Assessment of wrist joint inflammation in patients with rheumatoid arthritis by quantitative two- and three-dimensional power Doppler ultrasonography

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Abstract

Objective

We aimed to compare the use of computer-aided quantification methods with 3 different power Doppler ultrasonography (PDUS) modes to assess wrist inflammation in patients with rheumatoid arthritis (RA).

Methods

This study enrolled 49 patients (60 hand joints) with RA. Clinical parameters (rheumatoid factor [RF], erythrocyte sedimentation rate [ESR], and C-reactive protein [CRP]) were measured and pain was evaluated by a visual analogue scale (VAS, range: 0 to 10). Imaging of the affected wrist joints was performed with 2D- and 3D-PDUS imaging. The 2D imaging used a volumetric transducer and a linear transducer and the 3D imaging employed a volumetric transducer. Software was used to calculate the vascularisation index (VI), flow index (FI), and vascularisation flow index (VFI) under different measurement conditions.

Results

There were 8 males and 41 females, with an average age of 47.59±15.17 years, and average VAS score of 3.63±2.22. In 2D-PDUS with a linear probe, there were significant correlations of ESR with VI and VFI, and of CRP with area, VI, and VFI ($p<0.05$ for all comparisons). In 3D-PDUS, there was a significant correlation of CRP with VFI ($p<0.05$). In all 3 measurement modes, there were moderate or high levels of inter- and intra-operator agreement in measurement of area/volume, VI, FI, and VFI.

Conclusion

All 3 PDUS measurement modes had high accuracy and reliability in assessment of wrist inflammation. These results suggest that use of a 3D transducer, which is more expensive and time-consuming, is not necessary for assessment of wrist inflammation.

Key words

rheumatoid arthritis, power Doppler ultrasonography, ESR, CRP, synovium, wrist

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Introduction

Rheumatoid arthritis (RA) is an autoimmune disorder characterised by pain and inflammation of the synovial joints and dysfunction of one or more major organ systems (1). RA typically begins in middle-age with the onset of synovitis, is more common in females, and numerous genetic factors affect it pathogenesis (2). The prevalence is 0.5–1% in the U.S. and northern Europe, 0.3–0.5% in southern Europe, and 0.1–0.3% in Asia (3). Based on the 1987 diagnostic criteria of the American College of Rheumatology (ACR), the incidence rates have similar geographic variation (24–45 cases/100,000 person-years in the U.S. and northern Europe; ~9–24 cases/100,000 person-years in Southern Europe; and 22 cases/100,000 person years in Taiwan) (1, 3-5). The joint pain and other symptoms associated with RA typically change in intensity over time (1). However, there is a progressive and inexorable deterioration of the synovial joints, and this leads to deformation and ultimately to permanent disability (6).

Diagnosis of RA is based on clinical and laboratory data, and an accurate diagnosis is required for implementation of suitable treatment and assessment of treatment efficacy (1). The use of modern imaging methods, including magnetic resonance imaging (MRI) and ultrasound (US), indicated that patients who experience pain relief still have signs of inflammation, including synovitis and osteitis (7, 8). In fact, increased vascularisation and inflammation is associated with more severe bone destruction and poorer prognosis (9). Therefore, it is very important to have accurate and reliable imaging results so that appropriate therapy can be implemented and treatment efficacy can be evaluated. Many recent studies have assessed the severity of inflammation in RA by use of Doppler US to evaluate blood flow in movable joints (10-12). In the past, RA was diagnosed by semi-quantitative imaging methods, but more rigorous quantitative analysis of 3D images and sophisticated software packages are currently available (13). Nonetheless, few studies have used rigorous statistical methods for analysis of US images of the synovial joints of RA patients. Such studies are important for comparison of different imaging methods and quantification of the inflammation associated with disruption of wrist articulation. A recent study compared 3 different probe positions for US examinations of the wrists of RA patients (14). However, only one previous publication compared data obtained with different transducers, and this was an *ex vivo* study (15). Moreover, this study compared data obtained with different ultrasound equipment using the same transducer, not different transducers with the same ultrasound equipment.

The objective of this study was to compare the use of 2D- and 3D-power Doppler untrasonography (PDUS) with computer-aided quantification methods and statistical comparisons to assess wrist joint inflammation in Taiwanese patients with RA. In particular, we assessed intra- and inter-operator agreement of US measurements and the effect of different PDUS transducers.

Materials and methods

Enrolment criteria

This was a single-hospital, cross-sectional study that enrolled 49 patients (60 hand joints) between June 27, 2012 and April 17, 2013 by convenience sampling. Based on this sample size and an alpha level of 0.05, we expected an intraclass correlation coefficient (ICC) greater than 0.725 and a 95% confidence interval less than 0.2. All enrolled patients were diagnosed with RA based on 1987 American College of Rheumatology (ACR) criteria (4), complained of wrist joint pain during evaluation at the Rheumatology Clinic of Taichung Veterans General Hospital (Taiepi, Taiwan) regardless of DAS28 score, and were at least 20 years old. Patients were excluded if they had severe wrist joint deformity that did not allow 3D PDUS assessment, symptoms or signs suggesting infection, urine dipstick test results positive for nitrites, no grey-scale US evidence of wrist synovitis, and no detectable wrist joint intrasynovial Doppler signal by 2D PDUS. All participants signed informed consent agreements and received clinical, laboratory, and 2D/3D PDUS assessments as described below.

Clinical and laboratory assessment

Clinical evaluation was performed independently by a rheumatologist who was blinded to the PDUS findings. The following data were recorded for each patient at study entry: age, gender, and presence of rheumatoid factor (RF). Blood samples were taken within 24 h for ESR and CRP analysis by standard laboratory techniques. The possibility of co-existing infection was excluded by use of a structured screening questionnaire, physical examination, and urinanalysis. A patient was excluded if symptoms or signs suggested infection or if the urine dipstick test was positive for nitrites. Scores on a global pain intensity visual analogue scale (VAS, range: 0-10) and a VAS for overall assessment of disease activity were recorded.

US protocol

The participants underwent 3 consecutive US assessments in a dark room at 25ºC within 30 min of clinical evaluation. The two sonographers (H.H. Chen and K.L. Lai) are certified rheumatologists experienced in musculoskeletal ultrasonography, were unaware of previous clinical, laboratory, and radiographic findings, and were not involved in treatment decisions. H.H. Chen performed the first and third US assessments and K.L. Lai performed the second US assessment. The US images and data were stored by another sonographer who performed US assessments of the same patients. Patients were asked not to talk about their clinical symptoms with the US examiners and the US examiners were asked not to talk with each other about their findings. The sonographers informed the rheumatologists who cared for these patients based on US findings.

2D PDUS

Synovial blood flow was evaluated by PDUS in wrist joints with the scanning method described above. The 2D PDUS imaging was performed by selecting a region of interest (ROI) with high Doppler signal intensity, including the bony margins, articular space, and a variable view of surrounding tissues (Fig. 1). PDUS settings had a pulse repetition frequency of 500 Hz and a low wall filter. Colour gain was set just below the level at which colour noise appeared underlying bone, with no flow visualised at the bony surface. Active synovitis was defined by the presence of an intrasynovial PDUS signal. Patients with no detectable intrasynovial Doppler signal by 2D PDUS with both transducers were excluded. For patients with active synovitis in both joints, an overall US joint index for the power Doppler signal (sum of power Doppler signal scores from each joint) was calculated at each US assessment.

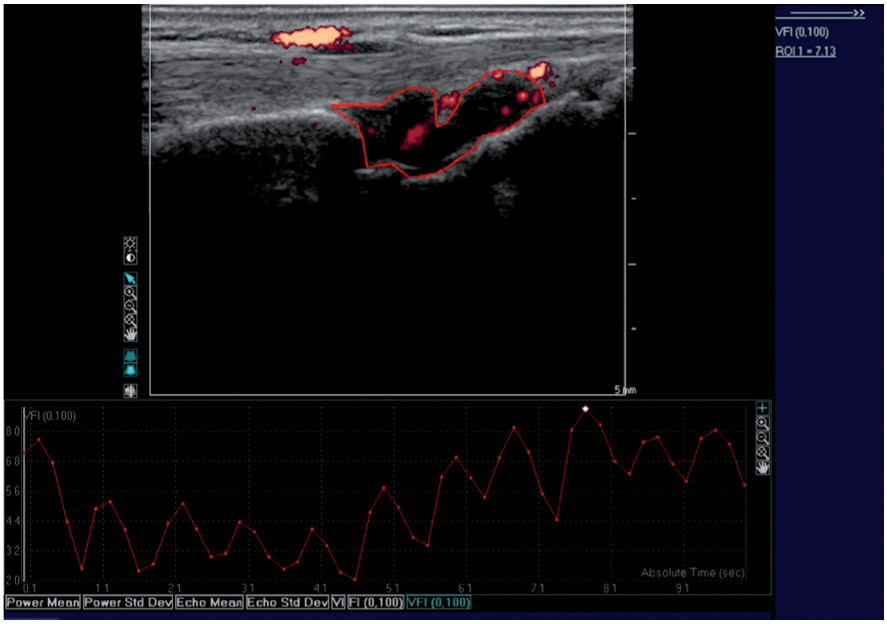

Fig. 1. Procedure used for analysis of 2-dimensional power Doppler ultrasound (2D-PDUS) images. The upper figure shows the manually selected region of interest (ROI) of a wrist joint, based on QLAB software provided by Philips. The ROI was calculated automatically thereafter. The lower figure shows the change of the velocity flow index (VFI), in accordance with the cardiac cycle. The largest VFI was selected if noise was absent in the ultrasound image. VI and FI data corresponding to the selected point were collected for analysis.

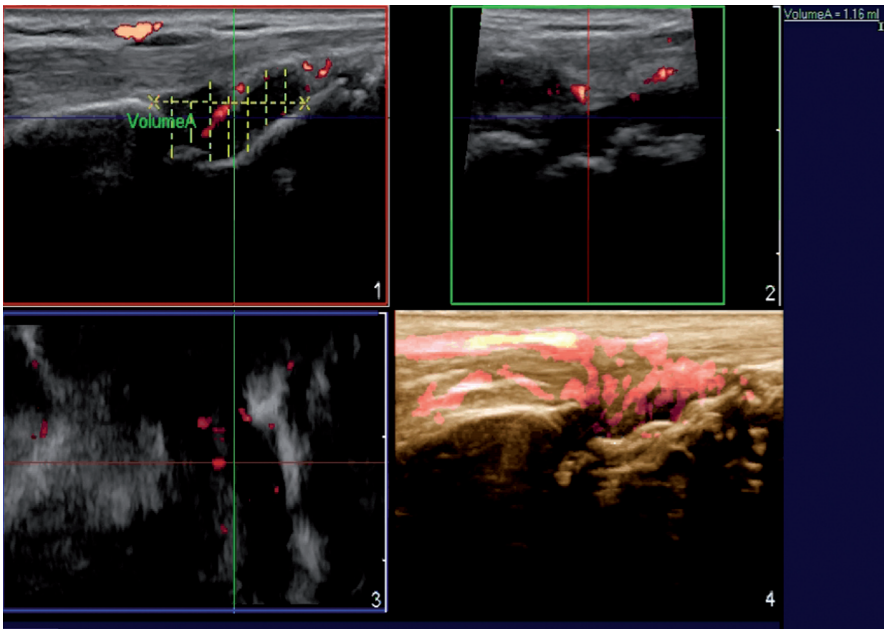

Fig. 2. Procedure used for analysis of 3-dimensional power Doppler ultrasound (3D-PDUS) images. In the longitudinal view of a wrist joint (1), the start and end points of the axis were first selected manually, and the QLAB software automatically generated 7 vertical lines for subsequent transverse views (2). After manual selection of the ROI (the joint capsule) for each transverse image, the volume, VI, FI, VFI were calculated automatically. Image 3 shows the bird's eye view. Image 4 shows the reconstructed 3D image.

3D PDUS

Immediately after acquisition of a 2D PDUS image, the ultrasonography machine was switched to 3D mode and measurements were performed in the same ROI, with the same volumetric transducer, and no movement of the probe (Fig. 2). Then the transducer automatically scanned 15 degrees to obtain a sequence of 2D PDUS images to provide the third dimension. The resulting truncated sector covering the joint capsule in a longitudinal plane was adjusted, and the sweep angle was set to ensure that a complete joint capsule volume was obtained if possible. The patient and the 3D probe remained as still as possible during volume acquisition. The 3D power Doppler function, provided by the Philips iU22 vascular software, was used to generate a 3-D image of the intra-articular blood vessels, in which grey-scale information of the surrounding tissue was already subtracted. If the volume measurement was completed without a power Doppler artifact, the data set was stored for later analysis. The acquired data were stored on hard disk as a cine loop, in which the 3D blood vessel tree can be viewed as it rotates, in order to enhance depth perception and provide a true 3D perspective.

Computer-aided quantification of 2D- and 3D-PDUS data

The Philips QLAB software was used for 2D and 3D ultrasound measurements, including measurement of the joint capsule volume and indices of blood flow within the joint capsule. The vascularisation index (VI, range: 0-100%) is the ratio of the number of colour voxels to the total number of voxels, *i.e.* a measure of the number of blood vessels (vascularity) in the synovium, and was expressed as a percentage of the joint capsule volume. The flow index (FI, range: 0-100%) is the mean power Doppler signal intensity inside the joint capsule, and is a measure of the average intensity of flow. The vascularisation flow index (VFI, range: 0-100%)is a combination of the VI and the FI. For analysis of the correlation of these PDUS indexes with clinical data, the indexes from three US assessments were averaged. If intrasynovial Doppler signals were present in both wrists, the PDUS indexes were summed prior to correlation analysis.

Primary and secondary endpoints

There were 2 primary endpoints:

i. significant correlation of 2D- and 3D-PDUS indexes (VI, FI, and VFI) with clinical data, including pain score, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP); and

ii. significant difference between 2D PDUS indexes obtained with a volumetric transducer and a linear ("hockey stick") transducer. The secondary endpoint was significant intra- and inter-operator agreement of 2D and 3D PDUS indexes for wrist joint vascularity.

Statistical analysis

Categorical variables are presented as counts and percentages. Two continuous variables (age and VAS score) had normal distributions and are presented as means and standard deviations (SDs). The other continuous variables (ESR, CRP, and RF) had non-normal distributions and are presented as medians and inter-quartile ranges (IQRs). Differences between the two-dimensional power Doppler ultrasonography (2D PDUS) data obtained by volumetric and linear transducers were compared using a paired *t*-test. Pearson's correlation coefficient (Pearson's *r*) was used to assess the associations between 2D and 3D PDUS data and VAS score. Spearman's rank correlation coefficient (Spearman's ϱ) was used to assess associations between 2D and 3D PDUS data and ESR, CRP, and RF. Intraclass correlation coefficients (ICCs) were used to compare measurement reliability (intra-operator and inter-operator agreement). The intra-operator agreement data were obtained from one operator who has 11 years of experience with PDUS. The inter-operator agreement data were obtained from two operators who had 11 years and 7 years of experience with PDUS. All statistical assessments were two-sided and a *p*-value of 0.05 was considered significant. Statistical analyses were performed with SAS software version 9.2 (SAS Institute Inc., Cary, NC).

Results

Table I summarises the basic demographic and clinical characteristics of the 49 enrolled patients and the 60 analysed hand joints. There were 8 males and 41 females and the average age was 47.59±15.17 years. The average VAS score was 3.63±2.22 (range: 0 to 10). The median (IQR) ESR, CRP, and RF values were 28.00 mm/h (21.00, 49.00), 0.66 mg/L (0.15, 2.06), and 39.50 IU/mL (0, 116.00), respectively. There were 37 right wrist joints and 23 left wrist joints subjected to analysis.

Table II shows the correlations of 2D and 3D-PDUS indexes with 4 clinical parameters. The results indicate no significant correlations of VAS score or RF with the 2D V, 2D L, or 3D PDUS indexes. However, in 2D L there were statistically significant correlations of ESR with VI (ϱ=0.3260) and VFI (ϱ=0.3259) ($p<0.05$ for both). There were also significant correlations of CRP with area (ϱ=0.3476), VI (ϱ=0.4292), and VFI (ϱ=0.4219) in 2D L, and with VFI in 3D (ϱ=0.3239) ($p<0.05$ for all).

Table III compares the results obtained by 2D PDUS with use of the volumetric and linear transducers. The average 2D PDUS VI and VFI obtained by the linear transducer were significantly higher than those obtained by the volu-

Table I. Demographic and clinical characteristics of enrolled rheumatoid arthritis patients (49 patients, 60 hand joints). Data are presented as mean ± SD, number (percentage), or median (IQR) as indicated.

Characteristic	
Age, years[1]	47.59 ± 15.17
Gender[2]	
Male	8 (16.33%)
Female	41 (83.67%)
Clinical data	
VAS score[1]	3.63 ± 2.22
ESR[3], mm/h	28.00 (21.00, 49.00)
CRP[3], mg/L	0.66 (0.15, 2.06)
RF[3], IU/mL	39.50 (0, 116.00)
Affected joint[2]	
Right wrist	37 (61.67%)
Left wrist	23 (38.33%)

Data are presented as [1]: mean ± standard deviation; [2]: number (percentage); [3]: median (IQR). VAS: visual analogue scale; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor.

metric transducer (VI: 21.16±14.11 *vs*. 15.10±11.01, $p<0.001$; VFI: 12.60±8.66 *vs*. 10.67±8.05, $p=0.006$). However, the average 2D PDUS FI obtained by the volumetric transducer was significantly higher than that obtained by the linear transducer (69.39±3.74 *vs*. 58.82±3.97, $p<0.001$).

Table IV shows the results of our analysis of intra-operator agreements, determined by calculation of ICCs. In 2D PDUS with the volumetric transducer, there was a moderate level of agreement in the FI (ICC of 0.7339), and high levels of agreement in area, VI, and VFI (ICCs of 0.9715, 0.9716, and 0.9707, respectively). In 2D PDUS with the linear transducer, all indexes had high levels of agreement (ICCs of 0.9103 to 0.9586). Notably, the ICC of the FI in 2D L was significantly higher than that in 2D V, as indicated by no overlap of the confidence intervals. In 3D PDUS, all indexes had high levels of agreement (ICCs of 0.9287 to 0.9751).

Table V shows the results of our analysis of inter-operator agreement, determined by calculation of the ICCs. In 2D PDUS with the volumetric transducer, there was a moderate level of agreement in FI (ICC of 0.8682), and high levels of agreement in area, VI, and VFI (ICCs of 0.9778, 0.9729, and 0.9728, respectively). In 2D PDUS with the linear transducer, there was a moderate level of agreement in FI (ICC of 0.8850), and high levels of agreement in area, VI, and VFI (ICCs of 0.9737, 0.9713, and 0.9660, respectively). In 3D PDUS, there was poor agreement in area (ICC of 0.3681), moderate agreement in FI (ICC of 0.8399), and high agreement in VI and VFI (ICC of 0.9745 and 0.9739, respectively).

Discussion

The objective of this study was to compare the performance of different PDUS measurement modes (2D with a volumetric probe, 2D with a linear probe, and 3D with a volumetric probe) in the evaluation of wrist joint inflammation in patients with RA. It might be expected that 3D-PDUS would provide more accurate and reproducible results because this mode provides a significantly larger data set. However, our statistical analy-

Table II. Correlation of 2D/3D-PDUS indexes with clinical data.

	VAS score†	ESR‡	CRP‡	RF‡
2D V				
Area	0.1179	0.0740	0.2341	0.1485
VI	0.1638	0.1495	0.2453	-0.0702
FI	0.0003	0.0351	0.0438	-0.1482
VFI	0.1540	0.1472	0.2325	-0.0730
2D L				
Area	0.1697	0.2421	0.3476*	0.1620
VI	0.2264	0.3260*	0.4292*	0.0827
FI	0.1757	-0.0463	0.0383	0.0289
VFI	0.2247	0.3259*	0.4219*	0.0801
3D				
Volume	0.1335	0.1009	0.1139	0.0811
VI	0.2172	0.1650	0.3342	0.0319
FI	0.1218	0.1038	0.1267	-0.0536
VFI	0.2155	0.1522	0.3239*	0.0313

*Significant correlation ($p<0.05$); †Assessed by Pearson's correlation coefficient; ‡Assessed by Spearman's rank correlation coefficient.
2D: two-dimensional; 3D: three-dimensional; PDUS: power Doppler ultrasonography; VAS: visual analogue scale; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor; V: volumetric probe; L: linear probe; VI: vascularisation index; FI: flow index; VFI: vascularisation flow index.

Table III. Comparison of 2D PDUS indexes obtained by volumetric and linear transducers. Data are presented as means ± standard deviations.

	Volumetric transducer	Linear transducer	*p*-value
Area	82.83 ± 27.88	80.62 ± 24.55	0.272
VI	15.10 ± 11.01	21.16 ± 14.11	<0.001*
FI	69.39 ± 3.74	58.82 ± 3.97	<0.001*
VFI	10.67 ± 8.05	12.60 ± 8.66	0.006*

*Indicates a significant difference ($p<0.05$) based on a paired *t*-test.
2D: two-dimensional; PDUS: power Doppler ultrasonography; VI: vascularisation index; FI: flow index; VFI: vascularisation flow index.

Table IV. Intraclass correlation coefficients (95% CIs) for intra-operator agreement.

	2D V	2D L	3D
Area /Volume	0.9715 (0.9531, 0.9828)	0.9586 (0.9321, 0.9749)	0.9610 (0.9360, 0.9764)
VI	0.9716 (0.9532, 0.9828)	0.9348 (0.8939, 0.9603)	0.9751 (0.9590, 0.9850)
FI	0.7339 (0.5935, 0.8310)	0.9103 (0.8552, 0.9451)	0.9287 (0.8842, 0.9565)
VFI	0.9707 (0.9518, 0.9823)	0.9291 (0.8849, 0.9567)	0.9737 (0.9567, 0.9841)

CI: confidence interval; 2D: two-dimensional; 3D: three-dimensional; V: volumetric probe; L: linear probe; VI: vascularisation index; FI: flow index; VFI: vascularisation flow index.

Table V. Intraclass correlation coefficients (95% CIs) for inter-operator agreement.

	2D V	2D L	3D
Area /Volume	0.9778 (0.9634, 0.9866)	0.9737 (0.9567, 0.9841)	0.3681 (0.1314, 0.5651)
VI	0.9729 (0.9554, 0.9836)	0.9713 (0.9527, 0.9826)	0.9745 (0.9580, 0.9846)
FI	0.8682 (0.7901, 0.9186)	0.8850 (0.8159, 0.9292)	0.8399 (0.7473, 0.9005)
VFI	0.9728 (0.9552, 0.9836)	0.9660 (0.9441, 0.9794)	0.9739 (0.9570, 0.9842)

CI: confidence interval; 2D: two-dimensional; 3D: three-dimensional; V: volumetric probe; L: linear probe; VI: vascularisation index; FI: flow index; VFI: vascularisation flow index.

sis showed that 2D- and 3D-PDUS both had similarly high accuracy and reliability. In fact, 2D-PDUS with the 7-15 MHz linear ("hockey stick") transducer detected more Doppler signals than the 5-13 MHz volumetric transducer. Our calculation of ICCs indicated that all three measurement modes had very good intra- and inter-operator agreement. This is the first study to assess the reliability of computer-aided quantification of 2D- and 3D-PDUS imaging for assessment of wrist joint inflammation in RA patients and to compare the performance of different transducers for 2D-PDUS quantification in these patients.

A 2007 review of the use of semi-quantitative and quantitative PDUS for evaluation of synovial infusion in the joints of patients with RA concluded that the absence of a reproducible method for quantification is one of the main disadvantages of this method compared with MRI and contrast-enhanced US (16). A 2006 study reported that 2D-PDUS with a 10-14-MHz linear probe was able to identify rapid and significant changes in the synovial perfusion of the wrist joints of patients with RA who were given adalimumab, a TNF-α inhibitor (17). In agreement, a more recent study indicated that 2D-PDUS was effective for assessment of therapeutic response of 24 RA patients who were treated with adalimumab, with good-to excellent inter-observer reliability and moderate inter-machine reliability (18). Terslev *et al*. studied 8 patients with RA and 27 healthy controls and reported that PDUS had high sensitivity and moderate specificity in the measurement of vascularisation of inflamed synovia of multiple joints (19). Filippucci *et al*. (20) reported good-to-excellent agreement for 2D and 3D PDUS in evaluation of joint inflammation and bone erosion. The principal clinical contribution of the present study is that the quantitative data provided by 2D-PDUS with a linear or volumetric transducer was just as accurate and reliable as the quantitative data provided by 3D-PDUS. For the software that we used (QLAB), only ~30 s are needed to analyse the 2D data, but more than 3 min is needed to analyse the 3D data. In addition, a 3D sensor is significantly more expensive. Thus, our results indicate a clear advantage in the use of 2D-PDUS for evaluation of wrist joint synovia.

The present study had several limitations. First, there were only 49 patients and all of the patients were from a limited geographic region. Second, we used the 1987 ACR criteria (4) rather than the 2010 ACR criteria (21) for diagnosis of RA because most of these subjects (42/49) were diagnosed before 2010. Finally, we only assessed wrist joint inflammation at one point in time, and did not perform longitudinal follow-ups or assess the response to various treatments. In conclusion, our analysis of the use computer-aided quantification data for wrist joint vascularity in patients with RA by use of 2D- and 3D-PDUS indicated that all 3 tested methods had good accuracy and reproducibility in measurement of wrist vascularity. These results provide no basis for the use of a 3D-PDUS transducer, which is more expensive and more time-consuming, for measurements of wrist joint inflammation.

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