Agreement between semiquantitative and quantitative Doppler scoring systems for the assessment of synovial pathological vascularisation in rheumatoid arthritis

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Abstract

Objective

To compare colour Doppler (CD) versus power Doppler (PD) semiquantitative and quantitative scoring of synovial vascularisation and to evaluate the relationship between semiquantitative and quantitative scores in patients with rheumatoid arthritis (RA).

Methods

One hundred RA patients underwent B-mode, PD, and CD assessments of 12 joints at two European centres. Each joint with synovial hypertrophy (SH) detected on B-mode was semiquantitatively scored (0-3) for PD (SPD score) and CD (SCD score) synovial signal. PD and CD synovial signal were also quantitatively scored (0-100%) (QPD and QCD scores, respectively) using a software integrated in the US equipment for counting the colour fraction.

Results

We found SH in 184 joints. SPD and SCD agreed in 92.3% (95%CI: 88.4; 96.2%) of paired scores, with Kendall rank correlation coefficient tau-b=0.95. QPD and QCD scores were highly correlated (Pearson's coefficient=0.70) but Blamd-Altman plot showed insufficient agreement, being the QCD scores systematically slightly higher than the QPD scores. The comparison of mean values of QPD and QCD between scores of SPD and SCD, respectively, showed significant differences between grade 0 and grade 1 ($p<0.001$), and grade 2 and grade 3 ($p=0.042$ and $p=0.007$, respectively) but not between grade 1 and 2 ($p=0.154$ and $p=0.150$, respectively).

Conclusion

The SPD and SCD scores were concordant and the QPD and QCD scores highly correlated but were not concordant. There was an overlap between SPD and SCD mild and moderate scores regarding QPD and QCD scores.

Key words

ultrasound, Doppler, rheumatoid arthritis, synovitis, semiquantitative and quantitative scoring systems

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Significance and innovation:
1. Semiquantitative and quantitative scoring systems are used to grade synovitis vascularisation by power and colour Doppler.
2. Semiquantitative scores were concordant and quatitative scores were correlated.
3. There was consistency between semiquantitative and quantitative power Doppler and colour Doppler for moderate and severe scores.

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by intra-articular and periarticular synovial inflammation (*i.e.* synovial proliferation and angiogenesis) (1). Synovitis can damage the cartilage, bones, capsule, tendons, and ligaments with consequent joint deformities and severe joint function impairment.

Within the last decade, technological improvements in ultrasound (US) image resolution of musculoskeletal (MS) structures have led to an increasingly important role of this imaging tool in the evaluation and monitoring of patients with RA and other inflammatory arthritides based mainly on its higher capacity in detecting synovitis, when compared to clinical examination (2-4). MSUS is a routinely available, non-invasive, repeatable as many times as required at the time of consultation, and relatively inexpensive bedside technique with high patient acceptability. Colour Doppler (CD) and power Doppler (PD) techniques are able to detect synovial flow, which is an indirect sign of inflammatory activity (5-8). The presence of synovial Doppler signal has demonstrated strong predictive value in relation to structural damage progression and disease flare in both active and remission RA patients (9-13). The detection of synovial hypervascularisation is therefore of particular importance in the rheumatological evaluation and assessment of RA patients.

To the best of our knowledge only a few studies have compared different Doppler modalities (*i.e.* CD *vs.* PD) or different scoring systems (semiquantitative *vs.* quantitative) for synovial vascularisation detected by Doppler US (14-16). The objectives of this cross-sectional observational study conducted in RA patients were the following:

1. to compare semiquantitative scoring of synovial vascularisation by CD *versus* PD imaging;
2. to compare quantitative scoring of synovial vascularisation by CD *versus* PD;
3. to evaluate the relationship between semiquantitative *versus* quantitative scoring of synovial vascularisation by CD and PD.

Methods

Patients

One hundred patients [86 women, 14 men; mean (SD, range) age, 59.3 (13.4, 24–87) years] who fulfilled the American College of Rheumatology 1987 diagnostic criteria for RA (17) were consecutively included in a period of 3 years (17). They were recruited from the Rheumatology Departments of two European centres (Hospital Universitario Gregorio Marañón, Madrid, Spain, and Policlinico Umberto I - Sapienza Università di Roma, Rome, Italy).

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee of the Hospital General Universitario Gregorio Marañón, Madrid, Spain (the number of the study given by Ethics and Research Committee was 331/13) and the Policlinico Umberto I - Sapienza Università di Roma, Rome, Italy (the number of the study given by Ethics and Research Committee was 2965/13). Informed consent was obtained from all patients before study enrolment.

Clinical assessment

At each centre, all patients were evaluated by a local experienced rheumatologist, including the standard care clinical and laboratory assessments for RA patients (*i.e.* demographics, disease duration, Disease Activity Score for 28 joints (DAS28), presence of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), and presence of radiographic erosions. The treatment taken by the patients was also registered.

Ultrasound assessment

The US assessments were performed by two rheumatologists, one at each centre (EN at Madrid and AI at Rome), who have who have respectively 20 and 32 years of experience in MSUS of experience in MSUS. They were blinded to clinical, laboratory and radiographic data. All patients underwent B-mode, PD, and CD assessments of 12 joints (18). These joints were as follows: bilateral elbow (*i.e.* anterior and posterior recesses), wrist (*i.e.* radiocarpal, midcarpal, and distal radioulnar

joints; dorsal recesses), second metacarpophalangeal (MCP) joint (i.e. dorsal recess), third MCP joint (*i.e.* dorsal recess), knee (*i.e.* anterior and parapatellar recesses), and ankle (*i.e.* tibiotalar joint; anterior recess).

The US examinations were performed with a real-time scanner (LOGIQ E9, GE Medical Systems Ultrasound and Primary Care Diagnostics, LLC, Wauwatosa, WI, USA) equipped with a multifrequency linear matrix array transducer (ML6-15 MHz) used for elbow, wrist, knee, and ankle and a multifrequency linear hockey-stick transducer (L8–18 MHz) used for MCP joints. B-mode, PD, and CD settings were optimised for the different assessed joints before the study and standardised for the whole study (B-mode: frequency 13–18 MHz; gain 45–51. PD: frequency 6.3–12 MHz; gain 14–18; PRF 0.4–0.8. CD: frequency 6.3–11.9; gain 18–20; PRF 0.8).

Each joint was semiquantitatively scored (0–3) [0, absent; 1, mild; 2, moderate; 3, marked] for B-mode synovial hypertrophy (SH). SH was defined according to the Outcome Measures in Rheumatology Clinical Trials (OMERACT) as the presence of abnormal hypoechoic (relative to subdermal fat) intraarticular tissue that is nondisplaceable and poorly compressible (19). Joints with SH >0 were semiquantitatively scored for PD (SPD) and CD (SCD) synovial signal [0, no synovial signal; 1, ≤3 signals within the SH]; 2, >3 signals in less than half of the SH area; 3, signals in more than half of the SH area] according to the OMERACT synovitis scoring system (20). These scores corresponded to the maximum score for SH and PD/CD signal, respectively, obtained from any one of the synovial sites evaluated at each joint.

The presence of synovial effusion was also recorded in joints with SH. Joints with presence of PD or CD signal within SH were also quantitatively scored using a software for counting the colour fraction incorporated into the US machine (Q-Analysis, GE Healthcare). For this colour quantification, the investigators recorded a 4-s video sequence at the area with more colour detected during the scanning of each joint. The investigators drew a line that delimited the synovial area. Thereafter, the system showed the maximum (Max) measure of colour fraction (CF) over the entire video sequence acquisition, which was taken for analysis as quantitative score (0–100%) for PD (QPD) and CD (QCD) synovial signal. CF is defined as the fraction of pixels within a traced region which have a Doppler signal to those that do not have a Doppler signal.

Statistical analysis

Statistical analysis was performed using the statistical package IBM SPSS, v. 21.0 (SPSS, Chicago, IL, USA). Quantitative variables were summarised as mean, standard deviation, minimum and maximum and qualitative variables as absolute frequencies and percentages. Relationship between quantitative variables QPD and QCD was analysed with Pearson correlation coefficient and agreement was checked with Bland-Altman plot of the difference of paired data, QPD - QCD, against the average of these measurements (QPD + QPC)/2. The limits of agreement were calculated as 2 standard deviation of differences, and 95% confidence intervals were computed for mean of differences and limits of agreement. Agreement between ordinal variables SPD and SCD with 95% confidence interval was computed. Relationship between ordinal variables was analysed with Kendall rank correlation coefficient tau-b. To compare distribution of grades between SPD and SCD, marginal homogeneity test was performed, followed by McNemar test if needed. At each method, the change in the mean values of quantitative variable as the grades of the ordinal variable progress was tested by one-way ANOVA follows by linear trend test. Any p-value <0.05 was considered significant.

Results

Demographics and RA characteristics

The mean (SD, range) disease duration was 10.3 (8.0, 0.5–40) years. The mean (SD, range) DAS28 was 3.94 (1.15, 1.9–7,19). RF was positive in 65 patients and ACPA in 57 patients. Sixty-nine patients showed radiographic erosions. Forty-nine (49%) patients were treated with synthetic disease-modifying anti-rheumatic drugs (DMARDs), 17% (17%) with biologic DMARDs, and 28 (28%) with synthetic and biologic DMARDs. Six (6%) patients were not receiving DMARDs. Forty-one (41%) patients were taking oral prednisone.

US findings

In total, we assessed 1,200 joints. We found SH in 184 joints (15%) and synovial effusion in 133 (11%). The distribution of SH, SPD, and SCD scores are shown in Table I. The mean (SD, range) MaxCF was 11.22% (14.14, 0.00–86.40) for PD and 13.81% (16.32, 0.00–95.60) for CD.

Agreement between power Doppler and colour Doppler

The agreement between PD and CD was studied at two levels: quantitative, comparing QPD and QCD findings, and semiquantitative, comparing SPD and SCD findings.

At quantitative level, QPD and QCD showed a linear relationship with a Pearson coefficient of 0.842 (p<0.001), but the scatterplot showed a predominance of dots below the identity line (zero intercept and unit slope). The Bland-Altman showed an average of differences of -0.026 (CI95%: -0.043; -0.008), leaving the zero value out of the confidence interval (Fig. 1). This bias was due to QCD values were slightly higher than their paired QPD values. The limits of agreement were -0.187 and 0.136 including between them 94.4% of differences. Differences inside limits of agreement represented up to 14.3% of mean QPD, which was above desirable.

At semiquantitative level, agreement between SPD and SCD was obtained in 92.3% (95%CI: 88.4; 96.2%) of paired scores, with discrepancies in 14 out of 184 pairs (7.7%). Kendall rank correlation coefficient tau-b between SPD and SCD was 0.95 (p<0.001). Additionally, the marginal homogeneity test did not find any significant differences between marginal distribution of SPD and SCD scores (p=0.565). The crosstab (Table II) shows that the 14 discrepancies between SPD and SCD scores were

Table I. Distribution of SH, SPD, and SCD.

	SH		SPD		SCD	
Score	n	%	n	%	n	%
0	0	0.0	46	25.0	46	25.0
1	97	52.7	66	35.9	67	36.4
2	57	31.0	61	33.2	62	33.7
3	30	16.3	11	6.0	9	4.9
Total	184	100.0	184	100.0	184	100.0

SH: synovial hypertrophy; SPD: semiquantitative score for power Doppler synovial signal; SCD: semiquantitative score for colour Doppler synovial signal; n: number.

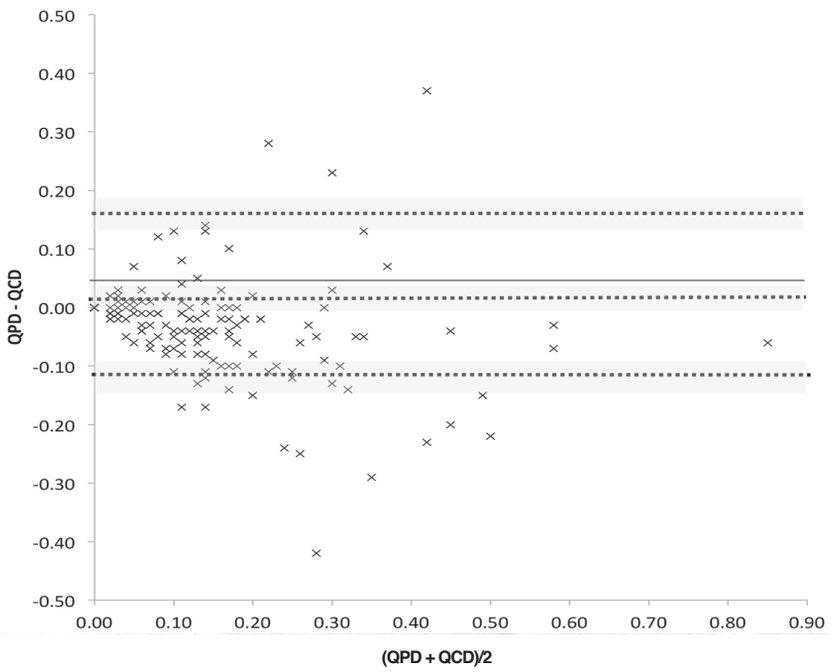

Fig. 1. Bland-Altman plot of differences (QPD - QPC) against mean values (QPD + QCD)/2. The central dotted line represents the mean of differences; the upper and lower dotted lines represent the limits of agreement; shaded areas: 95% confidence intervals for mean of differences and limits of agreement. QCD, quantitative score for power Doppler synovial signal; QPD, quantitative score for power Doppler synovial signal.

Table II. Cross table SPD score × SCD score. Cross absolute frequencies.

	SCD score				
SPD score	0	1	2	3	Total
0	46	0	0	0	46
1	3	63	3	0	66
2	0	4	56	1	61
3	0	0	3	8	11
Total	46	67	62	9	184

SPD: semiquantitative score for power Doppler synovial signal; SCD: semiquantitative score for colour Doppler synovial signal.

always between consecutive scores. These results suggested that agreement between SPD and SCD scores was adequate.

The progressivity of the semiquantitative variable was tested by one-way ANOVA with linear trend test. For both methods, one-way ANOVA demonstrated significant differences of means in QPD and QCD between SPD and SCD scores ($p<0.001$ in both). Moreover, a linear growing trend showing an increase of mean QPD and QCD as scores of SPD and SCD progressed was demonstrated ($p<0.001$ in both).

Table III displays the mean values of the QPD scores and QCD scores for each SPD score and SCD score, respectively. For PD scores, Games-Howell comparisons between the different grades were as follows; SPD=0 *vs*. SPD=1, $p<0.001$; SPD=0 *vs*. SPD=2, $p<0.001$; SPD=0 *vs*. SPD=3, $p=0.001$; SPD=1 *vs*. SPD=2, $p=0.154$; SPD=1 *vs*. SPD=3, $p=0.012$; and SPD=2 *vs*. SPD=3, $p=0.042$. There was an overlapping of QPD scores between SPD scores 1 and 2. For CD scores, Games-Howell comparisons between the different grades were the following: SCD=0 *vs*. SCD=1, $p=0.001$; SCD=0 *vs*. SCD=2, $p<0.001$; SCD=0 *vs*. SCD=3, $p<0.001$; SCD=1 *vs*. SCD=2, $p=0.150$; SCD=1 *vs*. SCD=3, $p=0.003$; and SCD=2 *vs*. SCD=3, $p=0.007$. Again, there was an overlapping of QCD scores between SCD scores 1 and 2.

Comparison of mean values of QPD and QCD between scores of SPD and SCD, respectively is shown in Figures 2 and 3. We used parametric test in order to check linear trend in means. Nevertheless, non-parametric test of Kruskal-Wallis offered similar results for QPD and QCD. Non-parametric tests confirm the findings with parametric tests. (Table IV).

Discussion

In recent years, Doppler modalities have been increasingly used to assess joint synovitis in arthritides and different scoring systems have been proposed to grade synovial perfusion in RA (21). The present study has demonstrated that semiquantitative scores assessed by CD and PD are concordant with no significant differences between their distribution. Thus, the semiquantitative scores appear to be independent by the Doppler modality that is used, being both similarly able to detect pathological flow within the synovial tissue of RA patients. This aspect is of particular value for ultrasonographers in their choice of the semiquantitative modality to use. The evaluation of the distribution of quantitative scores showed that they were highly correlated but not concordant. Indeed, the QCD scores were systematically slightly higher than the QPD scores, thus showing that CD detects more signal than PD when quan-

Table III. Comparison of QPD values between SPD scores and QCD value between CPD scores.

		QPD		
SPD	n	Mean	SD	CI95%
0	46	0.0%	0.0%	0.0%-0.0%
1	66	11.0%	13.6%	3.8%-7.4%
2	61	15.6%	10.9%	7.7%-13.8%
3	11	35.1%	20.3%	20.8%-31.5%
		QCD		
SCD	n	Mean	SD	CI95%
0	46	0.0%	0.0%	0.0%-0.0%
1	67	13.8%	13.8%	4.5%-12.0%
2	62	18.8%	13.1%	8.9%-16.1%
3	9	50.1%	20.5%	31.9%-53.5%

SPD: semiquantitative score for power Doppler synovial signal; QPD: quantitative score for power Doppler synovial signal; SCD: semiquantitative score for colour Doppler synovial signal; QCD: quantitative score for colour Doppler synovial signal; n: number; SD: standard deviation; CI: confidence interval.

Table IV. Comparison of QPD values between SPD scores and QCD value between CPD scores (non-parametric test).

		QPD		
SPD	n	Median	Q_1	Q_3
0	46	0.000	0.000	0.000
1	66	0.074	0.038	0.123
2	61	0.138	0.077	0.197
3	11	0.315	0.208	0.415
		QCD		
SCD	n	Median	Q_1	Q_3
0	46	0.000	0.000	0.000
1	67	0.120	0.045	0.195
2	62	0.161	0.089	0.239
3	9	0.535	0.319	0.607

SPD: semiquantitative score for power Doppler synovial signal; QPD: quantitative score for power Doppler synovial signal; SCD: semiquantitative score for colour Doppler synovial signal; QCD: quantitative score for colour Doppler synovial signal; n: number; $Q_1 - Q_3$: interquartile range.

titative assessment is used. This aspect appears to be of interesting value and should be taken into account in the quantitative analysis of pathological flow in RA.

In addition, our study demonstrated consistency between SPD and SCD moderate and severe scores and QPD and QCD scores and an overlap between SPD and SCD mild and moderate scores regarding QPD and QCD scores. Both assessment systems were consistent for absence of synovial Doppler signal. Quantitative and semiquantitative assessments are both valuable in detecting pathological flow, however, the intrinsic characteristics of them differ in terms of the modality used for signal scoring. In both CD and PD modes, semiquantitative and quantitative evaluations analyse and score the area of signal in grades 2 and 3. Conversely, grade 1 is scored on the basis of the number of signals by the semiquantitative scoring system and, instead, the area of signal is taken into account by QPD evaluation. This discrepancy in the assessment of flow may play a role in the results of the grading, making the semiquantitative evaluation different that the quantitative methods which is always based on the area of signal in all scores. However, because quantitative assessment is more time consuming than semiquantitative evaluation, its widespread use in the clinical practice is limited and it may gain a place particularly in research. Nevertheless,

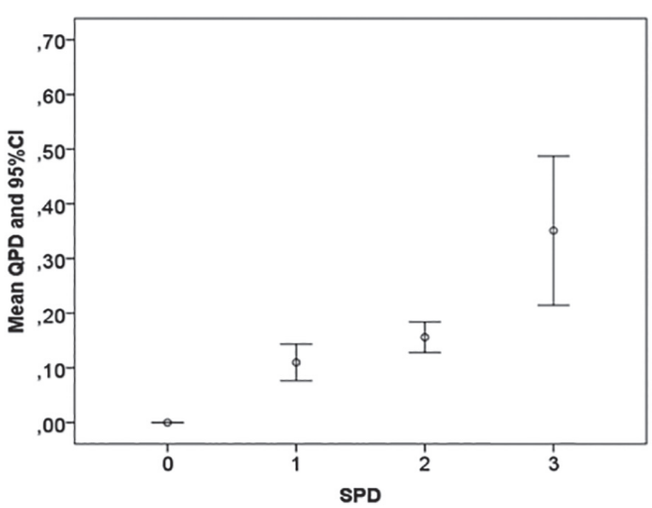

Fig. 2. Mean QPD and 95% confidence interval (95%CI) at SPD degrees. SPD: semiquantitative score for power Doppler synovial signal.

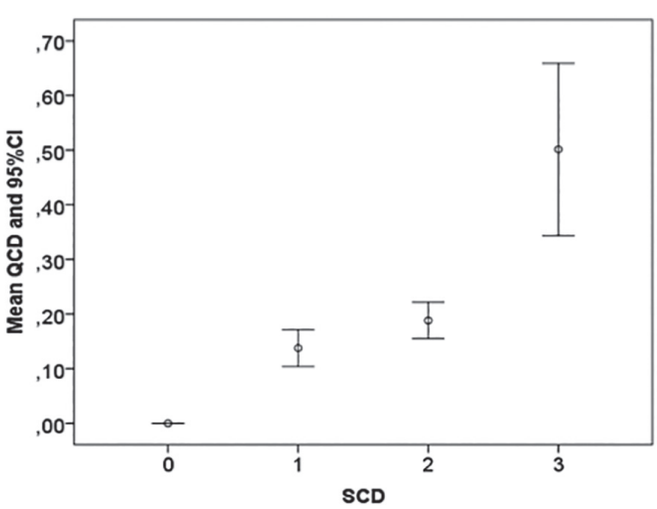

Fig. 3. Mean QCD and 95%CI at SCD degrees. SCD: semiquantitative score for colour Doppler synovial signal

the mentioned overlap between both scoring system for mild and moderate scores need further attention regarding a potential synovial Doppler cut-off point with either diagnostic or prognostic purpose.

CD and PD are the two most commonly used Doppler modes to assess synovial hypervascularisation in rheumatic diseases (22). They are the most studied and applied because they allow the simultaneous visualisation of grey-scale and Doppler findings, providing information on the exact anatomic distribution and on the entity of the blood flow (22, 23). In the most commonly used high-end US equipment, CD and PD are considered to have equal sensitivity in detecting pathological vascularisation in arthritides (16, 23, 24). This is mainly due to the advancing US technology and the correlated increased sensitivity of recent machines in detecting Doppler signal (23). By using both modes, either semiquantitative or quantitative scoring systems can be applied to grade the severity of synovial perfusion, however, there is not yet consensus on which of them might better reflect the pathological vascularisation in RA, although semiquantitative assessment seems to be more feasible clinical practice (23, 24).

Our study allowed us to assess a high number of joints, with a combination of small and large joints. However, a limitation of our research need to be addressed as we tested Doppler modes only in machines of a single manufacturer, while it would have been interesting to analyse the discrepancies also in other equipment. Nonetheless, this study was conducted with the highest end and newest equipment which aspect should minimise this bias.

In summary, this study, aimed to compare CD *versus* PD semiquantitative and quantitative scoring of synovial vascularisation in RA and to evaluate the relationship between scoring systems, demonstrated that semiquantitative PD and CD scores were concordant. Quantitative PD and CD scores were correlated but not concordant. Quantitative PD and CD scores were consistent with the respective semiquantitative scores for scores moderate and severe. However, PD and CD mild and moderate scores showed an overlapping of quantitative PD and CD values, respectively. Further longitudinal studies comparing the sensitivity to change of semiquantitative *versus* quantitative PD and CD scores are warranted.

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