# Reliability and Sensitivity of Joint Space Measurements in Hand Radiographs Using Computerized Image Analysis

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***ABSTRACT.*** ***Objective.*** To establish the sensitivity and reliability of proximal interphalangeal (PIP) and metacarpophalangeal (MCP) mean joint space measurements using standard clinical radiographs of healthy subjects, in order to determine the limits at which a change in radiographic joint space could indicate a change in actual joint size.

***Methods.*** Repeat hand radiographs of healthy subjects were taken using standard techniques at 3–5 day intervals with the hands flat (5 posteroanterior radiographs in 8 subjects) or in 6 different flexed positions on a single occasion (8 subjects). The mean joint space was determined using custom software and was validated manually. Measurement reproducibility within subjects, within films, and between hand positions was assessed by analysis of variance.

***Results.*** In repeat radiographs taken in the standard clinical position, the precision of individual joint space measurements indicates that changes > 0.11 mm (~7%) would represent an actual physical change in joint space width (with 95% probability). Averaging measurements across fingers for a single subject decreases the detectable change to 0.05 mm (~3%). With increasing flexure, radiographic joint space tended to increase in MCP and decrease in PIP.

***Conclusion.*** Mean finger joint space measured from standard clinical radiographs is a reliable and sensitive measurement in healthy subjects even with some change in hand position. Work is required to establish whether the joint space change measured from serial radiographs of patients with arthritis over a period of 6–12 mo exceeds the detectable limits of change derived in this study. (J Rheumatol 2001;28:1825–36)

*Key Indexing Terms:*
STANDARD RADIOGRAPHY JOINT SPACE WIDTH HAND
REPRODUCIBILITY COMPUTERIZED IMAGE ANALYSIS

The evaluation of radiographic joint space narrowing plays an essential role in assessment of disease progression in rheumatoid arthritis (RA) and osteoarthritis. Radiological scoring systems were first described for this purpose more than 40 years ago[1,2]. In early joint disease, when the most important opportunity to prevent irreversible joint destruction occurs[3-5], radiographic changes may be slight and insignificant to the eye. This makes assessment of the effects of disease-modifying treatment especially difficult. Thus, research to improve the sensitivity of radiological scoring has continued[6-11]. Several groups have described computerized methods for automatically detecting radiologic change[12-17]. In principle, compared to grading procedures, computerized measurement of the joint space offers the advantages of a continuous measurement scale, capable of calibration, such that measurements are sensitive, objective, observer-independent and reproducible. A sensitive measurement system could enable closer monitoring of the progress of individual patients with RA and also reduce the size and duration of clinical trials. To date, most quantitative investigations have concentrated on large joints such as the knee and hip. In hands, with comparatively small joint spaces, a major concern is that the measurement error will be proportionally larger and thus mask the effects of small changes in joint size due to disease progression or to disease modification by new drugs.

The summation of radiographic densities on a skeletal radiograph is a 2 dimensional representation of the 3 dimensional anatomic structure. In the 2 dimensional radiograph, difficulties occur in correctly identifying the joint structure and the positioning of the joint relative to the x-ray source, and the image plane becomes important. In this study, computer software identifies the same radiographic features used in scoring joint space narrowing in the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints. Using these landmarks, the program determines the mean joint space width (mean JSW) taken over the breadth of the joint.

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*Submitted October 17, 2000; revision accepted February 15, 2001.*

The object of this study is to establish the sensitivity and reliability of mean JSW measurements in standard clinical hand radiographs of healthy subjects. Radiographs were acquired in "good" conditions, when the hands were repeatedly radiographed in a standard flat position, and in less ideal conditions when hands were radiographed in differing positions. The variability that occurs when radiographs are taken, digitized, and measured, and that affects the magnitude and reliability of the mean joint space measurement, is quantified.

## MATERIALS AND METHODS

*Subjects.* Sixteen healthy male volunteers, mean age 48 years (range 44–52), were recruited from the GlaxoSmithKline volunteer panel. Volunteers were eligible for entry if they had passed a comprehensive medical examination and had not received radioisotopes or x-irradiation for any purpose within the previous year. Subjects were given a clinical interview within 14 days of the first study day, including assessment for symptoms or signs of joint disease, and were requested to abstain from strenuous hand exercise (e.g., playing squash or gardening) for 24 h prior to each study day. Subjects were fully informed of the investigation's purpose, signed consent forms prior to study entry, and were expressly allowed to withdraw at any time without having to state a reason.

*Study design.* The investigation was conducted according to the Declaration of Helsinki and relevant good clinical practice guidelines, with local ethics committee approval. Radiographic procedures were subject to UK Ionising Radiations Regulations, 1985, and internal Written Systems of Work. The investigation was in 2 parts.

*1. Investigation of repeat radiographs in the flat hand position (Repeat Study).* Five posteroanterior (PA) paired wrist-and-hand radiographs were taken in 8 subjects at 3–5 day intervals. Each subject placed his wrist and hands flat, with the fingers extended and splayed (standard clinical view), but without other instructions. With this design, real organic change in the joint space was expected to be negligible and any within-subject variation reflects the reliability, or reproducibility, of joint space representation in repeat radiographs under standard clinical conditions.

*2. Investigation of the effect of hand position on measurement reliability (Position Study).* Paired wrist-and-hand radiographs were taken in the other 8 subjects during a single visit with the hands in 6 different, carefully arranged positions (Figure 1). With this design, there should be no real organic change and the within-subject variation reflects the reproducibility of joint space representation in radiographs with some change in hand position. The 6 positions were: (1) PA view of the hands placed flat and relaxed (standard clinical view as used in the Repeat Study); (2) anteroposterior (AP) view of the hands placed flat and relaxed; (3) PA view of the hands placed flat on a clear film template, with the fingers extended and the medial aspect of the middle finger aligned with the forearm. The hands were outlined on the template with marker pen to record their position. Without disturbing the positions of the other fingers, each PIP in turn was carefully flexed to a right angle and the position of the finger tip marked on its outline (position = "fully flexed"). Distances along the finger outline, between the flexed joint and the tip, were then marked off, at 1/3 (nearest the tip) and 2/3. Three further radiographs were then taken using these positions: (4) PA view with the fingers flexed 1/3; (5) PA view with the fingers flexed 2/3; (6) as (5), but with the hand relaxed and the wrist allowed to rotate laterally.

Before each radiograph was taken, the positioned hands were photographed both from above and laterally (Figure 1). Radiographs were recorded using a video camera linked to the digitization card in a computer. Joint spaces were measured using custom image analysis software. Eight joint spaces were measured on each hand — the PIP and the MCP joints on the index, middle, ring, and little fingers. As the features being identified were relatively small, the effect of digitizing the image was important. Hence, triplicate measurements were made for each joint with the radiographic image recaptured for each reading to ensure random pixelation. With this design, the variation in triplicate measurements reflects the reliability of the computerized method of measuring JSW from a radiograph including the effect of digitization.

*Radiography.* The x-ray source was a filtered (4 mm Be, 2.5 mm Al) Siemens Opti 12 HSG microfocus tube with a spot size of 0.6 $mm^2$ and an emission angle of 20°. In accordance with normal clinical practice, for each volunteer, both hands were radiographed close together with the same exposure but using separate abutting films to avoid hand positioning complications. Exposures were 40–45 kV at 12 mAs. The beam was centered on the midline between the 2 films and on the line passing through the MCP joints. The target to film distance was set at the maximum attainable of 143 cm to optimize projection.

To protect subjects, the x-ray beam was collimated to the film area, which was laid over a 2 mm thick lead sheet to prevent transmission through to other parts of the seated subject's body. The subject also wore a 0.35 mm lead-equivalent protective apron covering the torso. The total x-ray exposure to the hands of each subject was predicted to be 1.17 mSv. The exposure was monitored with thermoluminescence detectors for the duration of the study to verify this estimate.

Mammography film combination (SO177, Kodak) was used, with one hand per plate. The films were processed using an X-150 medical film processor (Varispeed Ltd.) following the manufacturer's recommendations; development time was 150 s at 33–35°C.

*Image capture.* Radiographs were viewed on a standard illuminated light box with a Hitachi KP-141 video camera with $\gamma$ set at 1.0 and a field of view $42 \times 32$ mm. The camera images were captured onto an image capture card (IC-PCI card, Imaging Technology Inc.), using macros written within Optimas image analysis software (version 6.1, Media Cybernetics)*. Captured images had 8 bit pixel depth giving 256 grey levels. The highest level was encoded to display green as a visual aid when adjusting the camera aperture for optimal image brightness.

The camera image scale was set to ensure optimum resolution of the relevant joint features (~17.4 pixels/mm). Increasing the magnification (i.e., more pixels/mm) made the trabecular bone detail and the granular structure of the film more evident. The joint margin algorithm detected and tended to follow this detail instead of the main subchondral margin and no advantage was gained. Camera position was rigidly maintained and the image scale subjected to frequent calibration checks.

*Image capture calibration.* A standard microscope slide was found to be ideal in size and manufacturing precision for calibration purposes. Using a digital micrometer, width measurements were made at several points to give a mean width of 25.805 mm [standard deviation (SD) 0.006 mm].

An image of the slide was captured and, using the Optimas calibration procedure, the clearly defined edges of the slide were pinpointed and the pixel resolution determined based on the known width measurement. After repeating the procedure 5 times, the calibration was set at the mean value of 0.05735 mm/pixel (~17.4 pixels per mm, equivalent to 440 dots per inch). Sets of 3 measurements were taken at regular intervals to check that the calibration had not changed (3 times per day and additionally after measurement of each subject's set of radiographs). The results of these calibrations were recorded and indicated a maximum error of 0.36% (95% probability limits) in these measurements. There was no drift in calibration.

* The joint space measurement software consists of macros, written in the Optimas macro language ALI, for incorporation into Optimas image analysis software (version 6.1; Media Cybernetics Inc., Silver Spring, MD 20910, USA). The Optimas product is currently undergoing replacement by Media Cybernetics, but the macros are available from the corresponding author under collaborative agreement as source code, including C source code employed for certain specific algorithms.

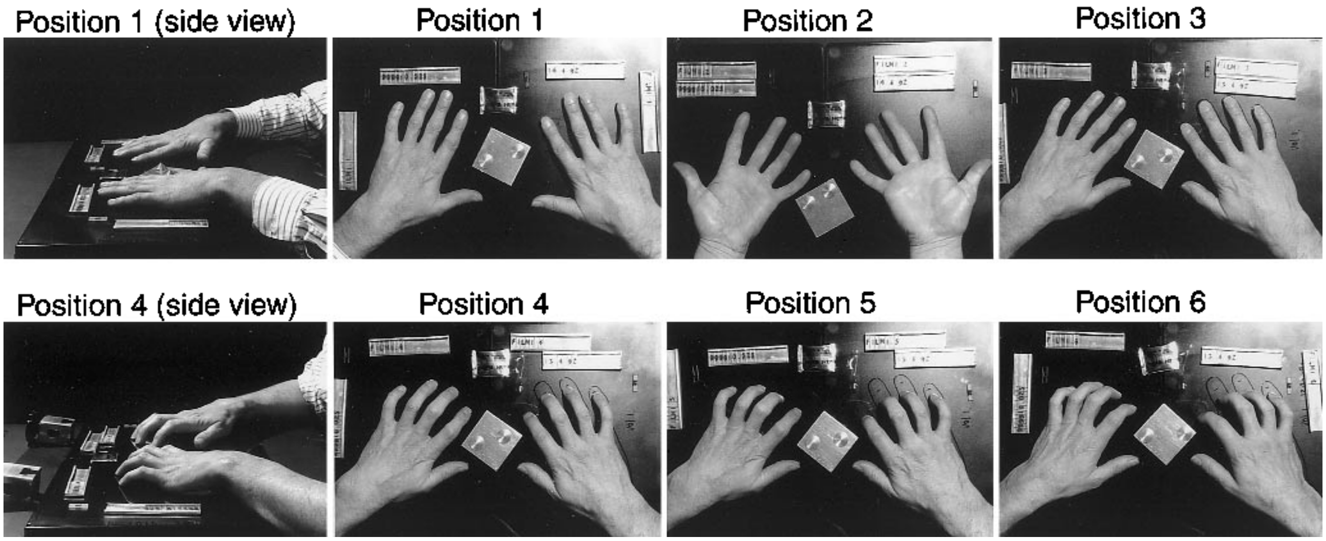


*Figure 1*. The 6 different hand and wrist positions radiographed in the Position Study. The hands were placed on paired film cassettes. Position 1 corresponds to the hand position used in the Repeat Study. In position 3, the fingers were outlined on a clear plastic film template. Marks for the fingers flexed 1/3 (Position 4) and 2/3 (Positions 5, 6) can be seen. Also shown are identifiers, a reference density step wedge, and thermoluminescent detectors used to assess exposure to ionizing radiation.

*Mean joint space measurement using computerized image analysis*. The computer analysis method is an updated and more robust version of software previously described[18]. The key areas of improvement are (1) employment of a Gaussian distribution to uniquely locate key features in the image; (2) tracking the features to locate continuous joint margins; and (3) determination of mean JSW based on averaging measurements of JSW at ~180 locations equally spaced across the breadth of the joint. The method is illustrated in Figures 2 and 3, which show unprocessed (A, C) and processed images (B, D) of MCP and PIP joints. Figure 2 illustrates joints where the location of the distal margin is unambiguous; Figure 3 shows joints where the distal margin is less well defined (see Monitoring program performance, below).

MCP joints are located in the digitized image by positioning 3 user-input points along the curved metacarpal head, with one point identifying the midpoint of the measurement arc. The remaining measurement process is automatic. The three points are used to calculate the approximate center of the metacarpal head from which ~180 radial lines of pixels traversing the joint space are sampled. To allow for MCP of differing size, the mean joint space is measured within a boundary arc ± 0.5 radian from the midpoint of the metacarpal head (between the straight green lines shown in Figure 2B). The metacarpal margin is identified from a position along each line at the point of maximum slope in radiographic density (Figures 2B, 3B: red boundary). The proximal phalanx margin is defined on the same radial line at the point of peak radiographic density across the joint space (Figures 2B, 3B: green boundary).

PIP joints are viewed horizontally and roughly located in the digitized image using a rectangular region of interest determined by the user (Figures 2D, 3D: green box). The same features of slope and peak are used to define the joint margins but, in contrast to MCP, the PIP joint margins are defined by sampling parallel, not radial, lines oriented vertically across the joint (red and green boundaries in Figures 2D, 3D). The outer limits of the proximal phalangeal articular margin are detected automatically, enabling the sampling process to be self-limiting.

In each of the MCP and PIP processes, after an initial pass through the data, the radiographic joint margins are precisely located using a Gaussian function in a tracking procedure. The Gaussian function optimally combines the conflicting criteria of insensitivity to noise and accuracy[19,20] and is thought to emulate the working of the eye[21]. Here it contributes substantially to the success of the software in reliably identifying valid anatomical joint margins despite changes in digitization of the image.

The initial pass through all potential measurement lines identifies a single line as an optimal starting point for the tracking procedure. Having identified the maximum slope (the proximal joint margin) and maximum peak (distal joint margin) positions on this line, these features are tracked around the joint starting from equivalent positions on adjacent and succeeding lines. This search for equivalent positions on succeeding lines is locally constrained to avoid detection of any higher but erroneous values lying beyond the joint margins.

Having located the radiographic joint margins on all lines, the mean JSW is calculated as their linear separation averaged over the defined joint breadth (averaging ~180 values). The horizontal straight red line in Figures 2D, 3D corresponds to accepted valid measurements across the PIP joint. Values are stored automatically in a spreadsheet. Due to the averaging of radiographic and image noise, mean JSW is expected to be a more reliable measure of joint space than single width measurements, such as the minimum or the midline JSW.

*Monitoring program performance*. Figures 2 and 3 show the typical range of variation in finger joint anatomy in the subjects. In comparison with Figures 2A and 2C, where the distal margin of the joint space is unambiguous, MCP and PIP joints could reveal a subchondral region of compacted bone that appeared in the radiograph as a parallel range of densities lying adjacent to the distal joint space margin (Figure 3A). Similarly, the compacted subchondral bone of MCP and PIP could appear thickened (Figure 3C). The automatic detection process could normally find appropriate joint margins but, where the joint margin was ambiguous, the operator could constrain the working domain to ensure that correct radiographic features were followed. The final stage of computer processing was displayed before a measurement was accepted (Figures 3B, 3D).

*Validation of computerized mean JSW measurements*. Computer measurements of mean JSW were compared to manual measurements by 2 observers each using 2 different methods. The radiograph of a well defined PIP joint was used, similar to that shown in Figure 2C. Measurements were made in triplicate by each observer for each method.

In the first manual method, the radiograph of the joint was examined under a microscope (×2.5 objective) using an eyepiece reticle with 0.05 mm graduations that had been checked against a 1 mm Zeiss stage micrometer of 0.01 mm precision. Manual measurements of JSW were taken at ~8 intervals along the joint and the mean values determined. As far as possible, the same landmarks were used as with the computer software.

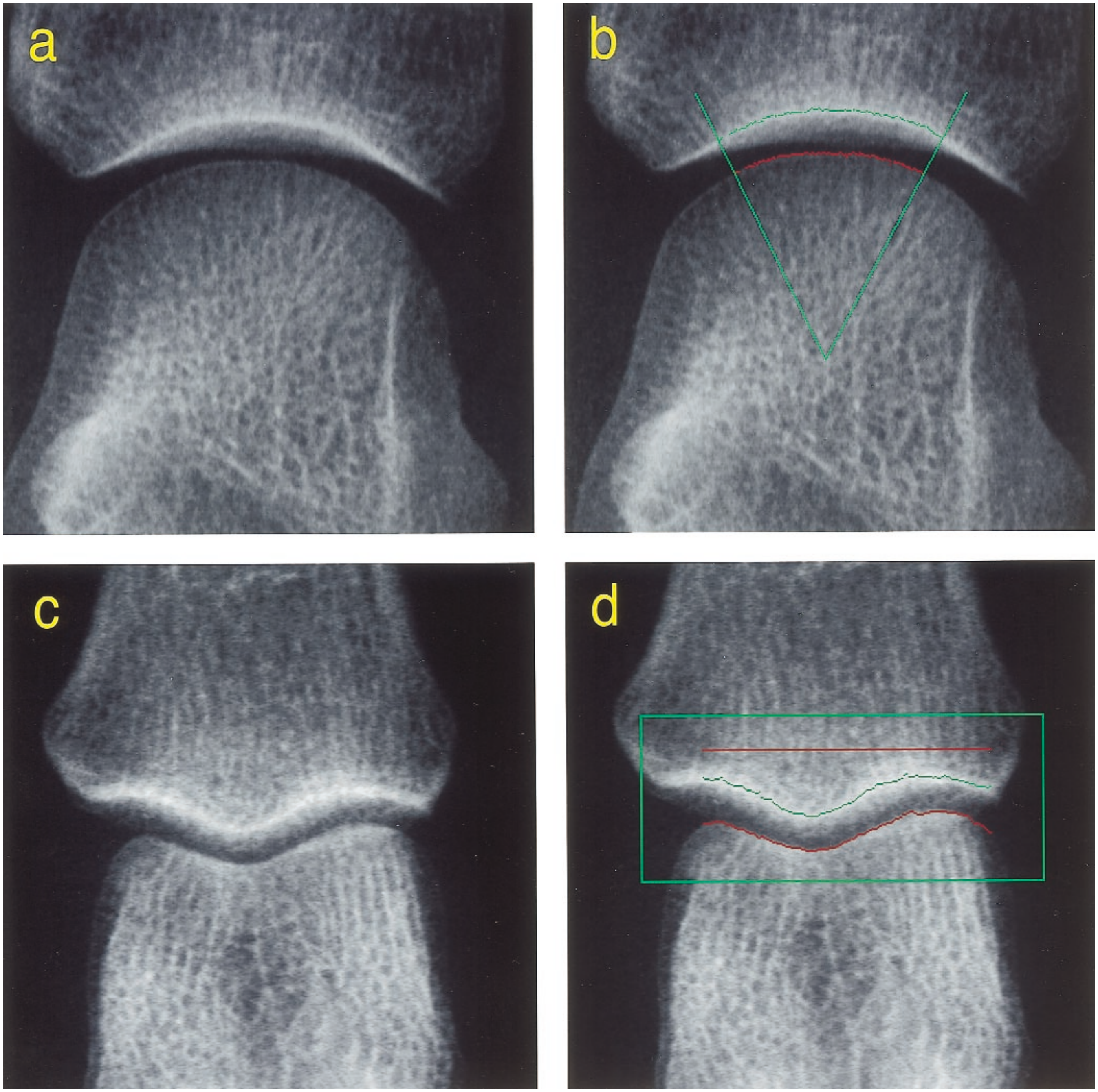


*Figure 2*. Anatomical landmarks used for computerized mean JSW measurement in MCP and PIP radiographs: (A, C) unprocessed radiographs; (B, D) processed images showing detection of the proximal (red) and distal (green) joint margins. The green sector in (B) identifies the 1-radian sector of MCP joint used to determine mean JSW. The rectangular box in (D) is input by the user to roughly locate the PIP joint. The horizontal red line corresponds to accepted valid measurements across the PIP joint.

In the second manual method, the radiograph was digitized (at the same magnification as in the computerized procedure) and standard Optimas distance routines were used to determine the length of lines placed manually across the joint space at ~8 positions along its breadth. The mean line lengths were then determined.

The results of the validation procedure (Table 1) show that the magnitude of the mean JSW measurements were almost identical. Although SD values for all sets of measurements were small (range 0.000–0.026 mm) the variation in the manual measurements is about 6 times greater than those for the computer results. These values indicate the difficulty of precisely locating joint margins by eye, even for a well defined joint, and the advantages of a computer program where the JSW can be evaluated at many more points along the joint margins.

This procedure validated the software calculation of mean JSW. The operator, continually checking the joint margins found by the software in the display, ensured valid working of the computer program for every joint. Thus, the computer program became a precise measuring tool in the hands of the operator.

*Validation of radiographic model of MCP joint*. To investigate the errors

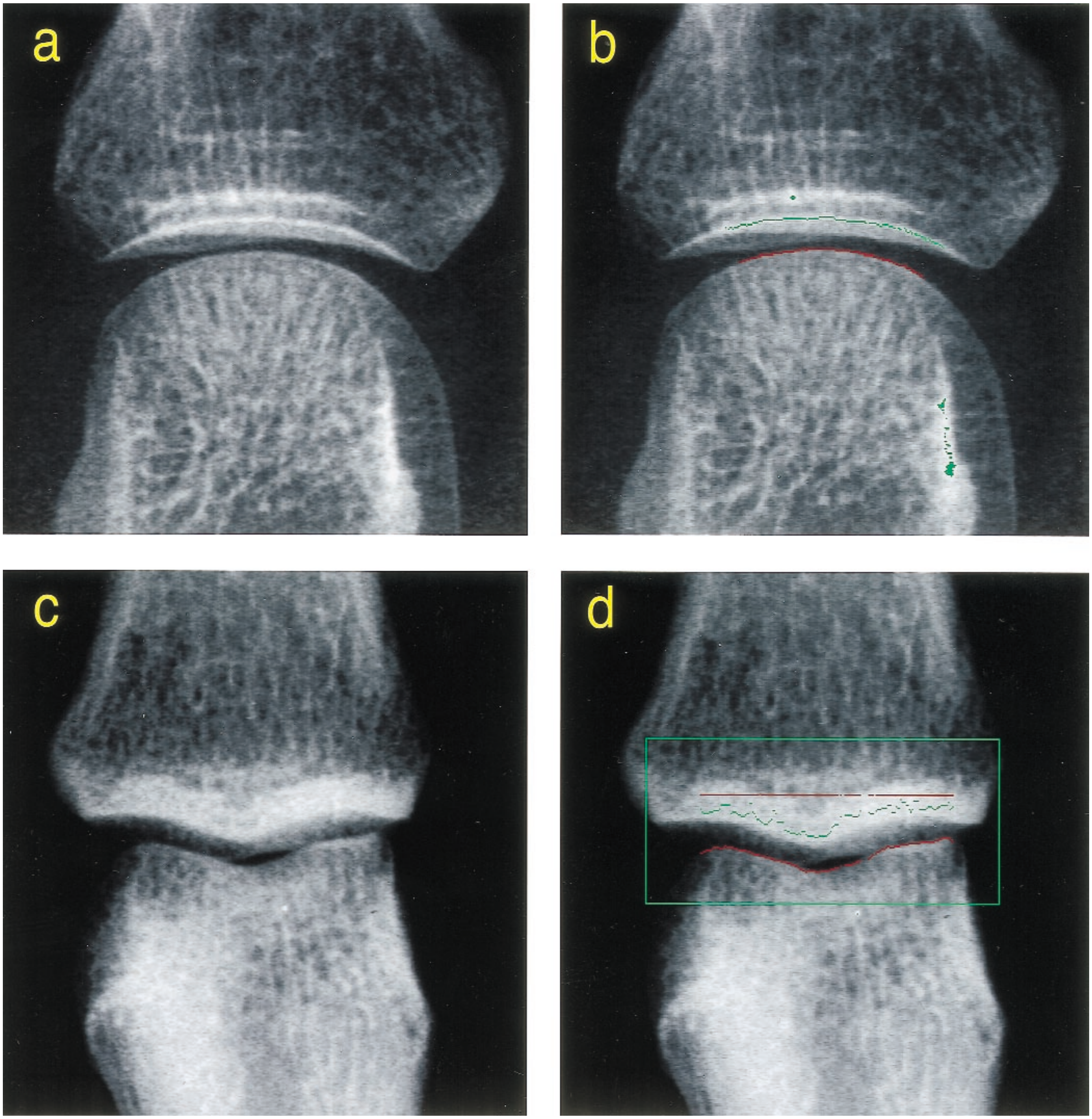


*Figure 3*. The effect of anatomical variation on the landmarks used for the computerized mean JSW measurement in MCP and PIP radiographs: (A, C) unprocessed radiographs; (B, D) processed images showing detection of the proximal (red) and distal (green) joint margins. In comparison with Figure 2, where the joint margins are unambiguous, in (A) a parallel range of subchondral compacted bone lies adjacent to the MCP distal margin, whereas in (C) the PIP distal margin is thickened. In (B) certain pixels distant from the margin are colored green, indicating that they are at the brightest level of the image intensity scale. These points have not been identified as lying on the joint margin. The rectangular box in (D) is input by the user to roughly locate the PIP joint. The horizontal red line corresponds to accepted valid measurements across the PIP joint.

inherent in the radiography of a 3 dimensional joint, a MCP model was developed (Figure 4). The model consists of an aluminum hemispherical ball and socket (diameter 15 mm) plated in gold (to simulate the subchondral radiographic densities) and mounted in a micrometer. Radiographs were taken on 2 separate occasions with calibrated openings of 0.25 to 3.00 mm in 0.25 mm increments.

Figure 5 shows that the "mean JSW" of the model, measured from the radiographs using the computer software, was very close to the actual

*Table 1*. Comparison of manual and computerized mean JSW measurements from a representative PIP radiograph (mean ± SD, mm). Measurements were made on n = 3 separate occasions by 2 independent observers using the computer program and 2 different manual methods. To determine mean JSW, the number of measurements made on a single occasion along the breadth of the joint was ~170 for the computer program and ~8 for each of the manual methods.

| | Observer 1, n = 3 | Observer 2, n = 3 | Total, n = 6 |
|---|---|---|---|
| Computer program | 1.28 ± 0.000 | 1.28 ± 0.003 | 1.28 ± 0.003 |
| Manual measurement: microscope | 1.27 ± 0.013 | 1.28 ± 0.025 | 1.28 ± 0.020 |
| Manual measurement: digitized | 1.27 ± 0.026 | 1.29 ± 0.006 | 1.28 ± 0.019 |

separation of the joint faces specified by the micrometer. An overall positive bias was detected, of +0.018 ± 0.014 mm (or +1.0% of MCP mean JSW for the 16 subjects; Table 2), indicating that measurements of JSW from radiographs may be very slightly, but consistently, high. The results give confidence in the accurate representation of finger joint space on radiographs.

*Statistical analysis*. The variation in JSW measurement derives from several sources, including differences between subjects, between joints, changes in hand positioning, and variations imparted by the measurement process itself. Standard analysis of variance techniques were used to analyze the data from each study, and these are described in detail below. Statistical analysis was carried out using SAS (v6.12). In general, results were considered statistically significant if there was less than 5% ($p < 0.05$) probability of their occurrence due to chance.

For the investigation of measurement reproducibility in the flat hand position (the Repeat Study), an analysis of variance was carried out for MCP and PIP joints fitting a nested hierarchical "mixed effects" model. The model contained random effects for subjects (variation between subjects, B), for joints (variation between joints within a subject, J), for repeat radiographs (variation between radiographs of each joint within a subject, R), and for measurement errors (variation between triplicate measurements from the same radiograph within a visit, E). A fixed effect for joints was also included. Thus, the variance components were $SD^2_B$, $SD^2_J$, $SD^2_R$, $SD^2_E$, respectively. These were estimated from the mean squares of the error terms by the method of restricted maximum likelihood[22]. Additionally, an analysis of variance was carried out for MCP and PIP joints, with JSW now averaged across the hand (MCP-hand and PIP-hand), fitting a nested hierarchical model with random effects for subjects (B), repeat radiographs (R), and measurement errors (E). Corresponding variance components, $SD^2_B$, $SD^2_R$, $SD^2_E$, were estimated from the mean squares of the error terms by the method of moments[22].

For the investigation of the effect of hand position on measurement reliability (the Position Study), an analysis of variance was carried out for MCP-hand, PIP-hand, and MCP+PIP-hand (where JSW was averaged over relevant joints in both hands) fitting a "mixed effects" model with fixed effect for position and random effect for subjects. The average of triplicate measurements for each radiograph was used in the analysis. Position 1 (hands flat) was regarded as the reference position for multiple comparisons using Dunnett's test[23], which compares all other positions to the reference position. Positions that were significantly different at the 5% level were identified and the within-subject variance $SD^2_{R(pos)}$ for the remaining positions was determined.

Further, the estimates of variability from the analyses were used to calculate an individual cutoff (ICO), defined according to Ravaud, *et al*[24]. It is calculated as the 95% probability range for the difference between 2 measurements, measured once, on the same individual in the absence of any systematic change, thus

$$ICO = \pm 2 \cdot \sqrt{2 \cdot SD^2} = \pm 2 \cdot \sqrt{2} \cdot SD$$

In the Repeat Study, $ICO = \pm 2 \cdot \sqrt{2} \cdot SD_S$ where $SD^2_S = SD^2_R + SD^2_E$.
In the Position Study, $ICO = \pm 2 \cdot \sqrt{2} \cdot SD_P$ where $SD^2_P = SD^2_{R(pos)} + SD^2_E$.
The use of $SD^2_{R(pos)}$ in the Position Study is appropriate for those hand positions for which the radiographic joint space shows no systematic change from the reference position.

Similarly, for a group of N subjects, the corresponding formula for the 95% probability range for the difference between the group average measurement taken on 2 separate occasions in the absence of any systematic change is given by the group cutoff thus

$$GCO = \pm 2 \cdot \sqrt{2\,(SD^2_R + SD^2_E) / N}$$

Hence, a difference in mean JSW measured from 2 radiographs taken on separate occasions for the same subject that exceeds the range defined by ICO (or group cutoff for a group of subjects) is unlikely to be due to chance (at the 5% level). Such a difference would be expected to reflect a systematic change in the data, in this case possibly due to joint positioning or to an actual physical change in mean JSW.

## RESULTS

*Joint space measurements in the subjects*. Table 2 compares mean JSW measurements for the 2 groups of subjects. Data are from the first radiograph in the Repeat Study and for the equivalent Position 1 in the Position Study (PA view of hands placed flat and relaxed, standard clinical view).

The average measurements of the 2 groups of subjects were similar, although individual subjects had widely varying joint size. PIP mean JSW varied between 0.76 mm and 1.77 mm (left little finger, subject 8, Position Study, and

*Table 2*. Variation between subjects in mean JSW (mean ± SD, mm). Variation in mean JSW between subjects, measured using the computerized method, was determined from the first radiograph in the Repeat Study and position 1 in the Position Study (standard PA clinical view), for n = 8 subjects in each study. For finger measurements, the left and right finger measurements were combined for each subject; for "hand," 8 MCP or PIP measurements were combined for each subject; for MCP+PIP-hand, 8 MCP and 8 PIP measurements were combined for each subject.

| | Repeat Study (n = 8) MCP | Repeat Study (n = 8) PIP |
|---|---|---|
| Index finger | 2.00 ± 0.216 | 1.50 ± 0.118 |
| Middle finger | 1.77 ± 0.237 | 1.48 ± 0.114 |
| Ring finger | 1.76 ± 0.243 | 1.28 ± 0.086 |
| Little finger | 1.69 ± 0.174 | 1.13 ± 0.123 |
| Hand | 1.81 ± 0.195 | 1.35 ± 0.098 |
| MCP+PIP-hand | 1.58 ± 0.130 | |
| | **Position Study (n = 8) MCP** | **Position Study (n = 8) PIP** |
| Index finger | 1.92 ± 0.291 | 1.41 ± 0.211 |
| Middle finger | 1.70 ± 0.311 | 1.37 ± 0.213 |
| Ring finger | 1.62 ± 0.307 | 1.15 ± 0.202 |
| Little finger | 1.63 ± 0.242 | 1.05 ± 0.149 |
| Hand | 1.72 ± 0.273 | 1.24 ± 0.182 |
| MCP+PIP-hand | 1.48 ± 0.212 | |

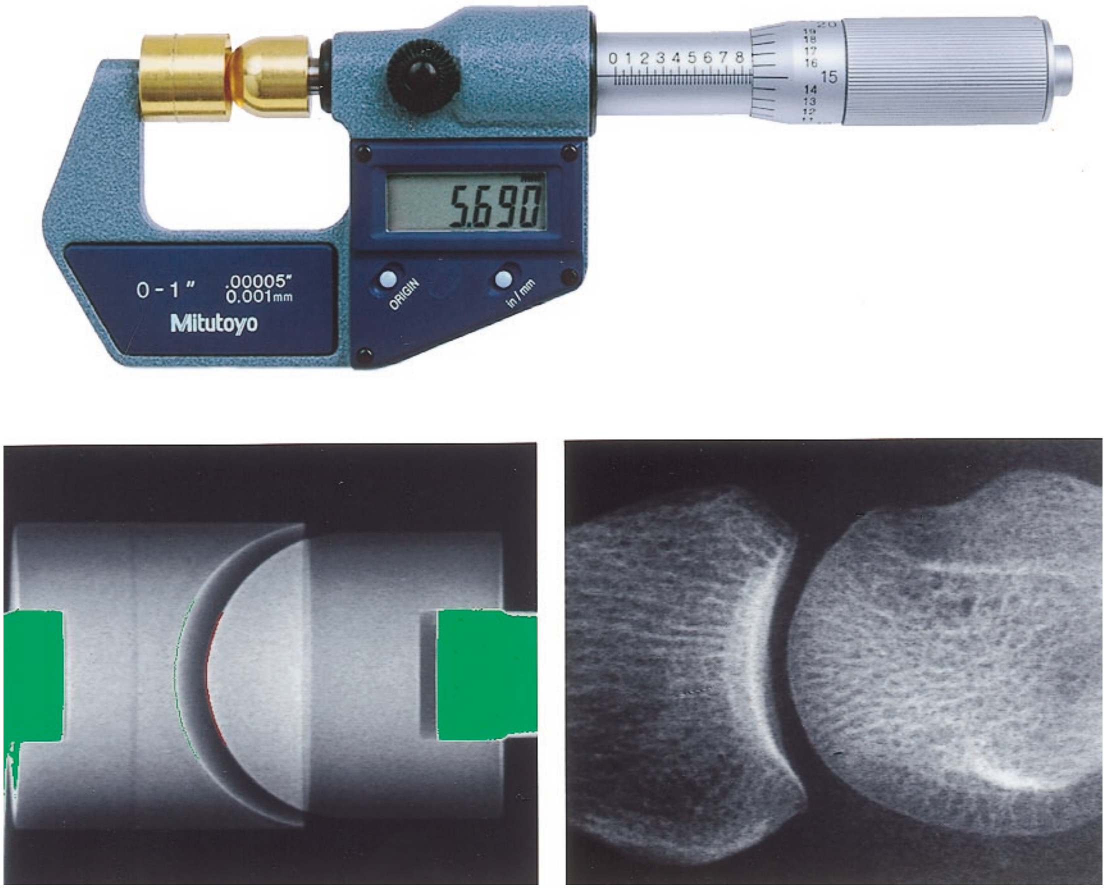


*Figure 4*. The radiographic model of a MCP joint. The gold plated aluminum ball and socket "joint" is mounted in a micrometer so separation of the "joint" faces can be controlled. Radiographs were taken at different calibrated openings. The radiograph shown is at a calibrated opening of 1.75 mm and illustrates the distal (green) and proximal (red) "joint margins" used by the software for mean JSW measurement together with a radiograph of a MCP joint for comparison. Green rectangular areas indicate the model mount, which, being radiographically dense, is at the brightest level of the image intensity scale (see also Figure 3B).

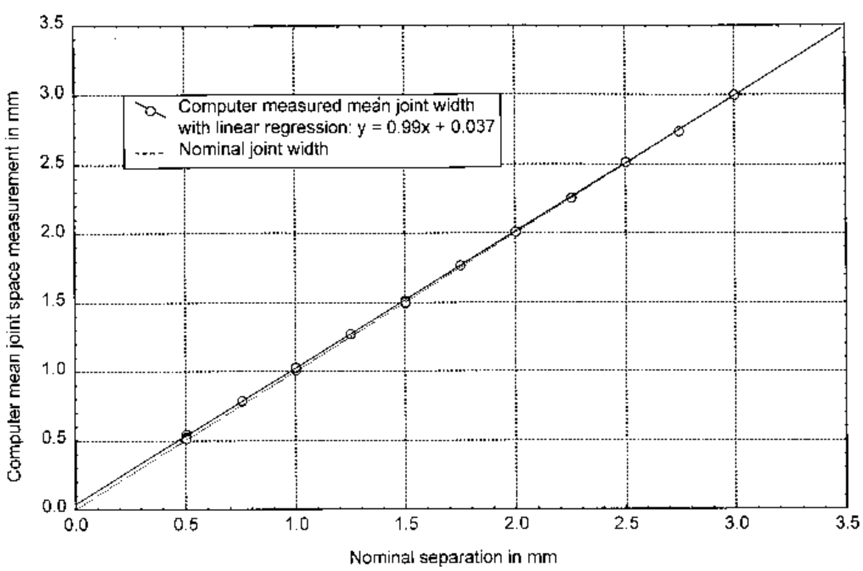


*Figure 5*. Comparison of the nominal and actual measurements of "mean JSW" from radiographs of the MCP model. Broken line indicates nominal values. Actual measurements (○) were 0.018 ± 0.014 mm (mean ± SD) larger, equivalent to a consistent deviation of +1.0% in MCP mean JSW for the 16 subjects in this study.

right middle finger, subject 3, Repeat Study, respectively). MCP mean JSW varied between 1.17 mm and 2.63 mm (right ring finger, subject 8, Position Study, and right index finger, subject 1, Repeat Study, respectively).

*Repeat Study.* Radiographs were taken over a period of 3 weeks. Although subjects were instructed to place their hands flat with fingers splayed, no special care was taken of hand position and templates were not used. Positional variation proved to be slight and there was no statistically significant difference in JSW as recorded on repeat radiographs.

Two joints of 4 fingers of 2 hands were measured, giving 16 observations per subject per radiograph, in triplicate, and a total of 1920 measurements. Analysis of variance provided the relative contributions of the variation between subjects (B); between radiograph within each subject (R, the effect of re-radiography, incorporating slight positional changes at each visit) and the measurement error (E, the variation in the triplicate measurements from each radiograph due to operator interaction and digitization). Table 3 gives standard deviations for the 2 components of variation: $SD_R$, $SD_E$, and the total within-subject variation, $SD_S$, for both individual and hand averaged JSW.

Table 3 shows that the within-subject variation $SD_S$ for individual MCP, PIP joints was in the range 0.03–0.04 mm (< 2.5% as a proportion of group mean JSW). For comparison, there was much greater variation in joint size between subjects within finger or hand (Table 2).

The precision of the computer measuring system was determined by considering the variation in triplicate measurements from each radiograph, $SD_E$ in Table 3.

Similarly, the reproducibility (or precision) of mean JSW on repeat radiographs for the same subject, using a single measurement per radiograph, was determined considering the total within-subject variation $SD_S$ and the formula for ICO in Materials and Methods. Thus, a change in mean JSW between serial radiographs in excess of the limits defined by ICO would represent a real organic change in JSW with 95% probability, provided that similar PA hand positioning had been employed for both radiographs. From Table 3, the ICO limits for individual MCP and PIP readings are ±0.11 mm and ±0.09 mm, respectively (or 6–7% of mean JSW). Considering MCP-hand, PIP-hand, and MCP+PIP-hand, mean JSW averaged over respective joints on both hands, the ICO limits are ±0.05 mm, ±0.04 mm, and ±0.03 mm, respectively (or 2–3% of mean JSW). Serial changes exceeding these limits would reflect real organic change rather than measurement variation for the same nominal PA hand position (with 95% probability). MCP+PIP-hand has a greater inherent precision than individual mean JSW measurements due to data averaging; however, it will not necessarily be as sensitive an index of joint disease if only a limited number of joints are affected.

*Position Study.* Flexion of the fingers was found to affect the measurability of the joint spaces. The intention was to measure 2 joints of 4 fingers of 2 hands, giving 16 observations (in triplicate) per subject per hand position, and a total of 2304 measurements for all 8 subjects and 6 hand positions. In practice, some PIP joints were unmeasurable because no joint margins were distinguishable on the radiographs and these joints were therefore omitted. MCP joints were measurable in all positions although in some cases the boundaries were poorly defined.

In Position 4, one PIP little finger joint (one out of 64) was omitted. In each of the more flexed Positions 5 and 6, a total of 9 PIP joints in 4 subjects from various fingers were

*Table 3.* Repeat Study: Variation within subject in mean JSW for repeat radiographs in the same nominal hand position (SD, mm). Variation in JSW was contributed by (a) the observer's interactions with the computer system including image digitization (the measurement error $SD_E$ obtained from triplicate measurements of each film); and (b) the radiographic instrumentation, film processing, and joint repositioning (the repeat radiograph variation $SD_R$ obtained by comparing average measurements from each of the 5 replicate radiographs). $SD_E$ and $SD_R$ accounted for the total variation between within-subject measurements, $SD_S$. Columns headed MCP and PIP show variations in individual joint measurements; columns headed "-hand" show variations in the average measurements per subject across all MCP joints, all PIP joints, or all MCP+PIP joints (averaging 8 or 16 measurements). The group mean JSW measurements are from Table 2. ICO is the individual cutoff described in Materials and Methods such that ICO defines when a difference in mean JSW between 2 radiographs taken on different occasions in the same subject is unlikely to be due to chance ($p < 0.05$). Thus, mean JSW changes that exceed ICO could be expected to reflect a systematic change in the radiograph — for example, due to a change in joint positioning or in the actual physical JSW.

| SD | MCP | PIP | MCP-hand | PIP-hand | MCP+PIP-hand |
|---|---|---|---|---|---|
| Group mean JSW | 1.81 | 1.35 | 1.81 | 1.35 | 1.58 |
| $SD_E$ | 0.014 | 0.022 | 0.005 | 0.009 | 0.005 |
| $SD_R$ | 0.034 | 0.023 | 0.018 | 0.010 | 0.008 |
| $SD_S$ | 0.037 | 0.032 | 0.019 | 0.013 | 0.010 |
| $ICO = \pm 2 \cdot \sqrt{2} \cdot SD_S$ | ± 0.106 | ± 0.090 | ± 0.052 | ± 0.038 | ± 0.028 |
| ICO as % of group mean JSW | ± 5.74 | ± 6.66 | ± 2.89 | ± 2.79 | ± 1.75 |

omitted. Due to the greater variability in the Position Study measurements, MCP-hand, PIP-hand, and MCP+PIP-hand data only were considered, mean JSW averaged over relevant joints of both hands per subject. The data were analyzed in a number of different ways to take account of the omitted joints, but primarily were analyzed as a single mixed effects statistical model using all available data; that is: full data for Positions 1–3; reduced data for one subject in Position 4; reduced data for 4 subjects in each of Positions 5 and 6.

Whichever way the omitted joints were taken into account, the conclusions remained the same: there was a significant change in PIP group average radiographic joint size when the hand position changed from Position 1 to 4, 5, or 6, and no significant change in PIP radiographic joint size from Position 1 to Position 2 or 3. Full data were available for MCP joints and similar conclusions could be drawn. However, whereas MCP radiographic JSW tended to increase in size (increase 7–11% for Positions 4-6), PIP radiographic JSW tended to decrease in size with hand flexure (reduction 6–8% for Positions 4–6).

Consequently, MCP+PIP-hand measurements, which aggregate MCP and PIP mean JSW values, were relatively stable and only the group average value for Position 5 was significantly different from Position 1 (increase 4%).

Table 4 also gives the total within-subject variation in hand averaged joint size, $SD_P$, for the 3 radiographically similar Positions 1–3 including the triplicate measurement error $SD_E$ from Table 3 (the Position Study analysis was based on the average of the triplicate measurements for each radiograph). All MCP and PIP joints were measurable in these 3 positions. Values for ICO reflect the limits outside which a change in hand averaged mean JSW would reflect real organic change rather than radiographic measurement variation for similar changes in hand position (with 95% probability).

Comparing values of ICO in Table 3 (0.05 mm for MCP-hand, 0.04 mm for PIP-hand) with values in Table 4 (0.19

*Table 4.* Position Study: Variation within subject in mean JSW for repeat radiographs in 6 different hand positions (mm, 8 subjects). MCP-hand, PIP-hand, MCP+PIP-hand indicate the mean JSW values are averaged over the respective joints of both hands. Values are then averaged over all subjects in each position. "Change" = paired change in hand JSW with respect to comparable joints in position 1, also shown as percentage of the group mean JSW in position 1. PIP-hand and MCP+PIP-hand values for group mean JSW and change are affected by the following missed measurements in the flexed positions: in position 4 one PIP joints; in each of positions 5 and 6 a total of 9 PIP joints in 4 subjects.

| | Position | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 |
| MCP-hand | | | | | | |
| Mean JSW | 1.718 | 1.730 | 1.691 | 1.835* | 1.909* | 1.840* |
| Change (mm) | — | 0.012 | –0.027 | 0.116 | 0.190 | 0.121 |
| % | — | 0.70 | –1.57 | 6.77 | 11.08 | 7.06 |
| For Positions 1–3, $SD_P$ = 0.067 mm<br>ICO = $\pm 2 \cdot \sqrt{2} \cdot SD_P$ = ±0.190 mm (±11.0% of mean JSW in position 1) | | | | | | |
| PIP-hand | | | | | | |
| Mean JSW | 1.241 | 1.219 | 1.226 | 1.170* | 1.159* | 1.130* |
| Change (mm) | — | –0.023 | –0.015 | –0.072 | –0.086 | –0.097 |
| % | — | –1.81 | –1.22 | –5.79 | –6.91 | –7.80 |
| For Positions 1–3, $SD_P$ = 0.021 mm<br>ICO = $\pm 2 \cdot \sqrt{2} \cdot SD_P$ = ±0.059 mm (±4.8% of mean JSW in position 1) | | | | | | |
| MCP+PIP-hand | | | | | | |
| Mean JSW | 1.480 | 1.474 | 1.459 | 1.504 | 1.546* | 1.470 |
| Change (mm) | — | –0.005 | –0.021 | 0.022 | 0.052 | 0.012 |
| % | — | –0.36 | –1.42 | 1.50 | 3.54 | 0.82 |
| For Positions 1–3, $SD_P$ = 0.038 mm<br>ICO = $\pm 2 \cdot \sqrt{2} \cdot SD_P$ = ±0.107 mm (±7.2% of mean JSW in position 1) | | | | | | |

* Positions in which group mean JSW was significantly different from Position 1 (Dunnett's test). The within-subject variability due to position ($SD_P$ and ICO) considered Positions 1–3 only and includes the error due to $SD_E$ from Table 3, see Materials and Methods.

mm and 0.06 mm, respectively) reveals that, for the 3 radiographically similar hand Positions 1–3, the within-subject variability in radiographic JSW increased 2 to 4-fold due to the predefined changes in physical hand position (increase from 3% to 5–11% of mean JSW). These changes in hand position appeared to affect MCP joints more than PIP joints.

## DISCUSSION

If the progress of arthritic joint disease is to be assessed using the degeneration of the MCP and PIP radiographic joint space, then the reliability of the radiographic representation of joint space and its means of measurement need to be fully explored. We report for the first time an exploration of both these sources of error in standard hand radiographs.

The reliability of the computer software in determining the mean joint space width from hand radiographs, including the effect of image digitization, was examined by considering the variation in triplicate readings of 640 joints in 40 radiographs. Comparisons to manual measurements show the computerized method to be highly accurate with the advantage of better reproducibility (Table 1). As the hand joints are small, single measurements such as minimum, or midline, JSW are sensitive to radiograph granularity. For this reason, the mean radiographic JSW is considered a more reliable measure.

The second source of error, the degree to which 3 dimensional finger joints are reliably and precisely represented on radiographs, has been investigated by considering repeat radiographs with the hands in the standard clinical PA position, and in varying, increasingly flexed, positions (Figure 1). Repeat radiographs in the same nominal position were taken at 3–5 day intervals to allow for small changes in hand position without any change in organic joint space. The possibility of averaging mean JSW across all MCP or PIP joints in both hands for a subject allows an opportunity to increase the reproducibility of the JSW measure. For an individual subject, a physical change in mean JSW of ±0.11 mm (~7%) for individual joints and ±0.03–0.05 mm (2–3%) for values aggregated across both hands could be detected with 95% probability — ICO in Table 3, see Materials and Methods and[24]. For a group of 30 subjects, a change in mean JSW of ±0.01 mm (~0.5%) for MCP or PIP values aggregated across the group could be detected with 95% probability, using the group cutoff for N = 30 subjects in Materials and Methods. Further, radiographic measurements of a calibrated MCP model confirmed that hand radiographs could be expected to accurately reflect physical finger joint size (Figure 5).

In the past, the effect of position on radiographic joint space has been investigated mostly in the knee, where careful studies show it has a significant influence[25-27]. Here, in the Position Study, changes in hand position are shown to affect mean JSW. MCP joint space tends to appear greater with moderate finger flexion, whereas PIP joint space tends to appear smaller (Table 4). Although the anteroposterior (AP) view cannot physically be considered a small change in position, radiographically, PA and AP orientations provide similar views of the joint space. Considering the first 3 hand positions (standard clinical PA view, AP view, and extended PA view), there was no statistically significant change in either MCP or PIP hand averaged mean JSW. However, the within-subject variability in joint space measurements considering these 3 positions is greater than that found in the Repeat Study, which considered the same nominal hand position (0.05 mm increases to 0.19 mm for hand averaged MCP, 0.04 mm increases to 0.06 mm for hand averaged PIP, values for ICO in Tables 3 and 4). Thus, for a group of 30 subjects, a change in mean JSW of ±0.04 mm (2%) for MCP or ±0.01 mm (< 1%) for PIP values aggregated across the group could be detected with similar changes in hand position (with 95% probability, applying the group cutoff in Materials and Methods).

The measurement system described here is based on the use of standard clinical hand radiographs. Although radiographic scoring has been reported as insensitive to joint disease and as reflecting clinical evaluations poorly[28-32], other authors have reported a good correlation[33-36]. We have shown that careful positioning is essential to obtain the most precise measurements. Provided such care is taken, possibly using templates to record hand position in the first serial film, changes in the mean MCP-hand or mean PIP-hand joint size of as little as 0.05 mm, or about 3% (Table 3), would indicate an actual physical change in joint size in serial radiographs for a single subject (with at least 95% probability). Thus, the reproducibility of the mean JSW inherent in radiographs can be excellent for healthy subjects. The method needs to be tested on serial radiographs of arthritic patients both in the short term (1–3 weeks), to establish whether similar reproducibility applies when joints are affected by disease, and in the longer term (6–12 months), to determine over what (minimum) period the organic JSW change due to disease can be detected.

Additional variability in radiographic JSW measurements will occur in clinical studies where the joints are affected by disease. Possible sources of increased variability are: poor hand positioning, malaligned or distorted joint margins, the smaller JSW encountered in women and in joints affected by disease, and variations in radiographic technique and the inadvertent use of different radiographic landmarks to measure JSW in successive films. The variability due to random changes in radiography, hand position, and measurement landmarks can be controlled by establishing quality assurance procedures. However, unavoidable changes in hand position will arise if tender and swollen joints prevent full hand extension. Since this study, we have measured the mean JSW in a retrospective study of 240 patients with RA (male and female) using standard clinical radiographs taken at 2 time points up to 2 years apart. No difficulty was experienced in measuring the smaller JSW encountered in women and in joints affected by disease, although the ICO given in this study forms a greater percentage of JSW when the JSW is smaller. The software was not adversely affected by bone damage due to osteoporosis or erosions, although totally fused joints were unmeasurable and, as in the Position Study, excessive finger flexion sometimes resulted in joint margins no longer being distinguishable on the radiographs.

When JSW remains measurable, changes in hand flexion due to diseased joints increase measurement variability. It is this variability we attempted to investigate in the Position Study, although it is recognized that the model, using healthy volunteers, has limitations. The effects of flexion also have implications for scoring procedures of arthritis radiographs. In particular, an organic reduction in patient MCP joint space could be masked on a radiograph by an apparent increase in size due to finger flexion. Further, scoring procedures measure joint space narrowing *per se*: the possibility that JSW increases during arthritis (either through positional effects or because of cartilage changes) is rarely discussed.

The possible effect of relatively advanced disease on joint space measurement requires specific study, as do the questions, and possible novel observations, stimulated by the introduction of a new methodology. However, it should be emphasized that the value of a sensitive measurement system lies in the detection of progressive disease early on, so that the benefits disease-modifying treatments may bring to the patient can be determined before the irreversible joint destruction that characterizes late disease has occurred.

The computerized method discussed here is capable of simplification. Measurements were taken in triplicate; however, the data suggest that single JSW measurements (as used in the ICO and group cutoff limits presented here) would be adequate in practice. At present, the final measurement stage is shown on the screen so that the operator is provided with a quality assurance step before accepting the automatic measurement. In principle, further error checking procedures could be built into the joint space measurement algorithm and this process could be automated. Software has already been designed to locate joints within hand radiographs[37], and hence in principle it should be possible to digitize and measure a whole radiograph without requiring the operator to capture each joint separately. These procedures would save time in a clinical analysis and would enable the validity of radiographic joint space change compared to clinical evaluations to be explored further.

The results of this investigation suggest that computerized measurement of radiographic joint space in hand radiographs meets the requirements of a good measuring system[38,39]: it is feasible (cost and usage), precise (reproducibility), sensitive (detection of small changes due to disease), and expected to be valid (true reflection of the progress of disease). It introduces the possibility of reducing both patient numbers and the length of clinical trials when investigating disease-modifying treatments and also, with careful hand positioning, the possibility of monitoring individual patient progress.

## ACKNOWLEDGMENT

The authors thank Chris David for reprographics help; John Lyons for construction of the MCP model; Peter Hunter for computing support; Jane Dacre, Jacinta Nickson, and John Shorter for contributions to the methodology; Dan Baker, Byron Jones, Ron Leslie, Brian Macdonald, and Robert Murdoch for helpful advice and critically reading the manuscript.

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