners (Y.Y. and R.K.) who were blinded to the clinical findings of the patients.

Statistical analysis

Statistical analysis was performed using the Stat View J – 5.0 software package for Apple Macintosh. Differences between groups were tested by Student's unpaired *t*-test. *P* values less than 0.05 indicated significance.

Results

The power Doppler sonographic evaluation of the synovial vascularization grade had agreement of 80% between the two examiners. Representative power Doppler sonograms of intraarticular vascularization in the present patients are shown in Fig 1. Intensity of vascularization in four knee joints of four patients was graded as grade 0 (no color-flow signals) (Fig. 1a), grade 1 (3 signals) (Fig. 1b), grade 2 (8 signals) (Fig. 1c), or grade 3 (10 signals) (Fig. 1d). Grades of synovial effusion in Fig. 1a–d were grades 0, 1, 2, and 2, respectively. Grades of synovial proliferation in Fig. 1a–d were grades 1, 1, 2, and 2, respectively. The distribution of intraarticular vascularization grade for the 47 joints examined was as follows: grade 0, six joints; grade 1, thirty joints; grade 2, eight joints; grade 3, three joints (Table 1). The mean grades of clinical activity of the joints, synovial effusion, and synovial proliferation for each vascularization grade are shown in Table 1.

The joints were classified into two groups depending on the vascularization grade: group 1, grades 0 and 1 (36 joints); group 2, grades 2 and 3 (11 joints). The clinical activity of joints, synovial effusion, and synovial proliferation were then compared for the two groups. Clinical activity of joints was higher in group 2 than in group 1, but the difference was not significant. Grades of synovial effusion (1.64 ± 0.50 vs. 0.92 ± 0.69; $P < 0.01$) and synovial proliferation (1.55 ± 0.52 vs. 1.19 ± 0.40; $P < 0.05$) were significantly higher in group 2 than in group 1 (Table 1).

For each patient, the mean of the vascularization grades of the left and right knees was designated as that patient's mean vascularization grade, which was compared with disease duration, CRP, ESR, and RF. The number of patients with each mean vascularization grade were as follows: grade 0, two patients; grade 0.5, one patient; grade 1.0, thirteen patients; grade 1.5, five patients; grade 2, one patient; grade 2.5, two patients (Table 2). The mean values for each factor are shown in Table 2. The patients were classified into two groups according to the mean vascularization grade, as follows: group 1, grades 0, 0.5, and 1.0 (16 patients); group 2, grades 1.5, 2.0, and 2.5 (8 patients). The values of four factors were then compared for these two groups. Group 2 had significantly shorter mean disease duration (3.56 ± 1.72 vs. 8.25 ± 6.36; $P < 0.01$) and significantly higher CRP levels (5.60 ± 3.71 vs. 3.24 ± 2.40; $P < 0.05$) than group 1. The mean values of the ESR and the RF levlels were higher in group 2 than group 1. The difference between these two indices was not significant.

Changes in intraarticular vascularization during treatment were examined in two patients by power Doppler sonography, and improvement of intraarticular vascularization was found in both patients. As seen in Fig. 2, the initial grade 3 vascularization (Fig. 2a) of patient K.A. was reduced to grade 2 (Fig. 2b) after 6 weeks of treatment with methotrexate (Rheumatrex; weekly 6-mg doses). This coincided with improvement of clinical activity of patient K.A.'s joints from grade 2 to grade 1, and a decrease in the CRP level from 9.4 mg/dl to 3.8 mg/dl. During the same period, the synovial effusion of patient K.A. changed from grade 2 to grade 1, and synovial proliferation remained at grade 2.

Discussion

Power Doppler sonography (PDS) is thought to be a reliable method for evaluating synovial vascularization, as there was a fairly high agreement rate (80%) between the

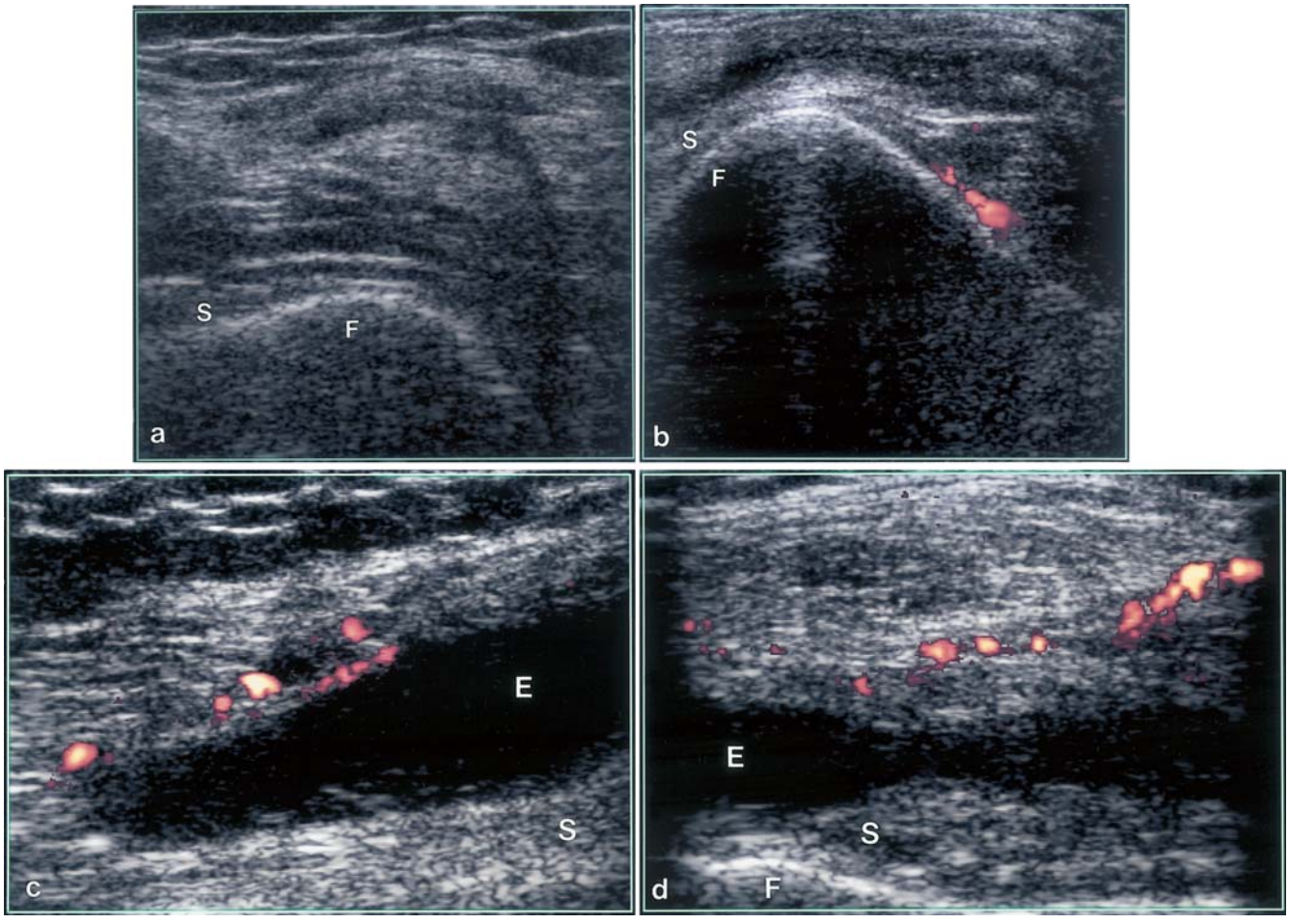

Fig. 1. Power Doppler sonographs. **a** No color-flow signals (grade 0) observed on a transverse scan at the suprapatellar aspect of the right knee of patient S.E. **b** Three color-flow signals (grade 1) observed on a transverse scan at the suprapatellar aspect of the left knee of patient Y.A. **c** Eight color-flow signals (grade 2) observed on a longitudinal scan at the suprapatellar aspect of the right knee of patient K.K. **d** Ten color-flow signals (grade 3) observed on a transverse scan at the suprapatellar aspect of the right knee of patient K.A. *E*, effusion; *F*, femur; *S*, synovial proliferation

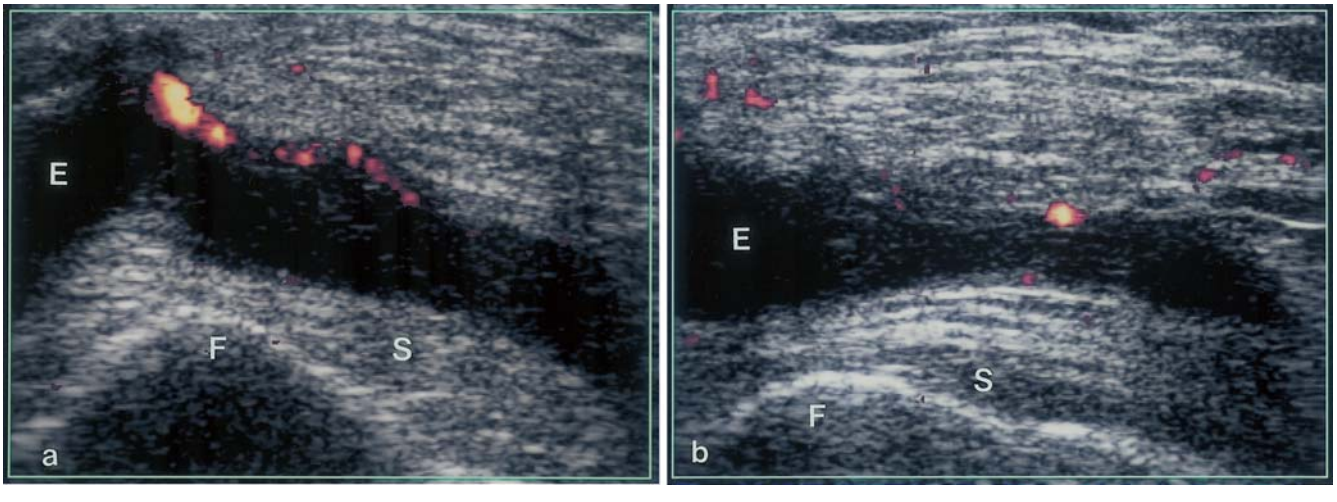

Fig. 2. Power Doppler sonographs. **a** Nine color-flow signals (grade 3) observed on the transverse scan at the suprapatellar aspect of the right knee of patient K.A. examined on February 26, 2003. **b** Seven color-flow signals (grade 2) observed on the transverse scan at the suprapatellar aspect of the right knee of patient K.A. examined on April 9, 2003. *E*, effusion; *F*, femur; *S*, synovial proliferation

Table 1. Correlation between grade of intraarticular vascularization measured by power Doppler sonography and the clinical and articular findings measured by gray scale sonography

Grade of intraarticular vascularization	No. of joints	Grade of clinical activity of joints	Gray scale sonography	
			Grade of synovial effusion	Grade of synovial proliferation
0	6	1.00 ± 0.00	1.00 ± 0.82	1.17 ± 0.37
1	30	1.03 ± 0.60	0.90 ± 0.65	1.20 ± 0.40
0 + 1	36	1.03 ± 0.56	0.92 ± 0.69	1.19 ± 0.40
		NS	**	*
2	8	1.13 ± 0.60	1.50 ± 0.50	1.38 ± 0.48
3	3	2.00 ± 0.00	2.00 ± 0.00	2.00 ± 0.00
2 + 3	11	1.36 ± 0.67	1.64 ± 0.50	1.55 ± 0.52

See the text for grades of intraarticular vascularization, clinical activity of joints, synovial effusion and synovial proliferation
Results are given as the mean ± SD
* $P < 0.05$; ** $P < 0.01$

Table 2. Correlation between intraarticular vascularization measured by power Doppler sonography and clinical and laboratory findings of the patients

Grade of intraarticular vascularization	No. of patients	Duration of disease (years)	CRP (mg/dl)	ESR (mm/h)	RF (IU/l)
0	2	3.0 (2)	1.35 (2)	12 (1)	25.5 (2)
0.5	1	2	1.7		0
1.0	13	9.54 ± 6.03 (13)	3.68 ± 2.37 (12)	55.56 ± 28.40 (9)	371.83 ± 645.45 (6)
0 + 0.5 + 1.0	16	8.25 ± 6.36 (16)	3.24 ± 2.40 (15)	51.20 ± 31.56 (10)	253.56 ± 586.64 (9)
		**	*	ns	ns
1.5	5	3.10 ± 1.85 (5)	4.02 ± 3.45 (5)	56.20 ± 36.45 (5)	354.0 (2)
2.0	1	4	9.4	74	1010
2.5	2	4.5 (2)	7.65 (2)	74.5 (2)	5225 (1)
1.5 + 2.0 + 2.5	8	3.56 ± 1.72 (8)	5.60 ± 3.71 (8)	63.00 + 34.40 (8)	1735.75 + 2364.37 (4)

The grades, duration of disease, CRP, ESR, and RF values are means. Numbers in parentheses are the number available
CRP, C-reactive protein; ESR, erythrocyte sedimentation reaction; RF, rheumatoid factor
* $P < 0.05$; ** $P < 0.01$

two examiners. Newman et al.[23] and Klauser et al.[22] reported quantitative estimation of vascularization in inflammatory synovium using a semiquantitative method of grading based on the number of power Doppler signals. Another quantitative method in which red-yellow pixels are counted using a digital image analyzer was reported by Walther et al.[14] Fairly good accord was reached when evaluating synovial vascularization between PDS and magnetic resonance imaging (MRI) findings[24] as well as between PDS and histologic findings in the resected synovial tissues.[14] We chose to use the Klauser et al. method because of its simplicity.

In the present study, the intensity of vascularization in the knee joints correlated with the intensity of synovitis, as indicated by the synovial effusion and synovial proliferation, which were similar to the results for synovial membrane thickness reported by Walther et al.[14] and the histologic vascularization in the pannus reported by Schmidt et al.[15] The grade of clinical activity of joints in the present study was greater in the high vascularization group than in the low vascularization group, although the difference was not significant. Klauser et al., however, found a significantly positive correlation between clinical activity of joints and synovial hypervascularity.[22] The difference between the present results and those of Klauser et al. may be due to the difference in disease duration; the mean disease duration was 6.7 years in our study but less than 6 months in the study by Klauser et al.

Concerning the correlation between inflammatory laboratory indices and the synovial vascularization grade, the reported results were controversial. In the present study, CRP, ESR, and RF values were greater in the high vascularization group than the low vascularization group, although a significant difference was found only for CRP. Qvistgaard et al.[16] found, however, a positive correlation of the intensity of synovial vascularization with ESR but not with CRP. In contrast, Carotti et al.[17] and Shahin et al.[25] found no correlation between synovial vascularization and the ESR. Such controversial results might be due to differences in such factors as the sites of the joints scanned, activity of other joints, or disease duration. We need a prospective study to confirm the significant correlation between the inflammatory laboratory indices and PDS grade of synovial vascularization.

Power Doppler sonographic evaluation of the therapeutic response of articular vascularization has been reported by Newman et al.[23] and Stone et al.[18] for RA patients treated with corticosteroids, and by Hau et al.[19] for RA patients treated with soluble tumor necrosis factor receptor

(etanercept) and patients with spondyloarthritis treated with infliximab.[26] Similarly, in the present study, improvement in the intensity of the vascularization in knee joints was confirmed by PDS in two patients treated with methotrexate.

Conclusions

Power Doppler sonography is an objective method suitable for evaluating vascularization during the early stage of joint inflammation. It can also evaluate the therapeutic effects on each joint of RA patients treated with disease-modifying antirheumatic drugs or potent biological agents that have recently become available.

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