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ORIGINAL ARTICLE

# Analysis of the factors which influence the measurement of synovial power Doppler signals with semi-quantitative and quantitative measures – a pilot multicenter exercise in Japan

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## Abstract

*Objectives.* This pilot multicenter exercise aimed to evaluate the inter-observer reproducibility of synovial power Doppler (PD) signals in rheumatoid arthritis (RA) patients and to determine the factors influencing the measurements.
*Methods.* Two representative RA patients were assessed by four independent experienced sonographers. The influence of machine difference, deterioration of the transducer and pulse repetition frequency (PRF) on the assessment of synovial PD signals was investigated.
*Results.* Intra-class correlation coefficient (ICC) for the scanner–reader reproducibility of semi-quantitative PD score was high (0.867). ICC for the inter-scanner reproducibility of synovial PD pixel count was higher than that of semi-quantitative PD score. The assessment of PD signals significantly differed between two machines with quantitative measurements but did not with semi-quantitative score. The assessment of PD signals with a deteriorated transducer was much less sensitive than that with an intact one. The semi-quantitative scores for PD signals were comparable between three different PRFs (500/800/1,300 Hz), whereas the pixel count was significantly lower with the highest one in the knee joint.
*Conclusions.* Measurement of PD signal can be substantially affected by deteriorated quality of the transducer, whereas the differences are relatively modest between machines with similar specifications and also between PRF settings within a low range.

## Keywords

Inter-observer reliability, Power Doppler, Pulse repetition frequency, Rheumatoid arthritis, Standardization, Ultrasound

## History

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## Introduction

The utility of musculoskeletal ultrasound in the management of rheumatoid arthritis (RA) has been extensively studied over the last decade. In particular, the advanced Doppler technique enabled the assessment of fine synovial blood flow, which represents synovial inflammation characteristic to RA. The synovial Doppler signals have been shown to be associated with the inflammation demonstrated by histopathology [1–3], magnetic resonance imaging [4–7], clinical and laboratory parameters [8–10], and also with subsequent radiographic progression [7,11–14]. This property of Doppler ultrasound to depict active and pathological inflammation has been reported to improve the accuracy of diagnosis [15–19] and optimize the assessment of disease activity of RA [11,20,21].

The more widely the Doppler ultrasound is used, the more important becomes the standardization of the measurement. As the assessment of reliability comprises an important part of the standardizing process, the OMERACT ultrasound task force [22] and many other investigators [7,23–29] have reported the reliability of Doppler ultrasound in RA. However, no studies, to our knowledge, have assessed both the reproducibility of interpretation of the acquired image between the sonographer and the independent reader and the reproducibility of the whole process including image acquisition between sonographers. Furthermore, only one recent study [29] has directly compared the reliability between semi-quantitative and quantitative measures, both of which have been shown to be useful in the measurement of synovial Doppler signals in RA.

Some factors that are considered to influence the sensitivity of the measurement for synovial Doppler signal, such as machine specification, deterioration of the transducer and pulse repetition frequency (PRF), are appreciated by ultrasound experts but mostly based on their experience and theory but not necessarily on the accumulated evidence from RA patients. In addition, the influence of these factors on synovial Doppler signal has not been compared yet between semi-quantitative score and quantitative measures.

In this pilot multicenter exercise, we separately evaluated the scanner–reader and inter-scanner reproducibility. We also aimed to determine the influence of machine difference, deterioration of the transducer and PRF setting on the assessment of synovial Doppler signals in RA patients. All measurements were performed with both semi-quantitative score and quantitative methods, enabling the comparisons between two different approaches.

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## Patients and methods

### Patients

Two representative patients receiving treatment for RA in Hokkaido Medical Center for Rheumatic Diseases gave written consent to be a subject to be examined in this pilot multicenter exercise. The study design and procedure were approved by the Ethics Committee of Chiba University. Both patients fulfilled the ACR 1987 revised criteria for the classification of RA [30] and had active synovitis with power Doppler (PD) signals both in the metacarpo-phalangeal (MCP) joint and in the knee joint on the previous ultrasound examination. Data were collected in a one-day exercise which was held in Hokkaido Medical Center for Rheumatic Diseases.

### Ultrasound examination

Ultrasound was performed in a temperature-controlled room using either HI VISION Avius (Hitachi Medical Corporation, Tokyo, Japan) or Prosound $\alpha 7$ (Aloka Co., Tokyo, Japan) with a linear array transducer (Hitachi EUP-L75 for HI VISION Avius, Aloka UST-5411 for Prosound $\alpha 7$). For Aloka UST-5411, two transducers in different conditions were used for comparison: a brand new one (intact transducer) and one which underwent extensive use [35 h/week (average) for 162 weeks] without proper maintenance (deteriorated transducer). The deteriorated transducer was apparently indistinguishable from the intact one. PRF was set at 1,300 Hz, the lowest setting, for Prosound $\alpha 7$ and at either 500, 800, or 1,300 Hz for HI VISION Avius for comparison. The third lowest wall filter out of six levels was applied for Prosound $\alpha 7$, and medium wall filter out of three levels was applied for HI VISION Avius, according to the manufacturers' recommendation.

An experienced sonographer (AN) performed a brief ultrasound examination before the data collection on the same day to identify the MCP and knee joints with the most increased PD signals for each patient. A scanning site within the joint was also determined in order to minimize the time required for image acquisition.

Four experienced sonographers from different institutes (KI, YS, SO and FS) performed the ultrasound scanning for the data analyses. Each pre-defined joint was scanned for five times under different conditions by each sonographer. All sonographers were blinded to the detailed clinical information, the condition of transducers, PRF setting and the information from scanning by other sonographers. Color gain was manually adjusted just below the level at which color noise appeared and the imaging plane with the most increased synovial PD signals was determined by the sonographer. Video images in the plane were recorded for a length of time containing at least three pulses. For the feasibility analysis, the time required to finish the image acquisition for each joint was also recorded.

Synovial PD signals were subjectively graded by the sonographer who performed the scan on a semi-quantitative scale of 0–3 (Grade 0, normal; Grade 1, mild; Grade 2, moderate; Grade 3, marked). An independent rater (AN) who was blinded to the score graded by the scanner also graded the PD signals based on the recorded images. Synovial PD signals were also evaluated using the software installed in the machine. Pixel count, which was defined as the automatically counted number of vascular flow pixels in the region of interest (ROI), was recorded. ROI was manually placed outlining the thickened synovium by a single sonographer experienced in this procedure (AN). Percentage of pixel count (% pixel count), which was defined as the proportion of the pixel count for PD signals to the total pixel count within the ROI, was also recorded.

The length of experience in musculoskeletal ultrasound for the five sonographers who scanned in this study ranged from 7 to 11 (median 8) years.

### Statistical analysis

Statistical analysis was performed using SPSS version 16.0J (IBM Japan, Tokyo, Japan). Normally distributed continuous data were summarized with means and standard deviation or 95% confidence interval (CI) and were analyzed using parametric tests (Student's t test, paired t test or one-way repeated measures ANOVA). Non-normally distributed data were summarized with medians and inter-quartile ranges and were analyzed using nonparametric tests (Wilcoxon's signed-rank test, Friedman's test or Spearman's rank correlation coefficient). Categorical data were summarized with percentages and were analyzed using chi-square test, Fisher's exact test or McNemar's test. $P$ values less than 0.05 were considered significant.

Inter-observer reproducibility was analyzed by calculating the intra-class correlation coefficient (ICC) (2,1) for absolute agreement.

## Results

### Patient characteristics

The 1st patient (Case 1) was a 55-year-old woman with a disease duration of 14 months. The patient had a clinically active disease (CDAI 33.3, CRP 112 mg/L) although she was receiving tocilizumab 8 mg/kg/4 weeks and prednisolone 7.5 mg/day. The 2nd patient (Case 2) was a 50-year-old man with a disease duration of 21 months. The patient did not show active disease by conventional measures (CDAI 5.0, CRP 0.1 mg/L) receiving the treatment with methotrexate 6 mg/week, tocilizumab 8 mg/kg/4 weeks and prednisolone 7.5 mg/day.

In the pre-study ultrasound examination, the joints and the sites for each patient were determined: the dorsal aspect of the right 2nd MCP joint and the medial aspect of the suprapatellar pouch in the right knee joint for Case 1, and the dorsal aspect of the left 2nd MCP joint and the lateral aspect of the suprapatellar pouch in the right knee joint for Case 2. Due to the time limitation, the knee joint of Case 2 was only assessed by two sonographers (KI and FS).

### Correlation between semi-quantitative score and quantitative measures

All available measurements in this exercise ($n = 70$) were used to collectively analyze the relationship between semi-quantitative score and quantitative measures. As shown in Supplementary Figure S1 available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2013.843763, the semi-quantitative score significantly correlated with the corresponding pixel count (2nd MCP $\rho = 0.743$, $P < 0.001$; Knee $\rho = 0.772$, $P < 0.001$). Correlation between semi-quantitative score and the corresponding % pixel count was also statistically significant but the correlation was comparatively weaker in the 2nd MCP joints (2nd MCP $\rho = 0.575$, $P < 0.001$; Knee $\rho = 0.779$, $P < 0.001$).

### Scanner–reader and inter-scanner reproducibility

Next, we assessed the scanner–reader reproducibility by comparing the semi-quantitative scores for synovial PD signals between the scanner and the independent reader. As shown in Supplementary Figure S2 available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2013.843763, the observed differences between scanner and reader were modest, and ICCs for these measurements were very high (0.809–0.911) (Table 1, left columns,

Table 1. ICCs for scanner-reader and inter-scanner reproducibility of the measurements for PD signals.

| | ICC (95%CI) for scanner–reader reproducibility | | | ICC (95%CI) for inter-scanner reproducibility | | |
|---|---|---|---|---|---|---|
| Measurement | Total | 2nd MCP | Knee | Total | 2nd MCP | Knee |
| Semi-quantitative score | 0.867 (0.799–0.914) | 0.911 (0.838–0.952) | 0.809 (0.658–0.897) | 0.757 (0.565–0.896) | 0.778 (0.547–0.929) | 0.757 (0.390–0.966) |
| Pixel count | NA | NA | NA | 0.872 (0.748–0.949) | 0.790 (0.567–0.933) | 0.884 (0.646–0.985) |
| % Pixel count | NA | NA | NA | 0.789 (0.610–0.912) | 0.767 (0.530–0.925) | 0.851 (0.570–0.981) |

CI, confidence interval; MCP, metacarpo-phalangeal joint; NA, not applicable.

1st row). These results suggest that the semi-quantitative grading of synovial PD signals can be reliably reproduced by another rater based on the recorded images.

Comparisons of the semi-quantitative scores for synovial PD signals between the four independent scanners who also graded the images are summarized in the gray-scale heat map in Figure 1. The differences between the scanners were modest, and thus, the ICCs for these measurements were high (2nd MCP 0.778, knee 0.757) (Table 1, right columns, 1st row). ICCs for the pixel counts for synovial PD signals between the four independent scanners were numerically even higher (2nd MCP 0.790, knee 0.884) (Figure 2; Table 1, right columns, 2nd row) than those for the semi-quantitative scores. ICCs for the % pixel counts were also high (2nd MCP 0.767, knee 0.851) (Figure 3; Table 1, right columns, 3rd row) but not as high as those for the absolute pixel counts. These results suggest that the measurements of synovial PD signals by experienced sonographers are reproducible in both small and large joints with both semi-quantitative scores and pixel-based measurements.

### Difference between machines

The semi-quantitative scores for synovial PD signals with two machines were comparable when other factors were matched (median 2 vs. 2, $P = 1.000$ for the 2nd MCP joint; median 2 vs. 2, $P = 0.564$ for the knee joint, Wilcoxon's signed-rank test) (Figure 1, 3rd and 4th rows). In contrast, the pixel counts for synovial PD signals were significantly smaller with Prosound α7 than with HI VISION Avius both in the 2nd MCP joint (mean 3732.6 vs. 7484.4, $P = 0.008$) and in the knee joint (mean 5312.0 vs. 9609.5, $P = 0.002$) (Figure 2, 3rd and 4th rows; Figure 4, upper panels). However, the difference in % pixel counts was less obvious both in the 2nd MCP joint (mean 23.0% vs. 35.3%, $P = 0.020$) and in the knee joint (mean 17.8% vs. 23.7%, $P = 0.058$) (Figure 4, lower panels). These results indicate that the assessment for synovial PD signals does not significantly differ between HI VISION Avius and Prosound α7 when semi-quantitative score is used, whereas it can significantly differ when pixel-based measurements, especially the absolute count without standardization, are used.

### Difference between conditions of a transducer

The semi-quantitative scores for synovial PD signals markedly decreased when ultrasound was performed with the deteriorated transducer both in the 2nd MCP joint (median 0 vs. 2, $P = 0.011$) and in the knee joint (median 0 vs. 2, $P = 0.024$, Wilcoxon's signed-rank test) (Figure 1, 4th and 5th rows). The pixel counts for synovial PD signals decreased even more significantly with the use of deteriorated transducer both in the 2nd MCP joint (mean 247.6 vs. 3732.6, $P = 0.005$, paired t test) and in the knee joint (median 485.8 vs. 5312.0, $P = 0.015$, paired t test) (Figure 2, 4th and 5th rows; Figure 5, upper panels). These results indicate that the condition of a transducer can substantially influence the measurement of synovial PD signals.

The PD gain values adjusted by the scanner unaware of the transducer condition were not significantly different between the two conditions (intact/deteriorated) of the transducer in the 2nd MCP joint [mean PD gain (dB) 63.6 vs. 66.6, $P = 0.609$, paired t test] but were significantly smaller with intact condition than with deteriorated one in the knee joint [mean PD gain (dB) 62.2 vs. 66.3, $P < 0.001$, paired t test]. The time required to obtain the images was not significantly different between the two conditions (intact/deteriorated) of the transducer either in the 2nd MCP joint [mean required time (sec) 108.7 vs. 100.7, $P = 0.629$, paired t test] or in the knee joint [mean required time (sec) 92.0 vs. 86.7, $P = 0.724$, paired t test].

### Difference between PRF settings

The semi-quantitative scores for synovial PD signals were comparable between the three different PRF settings (500/800/1,300 Hz) in the 2nd MCP joint (median 3 vs. 2 vs. 2, $P = 0.368$, Friedman's test) (Figure 1, 1st–3rd rows). In the knee joint, the semi-quantitative scores tended to be higher with the lowest PRF (500 Hz) than with the highest PRFs (800/1,300 Hz) but without statistical significance (median 3 vs. 2/2, $P = 0.097$, Friedman's test) (Figure 1, 1st–3rd rows). On the other hand, difference in the pixel counts for synovial PD signals between the three different PRF settings was not statistically significant in the 2nd MCP joint (mean count 10,020.0 vs. 8,711.0 vs. 7,484.4, $P = 0.263$, one-way repeated measures ANOVA), while the pixel count was significantly lower with the highest PRF (1,300 Hz) than with the lowest PRFs (800/500 Hz) in the knee joint (mean 20,967.8/19,232.7 vs. 9,609.5, $P = 0.001$, one-way repeated measures ANOVA, confirmed by paired t tests) (Figure 2, 1st-3rd rows; Figure 5, lower panels).

The color gain values adjusted by the scanner blinded to the PRF setting and the time required to obtain the images were not

| Machine | Transducer | PRF (Hz) | 2nd MCP joint | | | | | | | | Knee joint | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Case 1 | | | | Case 2 | | | | Case 1 | | Case 2 | | | |
| | | | Scanner | | | | Scanner | | | | Scanner | | Scanner | | | |
| | | | A | B | C | D | A | B | C | D | A | B | A | B | C | D |
| Avius | Intact | 500 | 2 | 3 | 2 | 3 | 3 | 3 | 2 | 3 | 2 | 2 | 3 | 3 | 2 | 3 |
| Avius | Intact | 800 | 2 | 3 | 2 | 2 | 2 | 3 | 2 | 3 | 2 | 2 | 3 | 2 | 2 | 3 |
| Avius | Intact | 1,300 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 2 | 2 | 2 | 2 | 2 | 2 |
| Prosound | Intact | 1,300 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 1 | 1 | 2 | 2 | 2 | 3 |
| Prosound | Deteriorated | 1,300 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 0 |

Figure 1. Comparisons of the semi-quantitative scores for synovial PD signals between four independent scanners. MCP, metacarpo-phalangeal; PRF, pulse repetition frequency; PD, power Doppler.

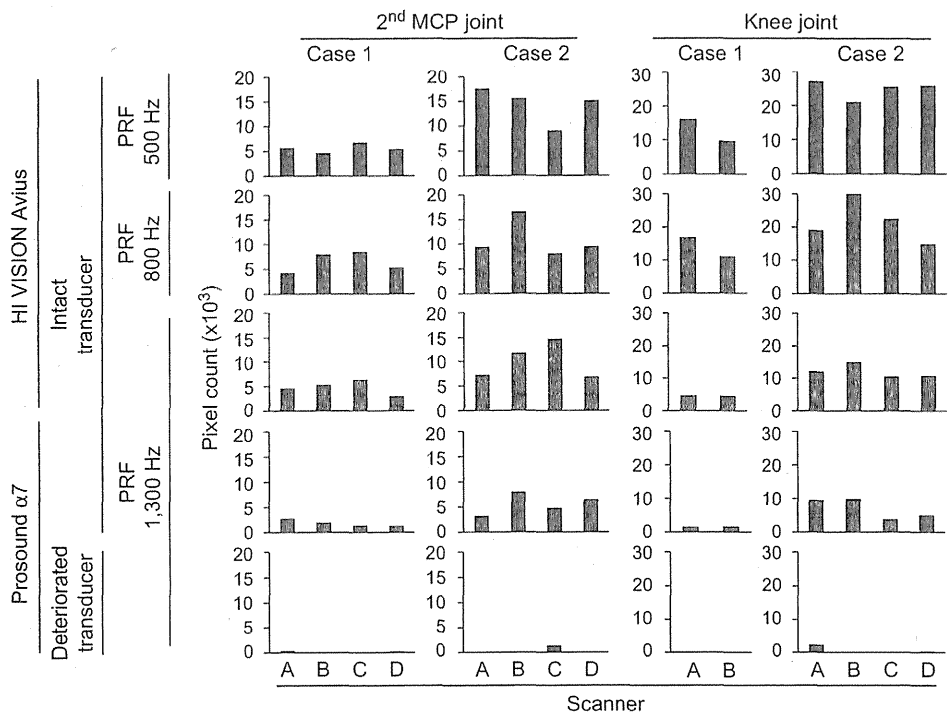


Figure 2. Comparisons of the pixel counts for synovial PD signals between four independent scanners. MCP, metacarpo-phalangeal; PRF, pulse repetition frequency; PD, power Doppler.

significantly different between the three PRF settings (500/800/1,300 Hz) either in the 2nd MCP joint [mean PD gain (dB) 39.3 vs. 40.5 vs. 40.6, $P = 0.359$; mean required time (sec) 140.1 vs. 102.8 vs. 183.3, $P = 0.059$, one-way repeated measures ANOVA] and in the knee joint [mean PD gain (dB) 38.7 vs. 38.7 vs. 39.8, $P = 0.098$; mean required time (s) 75.0 vs. 73.3 vs. 123.3, $P = 0.171$, one-way repeated measures ANOVA].

## Discussion

This exercise provided unique information on the inter-observer reproducibility of PD signal measurement comparing between semi-quantitative score and quantitative measures. In addition, our data confirmed that the inter-scanner reproducibility is lower than scanner–reader reproducibility (Table 1), which can be interpreted as that the image acquisition process actually gives rise to the variability of PD signal measurement. Our data also demonstrate that the PD signal measurement in the large joint is not necessarily less reproducible than that in the small joint when the scanning site is pre-specified and also confirmed the previous finding that the pixel count is more reproducible than semi-quantitative score (Table 1).

The previous studies demonstrated that the difference in the measurement of synovial PD signal can be considerable between

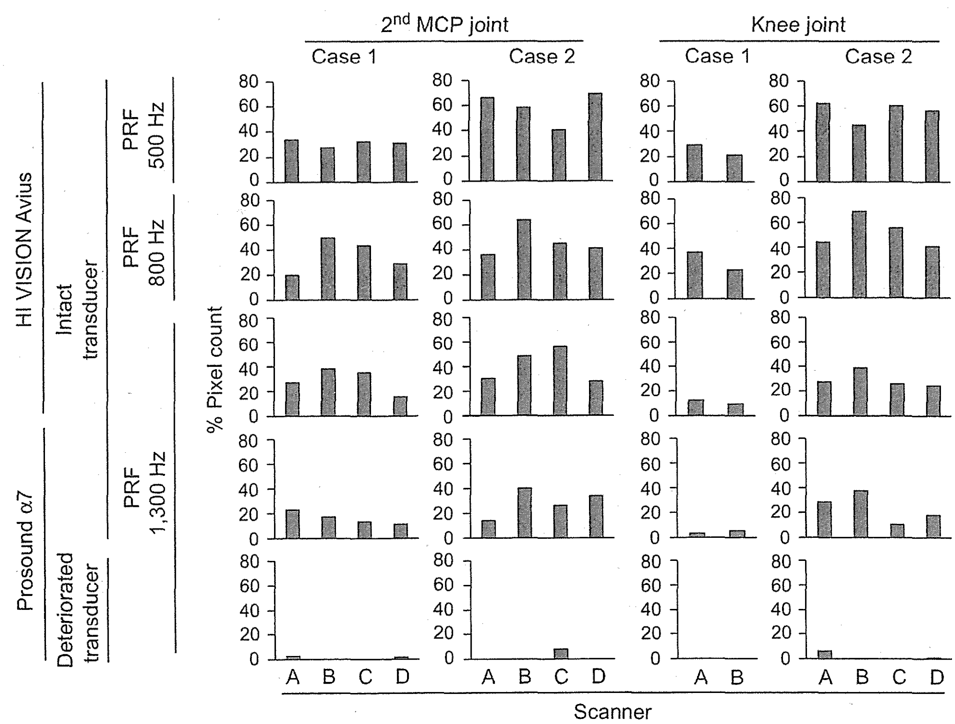


Figure 3. Comparisons of the % pixel counts for synovial PD signals between four independent scanners. MCP, metacarpo-phalangeal; PRF, pulse repetition frequency; PD, power Doppler.

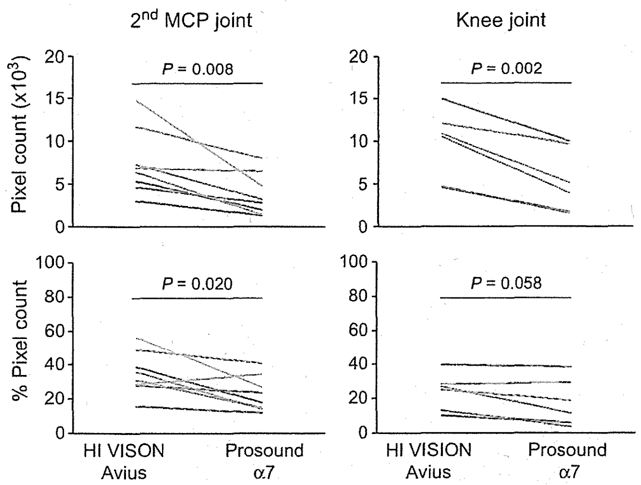


Figure 4. Comparisons of the pixel counts for synovial PD signals between two different machines. Pixel counts for synovial PD signals were compared separately for the MCP joints (left panels) and for the knee joints (right panels) either in the absolute counts (upper panels) or in the proportions to the total pixel counts in the ROI (lower panels). Each colored line represents the measurement of the same joint in the same patient by the same sonographer. *P* values were calculated using paired t test. PD, power Doppler; MCP, metacarpo-phalangeal; PRF, pulse repetition frequency; ROI, region of interest.

machines of different specifications [31,32]. In our study, the semi-quantitative scores for synovial PD signal were comparable between two machines of similar specifications (Figure 1, 3rd and 4th rows), whereas the pixel counts were significantly different especially without standardization with the pixel counts within the ROI (Figure 4). This discrepancy is probably explained by the superior sensitivity of pixel count, which makes the pixel-based

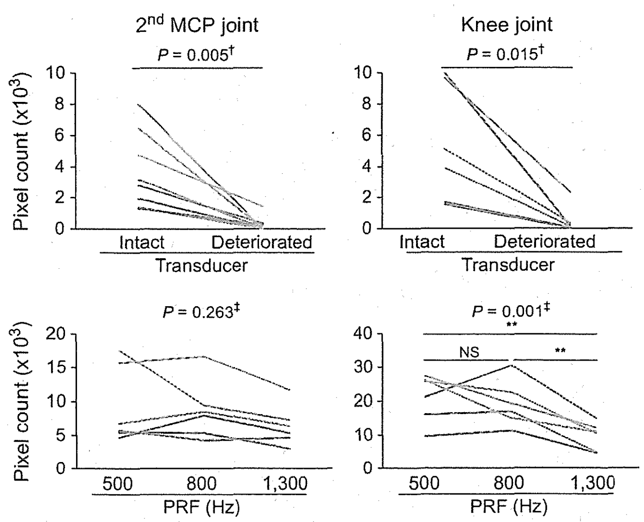


Figure 5. Comparisons of the pixel counts for synovial PD signals between two different conditions of a transducer and between three different PRF settings. Pixel counts for synovial PD signals were compared separately for the MCP joints (left panels) and for the knee joints (right panels). Comparisons were made between the two transducers (UST-5411) in different conditions using the same machine (Prosound α7) with the same setting (PRF 1,300 Hz) (upper panels) and between the three different PRF settings using the same machine (HI VISION Avius) with the same transducer (EUP-L75) (lower panels). Each colored line represents the measurement of the same joint in the same patient by the same sonographer. † paired t test. ‡ one-way repeated measures ANOVA, $^{**}P<0.01$ with paired t test. MCP, metacarpo-phalangeal; NS, not significant; PRF, pulse repetition frequency; PD, power Doppler.

measurement more susceptible to the subtle machine difference. Whether the experienced readers could be capable of unintentionally taking into account the machine difference in the semi-quantitative grading process is an interesting issue and needs further assessment.

The most striking, novel, and possibly controversial result in our study was that the sensitivity of a transducer to detect synovial blood flow can be markedly decreased by the extensive use without proper maintenance. Although the transducer evaluated in this study was an extreme case, our data imply that subtle and gradual deterioration in the quality of a transducer might insidiously affect the assessment without being noticed by the sonographer particularly with the pixel-based measures. To confirm and monitor the possible minor deterioration of transducers in daily practice, the ultrasound phantom specifically catered to evaluating the capability of a transducer to detect blood flow with a very low velocity needs to be developed.

In contrast, the influence of PRF settings on the synovial PD signals was modest. Although a low PRF with a low-wall filter is generally recommended to detect slow synovial blood flow [33,34], the difference between PRF settings was statistically significant only in the knee joint with the pixel-based measurement in our study. We had expected that sonographers would choose a decreased color gain for the low PRF and an increased color gain for the high PRF and would take more time to eliminate noise and motion artifact with the low PRF than with the higher one. However, the color gain values and the time required in a blinded condition were comparable, suggesting that the subtle difference between PRF settings within a certain range is not always discerned by sonographers. On the other hand, the pixel count was significantly lower with the highest PRF than with the lowest PRFs in the knee joint, demonstrating again the higher sensitivity of quantitative measures to detect minor differences. The result also indicates that the scanning for PD signals in deeper structures such as a knee joint needs higher sensitivity than that in more superficial structures such as an MCP joint.

Consistent with the previous studies [7,15,29], the semi-quantitative score correlated well with the pixel-based measures in our study. Supplementary Figure S1 available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2013.843763 illustrates that the scanners do not always discriminate between Grade 2 and 3 based on the area with PD signals. This was also consistent with the previous reports [7,29] even though these studies employed the grading system by Szkudlarek et al. [35] in which the difference between Grade 2 and 3 is determined by whether the area with PD signals exceeds a half of the synovial area. These data can be interpreted as either that the estimation of proportion of the area with PD signals by the scanner is inaccurate, that the determination of the boundary of thickened synovium is operator-dependent, or that the scanners grade the severity of pathological PD signals based on not only the pixel count but also the other factors (e.g. location, morphological pattern, consistency over time).

In conclusion, our data demonstrate that the measurement of PD signal can be substantially affected by deteriorated quality of the transducer, whereas the differences are relatively modest between machines with similar specifications and also between PRF settings within a low range. Our data also suggest that the standardization of machines and settings is needed especially when the quantitative measures are used. Because this is a pilot exercise which only evaluated joints with moderate to severe synovial PD activity, further assessment of joints with a wider range of activity including mild ones is necessary to confirm the results.

## Conflict of interest

None.

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## Supplementary material available online

Supplementary Figure S1 and S2.