Diagnostic Sensitivity and Specificity of Doppler Ultrasound in Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To evaluate the sensitivity and specificity of Doppler ultrasound (DUS) in diagnosing arthritis in the wrist and hands, and, if possible, to define a cutoff level for our ultrasound measures for inflammation, resistive index (RI), and color fraction.

Methods. Using DUS, 88 patients with active RA were selected for study and 27 healthy controls. A total of 419 joints were examined. The synovial vascularization was determined by color Doppler and spectral Doppler estimating the color fraction (the percentage of color pixels inside the synovium was the region of interest) and RI in wrist, metacarpophalangeal (MCP), and proximal interphalangeal (PIP) joints. Receiver-operator characteristic (ROC) curves were made for both US measures. Cutoff levels were selected from the ROC curves as the values with the optimum sensitivity and specificity.

Results. Analyses were carried out for small joints (MCP and PIP), wrists, and for all joints (pooled). Pooled joint analysis showed the area under the curve for both RI and color fraction was 0.84. The cutoff level for the color fraction was 0.01 and for RI 0.83. With these cutoff levels, the sensitivity and specificity for the color fraction were 0.92 and 0.73, respectively. For RI a sensitivity of 0.72 and specificity of 0.70 were found. Analysis of small joints and wrist gave very similar results.

Conclusion. DUS may detect vascularization of the inflamed synovium with a high sensitivity and a moderate specificity with selected cutoff levels. (First Release Dec 15 2007; J Rheumatol 2008; 35:49–53)

Key Indexing Terms:
ULTRASOUND DOPPLER SENSITIVITY
SPECIFICITY RECEIVER-OPERATOR CHARACTERISTIC CURVE

The use of Doppler ultrasound (DUS) in inflammatory conditions has increased in recent years. It is now used for the detection of synovial changes in rheumatoid arthritis (RA) and has been validated as a measure of hyperemia in the inflammation in RA[1]. Previous studies have shown that DUS can detect synovitis in small joints[2-4]. The degree of inflammation may be estimated using color or power Doppler and changes in the degree of activity may be monitored as changes in the amount of color pixels in the region of interest[5-7]. However, quantitative estimates of the degree of inflammation may also be obtained by estimating the abnormal synovial perfusion in the inflamed synovium by spectral Doppler using the flow profile of the vessels visualized in the inflamed synovium by color or power Doppler[8]. US has been shown to correlate to magnetic resonance imaging (MRI) in the detection of inflammation, albeit describing different aspects of inflammation[9,10]. DUS as a diagnostic tool requires reference values by which abnormal can be distinguished from normal. In a recent study we showed that Doppler activity was present in 11% of the hand and finger joints of healthy volunteers with no history of arthritis, hand or wrist trauma, or current symptomatology[11]. These findings were in accord with a previous study[2], but in contrast to other studies reporting negative Doppler findings in healthy controls[9,12]. The detection of arterial flow in the synovium depends on the sensitivity of the Doppler equipment, and the mere presence of color pixels cannot be interpreted as a sign of inflammation. There is an increasing interest in US in rheumatology practice[1,13] and this imaging technique may be suggested as an objective tool in diagnosis, although more work is required to determine its optimal role[14]. Before US may be qualified for diagnostic purposes, a number of confounding issues must be addressed, most notably the cutoff values for Doppler activity as compared to healthy subjects.

With reference to findings in healthy volunteers[11], the aim of our study was to evaluate the sensitivity and specificity for DUS in the wrist and hands in patients with RA, and, if possible, to define a cutoff level for the US measures.

MATERIALS AND METHODS

Subjects with RA. A total of 88 patients (65 women, 23 men, mean age 59 years, range 25–89) with active RA fulfilling the American College of Rheumatology (ACR) criteria[15] were included in our study. Wrist, metacarpophalangeal (MCP), and proximal interphalangeal (PIP) joints were clinically examined and a total of 122 joints were included with clinical signs of inflammation. Active RA was defined as a joint swelling and/or tenderness of > 1 on a modified Ritchie index of the joints studied. Sixty wrists and 62 MCP

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joints and PIP joints all had joint swelling and/or tenderness of ≥ 1. These joints served as affected RA joints. The mean disease duration was 10 years [standard deviation (SD) ± 9 yrs], the mean joint pain measured on a visual analog scale (VAS) in mm was 47.6 (SD ± 24.5). Biochemically, the mean erythrocyte sedimentation rate (ESR, mm/h) was 23.3 (± 19.4) and the mean C-reactive protein (CRP) 20.6 (± 23.7). Mean Health Assessment Questionnaire (HAQ) was 1.65 (± 1.25).

Healthy reference subjects. The data of 27 healthy volunteers (15 women, 12 men, mean age 45 yrs, range 18–93) from a previous study[11] were included in our study as statistical reference. The equipment, the machine settings, and the US examiner were identical for the 2 studies. The subjects were not currently engaged in heavy manual labor or sports activities with their hands and had no history of arthritis, hand or wrist trauma, or current symptomatology. None of the subjects had clinical signs of inflammatory or degenerative joint diseases. A total of 297 joints were examined — 11 joints per subject: wrist, MCP joints 1–5, and PIP joints 1–5. These joints serve as indisputably normal joints.

The healthy subjects had a mean ESR (mm/h) of 7.3 (± 5.5) and a mean CRP of 2.0 (± 1.9). There was a statistically significant difference between the ESR and CRP in the patient group compared to the healthy group ($p < 0.001$). The healthy subjects had a lower mean age (45 yrs, ± 18) than the patients with RA (59 yrs, ± 15; $p < 0.001$).

Estimation of joint inflammation. A joint was defined as inflamed if the clinical joint evaluation was graded ≥ 1 in either tenderness and/or swelling.

Clinical examination. Each patient filled in a HAQ, pain on a VAS (0–100 mm), and morning stiffness (minutes). ESR and CRP were obtained on the same day. All joints were assessed clinically by the same trained investigator, with a score of each joint for the degree of tenderness and swelling from 0 to 3. Only joints with swelling and/or tenderness ≥ 1 were included.

Ultrasound. The joints of the hands were examined with an Accuson Sequoia® device (Accuson, Mountain View, CA, USA) equipped with a 15 MHz linear array probe. All scans were performed between 9 and 11 A.M. The patient was examined in upright position with the hand of interest placed on a cushion, relaxed, and pronated.

The dorsal side of the wrist was scanned from side to side in the longitudinal plane and from proximal to distal in the transverse plane. The finger joints were scanned in the longitudinal plane only and the palmar aspects were not investigated. MCP1 and the PIP joints were scanned in an arc of 180° from the ulnar to the radial side. MCP2-5 were scanned in the regions that were accessible from the dorsal side: MCP2 and MCP5 in an arc of 150° and MCP3-4 in an arc of 120°.

The color Doppler settings were the same for all joints and all participants, with a gain setting just below the noise level using our setup for low-flow: Nyquist limit ± 0.014 m/s and 7 MHz Doppler frequency. With this setup all the color pixels in the image correspond to motion, i.e., blood flow. We used color and not power Doppler, because at present the 2 modalities have the same sensitivity on the Sequoia device. Additional information about direction and velocity of blood flow may be obtained from color Doppler but not from power Doppler. The presence of aliasing is not a concern when using color Doppler, as it is the presence of flow (amount of color pixels) that is of interest — not direction or velocity.

The synovial vascularization in the joints was visualized by color Doppler and the image with maximum color activity (if any) was selected for analysis. US flow pattern of the synovium in the joints with activity on color Doppler was evaluated with quantitative spectral Doppler with automatic calculation of the resistance index (RI). The RI is defined as [(peak systolic velocity – end diastolic velocity)/peak systolic velocity] and was determined in 3 arteries within the synovial membrane if possible, and a mean value was calculated as an estimate of the synovial inflammation. We used a maximum value of 1.00 for RI, because we have limited the analysis to one side of the Doppler baseline. The reason is that we sample small vessels and most often sample the artery and its concomitant veins simultaneously. The negative part of the arterial signal will then be obscured in the venous signal. When spectral Doppler measurements could not be measured due to lack of detectable vascularization in the examined wrist, the RI was noted to be 1.00, as the resistance in the synovial arteries was presumed to be the same as extrasynovial musculoskeletal flow. The examination time for each patient for the wrists and finger joints was approximately 15 minutes for the color Doppler examination and an additional 15 minutes for the spectral Doppler examination, depending on the number of available vessels.

Image evaluation. Quantitative estimation of the vascularization in the synovial membrane was performed using the color Doppler image with maximum color activity selected for analysis. The digitally stored color Doppler image in DICOM format was transferred to a processing program (Corel Photo-paint 7®). The synovium inside the color box was traced, thereby defining a region of interest. Using US, the cartilage, capsule, and possible fluid in the joint cannot always be distinguished and it therefore was included in the trace. Using a color recognition function, the amount of color pixels was expressed in relation to the total amount of pixels in the marked region of interest[16] — the color fraction.

Statistical analysis. Statistical analysis was performed using the Statistical Analysis System program. Student's t-test for unpaired data was used for evaluation of the total data set. All tests were 2-tailed and level of significance was chosen at 0.05.

Receiver-operator characteristic (ROC) curves were calculated for estimation of sensitivity and specificity for both RI and color fraction, comparing values from healthy subjects with those from patients with RA. The area under the ROC curve was calculated as a measure of the quality of the test. The values vary from 0.5 (no apparent accuracy) to 1.0 (perfect accuracy). Cutoff levels were selected from the ROC plots as the value with the optimum sensitivity and specificity. This optimum value varies with the intended use of the test, and we selected the value that gave the highest sum of sensitivity and specificity. This is the point on the curve with a tangent with a slope of 1.

Our study was approved by the local ethical committee and written informed consent was given by all participants.

RESULTS

Tables 1–3 show the clinical and US data for total joint data, the small joints (MCP and PIP joints), and the wrists including the area under the curve for ROC plots.

Significant differences between the RA group and the healthy group were found for the US measures for both the small joints alone and for the wrist.

Based on the ROC curves, the cutoff levels for the RI and color fraction estimated for finger joints and wrists are given in Table 4.

The pooled joint analysis gave results in the same range as the separate analysis for the wrist and small joints. The ROC curve for the pooled joint analysis may be seen in Figure 1. With these cutoff levels, the sensitivity and specificity of the color fraction were 0.96 and 0.53, respectively, for the small joints, 0.70 and 0.87 for the wrist joint, and 0.92 and 0.73 for the pooled joint analysis. Similar results for RI were sensitivity 0.99 and specificity 0.49 for the small joints, 0.85 and 0.90 for the wrist joint, and 0.72 and 0.70 for the pooled joints.

DISCUSSION

With the increasing Doppler sensitivity in the newest US machines it is now possible to detect synovial vascularization in clinically unaffected joints in healthy volunteers as shown in previous studies[2,11]. This makes it mandatory for further diagnostic use to differentiate between pathological flow and normal synovial perfusion.

Table 1. Pooled joint data (wrist joints, MCP, and PIP joints). Area under curve: RI 0.84, color fraction 0.84.

Feature	RA, mean ± SD	Healthy Joints, mean ± SD	p
n	122	297	
RI, mean	0.80 ± 0.17	1.00 ± 0.05	< 0.001
Color fraction	0.16 ± 0.18	0.006 ± 0.03	< 0.001
Joint tenderness (0–3)	1.5 ± 1.03	0	
Joint swelling (0–3)	1.5 ± 0.77	0	

MCP: metacarpophalangeal; PIP: proximal interphalangeal; RA: rheumatoid arthritis; SD: standard deviation; RI: resistive index.

Table 2. MCP and PIP joint data. Area under curve: RI 0.72, color fraction 0.75.

Feature	RA, mean ± SD	Healthy Joints, mean ± SD	p
n	62	270	
RI, mean	0.87 ± 0.17	1.00 ± 0.03	< 0.001
Color fraction	0.11 ± 0.16	0.002 ± 0.013	< 0.001

Abbreviations as in Table 1.

Table 3. Wrist data. Area under curve: RI 0.89, color fraction 0.85.

Feature	RA, mean ± SD	Healthy Joints, mean ± SD	p
n	60	27	
RI, mean	0.72 ± 0.14	0.96 ± 0.12	< 0.001
Color fraction	0.21 ± 0.18	0.044 ± 0.062	< 0.001

Abbreviations as in Table 1.

Table 4. Cutoff levels.

	RI Cutoff (95% CI)	Color Fraction Cutoff (95% CI)
MCP and PIP jonts	0.9 (0.83–0.97)	0.02 (0.014–0.025)
Wrist	0.85 (0.75–0.91)	0.04 (0.034–0.046)
Pooled joints	0.83 (0.75–0.90)	0.01 (0.003–0.016)

Abbreviations as in Table 1.

We compared DUS findings in healthy joints with findings in RA. We chose to investigate wrists, MCP, and PIP joints, which, apart from the toes, are the most frequently affected joints in RA and the most readily accessible to US examination. Our clinical experience — especially in the wrist joint — is that quite often arthritic activity persists on US without noticeable swelling. Our study included only joints with definite abnormalities in either tenderness and or swelling in the analysis.

We found that there was a statistically significant difference between the 2 Doppler measures (RI and color fraction) in the healthy group compared to the RA group both for the pooled joint analysis and for the separate joint groups. The 2 groups differed in age, with the control group being younger. Although it is optimal, it is difficult to create an age-matched control group, as osteoarthrosis changes and symptoms increase with age. With age, it therefore becomes increasingly difficult to recruit symptom-free individuals. As there are at present no data to support an age-related difference in synovial Doppler activity, we decided to accept a younger mean age in the control group than in the RA group.

The area under the ROC curve shows the diagnostic ability of the test[17,18] and was also used in a study by Scheel, *et al* in a new greyscale scoring system[19]. A high sensitivity almost always compromises the specificity. In our material, the wrist joint had a very acceptable area under the curve of 0.89 for RI and 0.85 for the color fraction. The small joint analysis had less specificity and sensitivity for both measures, indicating that a separate cutoff level for small joints and for wrists might be necessary, especially for clinical trials. The pooled joint analysis may be sufficient as guidance for daily clinical purposes, with an area under the curve for RI and color fraction of 0.84.

Also, based on these results, US may face the same prob-

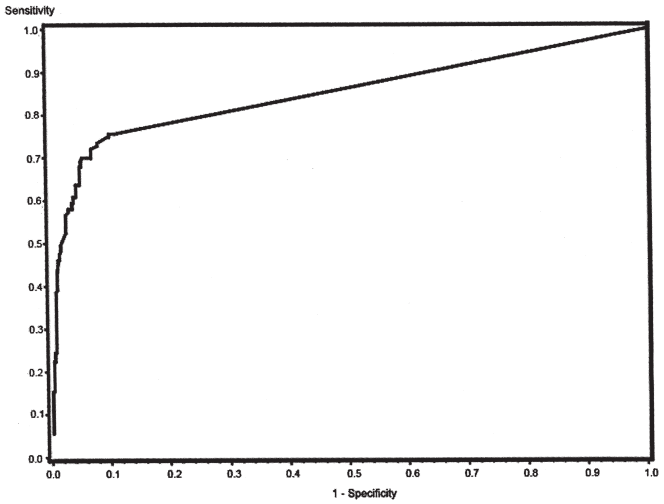

Figure 1. Receiver-operator characteristic (ROC) curve for the color fraction in the pooled joint analysis (wrist joints, MCP, and PIP joints) of 122 clinically active RA joints compared to 297 healthy joints. The cutoff level may be selected from the ROC curve as the value with the optimum sensitivity and specificity. This is the point on the curve with a tangent with a slope of 1.

lems with diagnosis of synovial changes in the small joints as seems to be the case for MRI[20]. Our study also showed very similar results for RI and color fraction in the wrist joint, in the small joint group, and in the pooled joint analysis, indicating cutoff values for RI in the range of 0.83–0.9 and for the pixel fraction in the range of 0.01–0.04. In other words a small percentage of color pixels may be present in the region of interest of these joints without indicating pathology.

We used the clinical examination as the gold standard, with the attendant possible biases. A joint may have permanent swelling after a previous arthritic attack and it is difficult to imagine a clinician scoring such joint as "normal." A better definition might be that of "remission," and the notion of normality should be discussed further. This will inevitably lead to a certain number of "false-negative" Doppler diagnoses and a lower sensitivity. With highly sensitive Doppler equipment, which can detect flow even in normal tissue, flow *per se* cannot be used as sign of inflammation. The cutoff level is necessary as a lower limit for abnormal flow, and with our values a very high sensitivity was obtained at the expense of specificity. The cutoff will in this connection vary with the definition of arthritis, which we set at any clinical abnormality, i.e., tenderness and/or swelling. In daily practice this might be too broad and, for example, imply a risk of including patients with fibromyalgia in the arthritis group[21]. A resolution to this discussion might be a longitudinal study with longterm followup of patients with joints with or without Doppler activity at baseline.

The cutoff levels for RI and color fraction suggested in this report define thresholds between normal and pathologic Doppler activity using advanced US equipment with a very sensitive Doppler. RI has not been studied extensively yet; however, in our hands it has been associated with the clinical status of the joints and may add further information about the joint status[10,22]. Longitudinal data on RI suggest that this measure may have a predictive value of its own and may distinguish tissue with remission from that with active disease[23].

The cutoff level for RI may be defined from the values of the healthy joints to be in the range from 0.83 to 0.9. The typical value in the arthritic joints was 0.8, which corresponds to our impression from daily clinic experience and also corresponds to the cutoff value, although in the reverse, used in nephrology for pathological flow in the transplanted renal artery. In the latter case the artery supplies a low resistance arterial bed where flow must be present throughout the cardiac cycle. Increasing RI values here signal pathology[24]. The values from the more than 100 joints tested in our study varied considerably, including several values above the cutoff level. It must be noted, however, that this value in the case of arthritis represents the mean of 3 independent measurements in the joint. It may be speculated that the synovial tissue in the arthritic joint has areas of varying degrees of inflammatory activity intermingled with collagenous tissue from former attacks, which may have healed with some persisting blood supply, as seen in histological analysis of the pannus[25]. Such heterogeneity would be expected in our patients, who had a mean duration of arthritis of 10 years with several intermittent recurrences and changes of therapy.

In the individual US equipment, confounders should be diminished by the use of constant settings including Doppler gain and with a standardized positioning of the probe, while the depth of the Doppler should be adjusted in each examination to assure a correct focus. DUS has been suggested as a reference for the evaluation of arthritic joints[26,27], while the notion of a cutoff level has not been defined before.

DUS may detect vascularization of the inflamed synovium with a high sensitivity. We found the cutoff level for the color fraction was 0.01 and for RI was 0.83, and speculate that other machines will provide similar results with the same settings. Further studies need to be carried out to elucidate this matter.

Doppler activity *per se* cannot be accepted as diagnostic of arthritis and cutoff levels are necessary due to the detection of flow in a number of normal joints.

REFERENCES

1. Ostergaard M, Szkudlarek M. Ultrasonography: a valid method for assessing rheumatoid arthritis? Arthritis Rheum 2005;52:681-6.
2. Hau M, Schultz H, Tony HP, et al. Evaluation of pannus and vascularization of the metacarpophalangeal and proximal interphalangeal joints in rheumatoid arthritis by high-resolution ultrasound (multidimensional linear array). Arthritis Rheum 1999;42:2303-8.
3. Lund PJ, Heikal A, Maricic MJ, Krupinski EA, Williams CS. Ultrasonographic imaging of the hand and wrist in rheumatoid arthritis. Skeletal Radiol 1995;24:591-6.
4. Grassi W, Lamanna G, Farina A, Cervini C. Synovitis of small joints: sonographic guided diagnostic and therapeutic approach. Ann Rheum Dis 1999;58:595-7.

5. Newman JS, Laing TJ, McCarthy CJ, Adler RS. Power Doppler sonography of synovitis: assessment of therapeutic response — preliminary observations. Radiology 1996;198:582-4.
6. Stone M, Bergin D, Whelan B, Maher M, Murray J, McCarthy C. Power Doppler ultrasound assessment of rheumatoid hand synovitis. J Rheumatol 2001;28:1979-82.
7. Terslev L, Torp-Pedersen S, Qvistgaard E, Danneskiold-Samsoe B, Bliddal H. Estimation of inflammation by Doppler ultrasound: Quantitative changes after intra-articular treatment in rheumatoid arthritis. Ann Rheum Dis 2003;62:1049-53.
8. Terslev L, Torp-Pedersen S, Qvistgaard E, Bliddal H. Spectral Doppler and resistive index. Acta Radiol 2003;44:645-52.
9. Szkudlarek M, Court-Payen M, Strandberg C, Klarlund M, Klausen T, Ostergaard M. Power Doppler ultrasonography for assessment of synovitis in the metacarpophalangeal joints of patients with rheumatoid arthritis: a comparison with dynamic magnetic resonance imaging. Arthritis Rheum 2001;44:2018-23.
10. Terslev L, Torp-Pedersen S, Savnik A, von der Recke P, Danneskiold-Samsoe B, Bliddal H. Doppler ultrasound and MRI of synovial inflammation in the hand in rheumatoid arthritis patients — a comparative study. Arthritis Rheum 2003;48:2434-41.
11. Terslev L, Torp-Pedersen S, Qvistgaard E, von der Recke P, Bliddal H. Doppler ultrasound findings in healthy wrists and finger joints. Ann Rheum Dis 2004;63:644-8.
12. Klauser A, Frauscher F, Schirmer M, et al. The value of contrast-enhanced color Doppler ultrasound in the detection of vascularization of finger joints in patients with rheumatoid arthritis. Arthritis Rheum 2002;46:647-53.
13. Backhaus M, Burmester GR, Gerber T, et al. Guidelines for musculoskeletal ultrasound in rheumatology. Ann Rheum Dis 2001;60:641-9.
14. Keen HI, Brown AK, Wakefield RJ, Conaghan PG. MRI and musculoskeletal ultrasonography as diagnostic tools in early arthritis. Rheum Dis Clin North Am 2005;31:699-714.
15. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
16. Qvistgaard E, Rogind H, Torp-Pedersen S, Terslev L, Danneskiold-Samsoe B, Bliddal H. Quantitative ultrasonography in rheumatoid arthritis: evaluation of inflammation by Doppler technique. Ann Rheum Dis 2001;60:690-3.
17. Metz CE. Basic principles of ROC analysis. Semin Nucl Med 1978;8:283-98.
18. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143:29-36.
19. Scheel AK, Hermann KG, Kahler E, et al. A novel ultrasonographic synovitis scoring system suitable for analyzing finger joint inflammation in rheumatoid arthritis. Arthritis Rheum 2005;52:733-43.
20. Conaghan P, Edmonds J, Emery P, et al. Magnetic resonance imaging in rheumatoid arthritis: summary of OMERACT activities, current status, and plans. J Rheumatol 2001;28:1158-62.
21. Leeb BF, Andel I, Sautner J, Nothnagl T, Rintelen B. The DAS28 in rheumatoid arthritis and fibromyalgia patients. Rheumatology Oxford 2004;43:1504-7.
22. Terslev L, Torp-Pedersen S, Qvistgaard E, et al. Effects of treatment with etanercept (Enbrel, TNRF:Fc) on rheumatoid arthritis evaluated by Doppler ultrasonography. Ann Rheum Dis 2003;62:178-82.
23. Varsamidis K, Varsamidou E, Tjetjis V, Mavropoulos G. Doppler sonography in assessing disease activity in rheumatoid arthritis. Ultrasound Med Biol 2005;31:739-43.
24. Skjoldbye B, Nielsen AH, Court-Payen M, et al. Perioperative Doppler ultrasonography: renal detection of renal graft perfusion. Scand J Urol Nephrol 1998;32:345-9.
25. Rooney M, Condell D, Quinlan W, et al. Analysis of the histologic variation of synovitis in rheumatoid arthritis. Arthritis Rheum 1988;31:956-63.
26. Szkudlarek M, Court-Payen M, Jacobsen S, Klarlund M, Thomsen HS, Ostergaard M. Interobserver agreement in ultrasonography of the finger and toe joints in rheumatoid arthritis. Arthritis Rheum 2003;48:955-62.
27. Grassi W, Filippucci E, Busilacchi P. Musculoskeletal ultrasound. Best Pract Res Clin Rheumatol 2004;18:813-26.