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Assessment of Proximal Finger Joint Inflammation in Patients With Rheumatoid Arthritis, Using a Novel Laser-Based Imaging Technique

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Objective. **To evaluate a newly developed laser-based imaging technique for the study of soft tissue changes and acute inflammatory processes of the proximal interphalangeal (PIP) joints in patients with rheumatoid arthritis (RA).**

Methods. **A novel imaging device was developed which allows the transillumination of PIP joints using laser light in the near-infrared wavelength range. In a first clinical followup study, a total of 72 PIP joints of 22 patients with RA and 64 PIP joints of 8 healthy controls were examined both clinically and with the new laser device. At baseline and at followup after a mean of 6 weeks, clinical signs of synovitis, the joint circumference, and the degree of pain were assessed for each PIP joint in order to determine the clinical degree of inflammation. Different features were extracted from the laser images and evaluated by a neural network.**

Results. **At baseline, 72 PIP joints in the RA patients showed clinical signs of inflammation. At followup, 45 PIP joints showed clinical improvement, 13 showed steady active inflammation, and 14 showed deterioration compared with the first visit. None of the 64 PIP joints in the healthy individuals showed any signs of synovitis. The inflammatory status of 60 of the 72 RA joints examined was classified correctly by laser examination and joint circumference determination, giving a sensitivity of 80%, a specificity of 89%, and an accuracy of 83% in detecting inflammatory changes in affected joints. Laser data and joint circumference determination of healthy joints at followup resulted in an accuracy of 85% in reproducing the image.**

Conclusion. **The new laser-based imaging technique allows the transillumination of PIP joints and gives information about the inflammatory status of the joint after processing through a neural network. Our data indicate that laser imaging may provide additional information in the early diagnosis of an inflammatory joint process and may prove particularly useful in assessing acute joint inflammation at followup.**

Rheumatoid arthritis (RA) is the most common inflammatory arthropathy, with 1–2% of the population being affected by this chronic, mostly progressive disease (1) that often leads to early disability and joint deformities (2,3). Recent studies have suggested that in the future, this devastating joint damage could perhaps be prevented, or at least delayed, by early diagnosis and treatment (4). This would lead to a considerable improvement in the overall prognosis for RA patients, particularly since new effective therapeutic approaches are now widely available. However, early diagnosis may prove difficult in the clinical setting, since the diagnosis of RA still mainly depends on clinical criteria. Until now, conventional radiography has been the standard method for detecting and quantifying destructive arthritis, but this method is very insensitive in detecting early erosive lesions. Other imaging procedures, such as ultrasound or magnetic resonance imaging (MRI), await evaluation as possible alternatives for the diagnosis of early arthritic changes (5–7). In contrast to conventional

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radiography, MRI provides information not only about osseous changes, but also about soft tissue changes, such as synovitis, effusions, and tendon abnormalities (8–11). The disadvantages of MRI are high costs and lack of standardization, while ultrasound is time consuming and observers need a tremendous amount of training.

Objective quantification of joint inflammation is a major challenge not only in the clinical diagnosis of RA, but also in the development of new drugs, especially biologicals. Therefore, novel methods for rapidly, objectively, and reproducibly assessing joint swelling are needed to supplement clinical assessment and radiography. Prapavat et al (12,13) recently showed that joint tissues such as bone, cartilage, and synovia have distinct absorption and scattering coefficients in vitro when analyzed with a laser light of a certain wavelength. They showed that there were significant differences in the optical properties of normal and pathologic tissue. Hence, we postulated that it should be possible to detect pathologic changes of the joints in vivo by analyzing the light transmitted through a finger joint. On the basis of these studies (12,13), we developed a laser-based imaging technique which allows the measurement of optical characteristics of joint tissue. By using a laser device that is positioned above the finger joint and a sensitive camera that visualizes the scattered light distribution below the joint, the optical characteristics of normal and inflamed joints can be detected and processed through a picture software program.

In this study, we present the first clinical results with this novel laser-based technique for the visualization of synovitis in the proximal interphalangeal joints (PIPs) of patients with RA. The results showed that with this novel technique, arthritis of the small finger joints can be detected and followed up with high sensitivity and specificity. This technique may therefore contribute significantly to the diagnostic armamentarium of rheumatologists by allowing an inexpensive and reproducible assessment of inflammatory joint changes.

PATIENTS AND METHODS

Patients. Over a period of 6 months, 22 consecutive patients (20 women [median age 42 years, range 22–75 years] and 2 men [median age 35 years, range 35–36 years]) with RA were included in the study. All patients were white and were recruited from the Rheumatological Outpatient Clinic, Georg-August-University Göttingen, Medical Center, Department of Nephrology and Rheumatology. All patients had clinical involvement of the finger joints and had been or were being treated with disease-modifying antirheumatic drugs. Radiographs of the hands were performed prior to investigation and did not show any signs of arthritic erosions. A total of 72 PIP joints were examined at baseline and during a followup visit after a mean duration of 42 days.

The study was approved by the local ethics committee. All patients gave their informed consent prior to investigation.

Clinical examination. All patients had RA according to the 1987 revised criteria of the American College of Rheumatology (formerly, the American Rheumatism Association) (14). All patients were examined by one investigator (AKS) on both visits. To assess the clinical degree of inflammation of each PIP joint, 3 diagnostic criteria were used on each occasion, as follows:

1. Each PIP joint was examined and the clinical arthritis activity was scored from 0 to 3 according to the degree of synovitis (swelling, tenderness, or warmth), where 0 = inactive, 1 = moderately active, 2 = active, and 3 = very active.
2. The patients were asked on each occasion to evaluate the degree of pain for each PIP joint, using a visual analog scale (VAS) of 0–10, where 0 = no pain and 10 = unbearable pain.
3. The circumference of each PIP joint (in mm) was measured with a conventional metric measuring tape.

For every joint examined, data for each parameter from baseline and followup visits were compared, and changes were rated as improvement (+), worsening (−), or no change (0). Moreover, taking all 3 parameters together, the overall course of inflammation for each joint was scored accordingly (as +, −, or 0, respectively). Only those joints that showed concordant changes in all 3 clinical parameters, or concordant changes in at least 2 parameters with the remaining parameter being unchanged, were included in the study. Results from the laser-based optical joint analysis and from the clinical examination were then correlated with each other. Since there were marked interindividual variations in optical joint characteristics, special attention was given to the intraindividual comparison of followup data. The clinical examination was done without knowledge of the diaphanography result.

Laser imaging. All PIP joints of the second through the fifth fingers of both hands were examined clinically (n = 176 PIP joints). Only the 72 PIP joints with definite signs of inflammation in the RA patients, joints with clinically clearly defined changes in their inflammatory status in the RA patients, and the 64 definitely healthy joints in the 8 healthy controls were included. It was necessary at this stage of the study to have precise clinical references; therefore, we excluded joints of RA patients that appeared clinically normal or only slightly inflamed.

The study was performed with a novel laser device that had been developed by the Department of Medical Physics and Laser Medicine at the Free University of Berlin in cooperation with Siemens (Erlangen, Germany). This apparatus allows the transillumination of finger joints by means of a laser light at a wavelength of 675 nm with an output power of 2 mW. For data acquisition, each finger was positioned in a specially designed

holder (Figure 1) to ensure positioning in the lateral and longitudinal planes. Finally, the finger joint was adjusted precisely by rotating and pushing the finger slightly back and forth. The scattered light distribution was detected by a charge-coupled device camera which is highly sensitive to near-infrared light (PCCam; PCO Computer Optics, Kehlheim, Germany). The camera system was connected to a PC (Pentium II, 300 MHz; Intel, Santa Clara, CA) with evaluation and picture processing software (Figure 2). The software was developed especially for this purpose (LabWindows/CVI; National Instruments, Austin, TX) and allows the examiner to acquire, display, and save the pictures together with additional clinical information in a data bank (Microsoft Access; Microsoft, Redmond, WA). Moreover, stored pictures from previous examinations may be viewed in parallel with the live image of the finger being currently investigated, thus allowing for the direct visual comparison of images.

In order to avoid artifacts, patients were required to wash their hands and use a conventional moisturizing cream to obtain a reproducible skin surface prior to the laser examination. Patients with clinically evident callus or stained fingers were not included in the study. The examination of 8 PIP joints takes ~5–10 minutes using the laser imaging technique. The laser imaging device was approved by an official security service for medical devices.

Controls. Eight healthy volunteers (3 women and 5 men, median age 28 years, range 26–37 years) without signs or symptoms of a rheumatic disease or other joint afflictions served as controls. All 64 PIP joints of both hands were examined at 2 time points, both clinically and with the laser imaging technique, and data were processed in the same way as described for the RA patients.

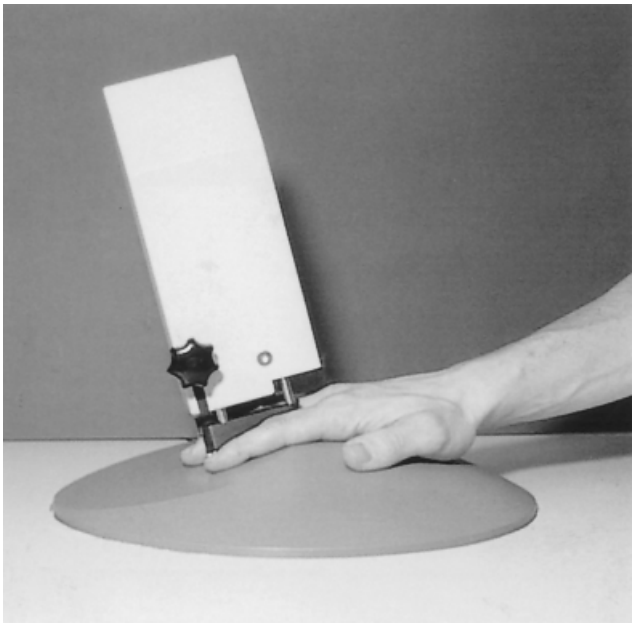

Figure 1. Administration of laser-based imaging examination. The patient's finger is placed in a specially designed holder to ensure reproducible positioning of the proximal interphalangeal joint. The laser light required for the transillumination is placed in the upper part of the apparatus.

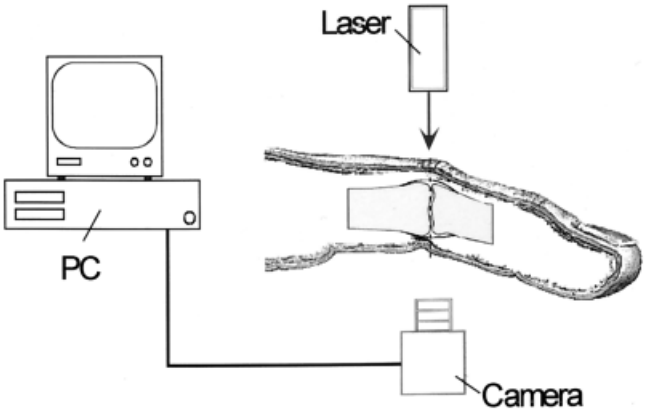

Figure 2. Set-up for the transillumination of finger joints. The PC is connected to the charge-coupled device (CCD) camera, which is placed below the finger joint. The CCD camera records the transillumination data, which can be evaluated with the picture processing software.

Statistical analysis. The computer evaluation was performed by extracting features from each laser image. In a preprocessing step, each picture (a 2-dimensional pixel matrix with 255 lines and 415 columns) was preprocessed by truncating the upper and the lower 20 lines to avoid boundary effects, and by compressing the picture to 43 lines and 83 columns (by averaging windows of 5×5 pixels) to reduce noise. Intensive evaluation showed that 2 features extracted from those images contained significant information about the rheumatic disease status of a finger joint. The first feature, f_1, is the maximum of all pixel row sums and represents the overall brightness of the transmitted light through the finger joint. The second significant feature was calculated using the horizontal pixel strip with the highest light intensity, which is typically near the vertical center of a joint. This feature, f_2, is the curvature (second derivative) of the light intensity of this horizontal strip at its maximum intensity, which is close to the horizontal center of the finger joint. In addition to these 2 features derived from the images, we used f_3, the circumference of the finger, as the third feature. The changes in the rheumatic disease status of a finger joint are characterized by the differences between the values of the 3 features in the 2 examinations. These differences in the 3 features, f_1, f_2, and f_3, were used as inputs for the neural network classifier.

Overall, we obtained data from 72 finger joints. To obtain a statistically relevant measurement of the performance of the system, the data sets were partitioned into 4 subsets. In turn, 3 of the subsets were used for training the neural network classifier, and 1 subset was used to test the performance of the classifier (i.e., the classification performance on data not used for training). The average performance of the neural network classifiers on the test data sets is an unbiased estimate of the true test set performance. For the neural network classifier, we used a standard multilayer perceptron (a network of formalized artificial neurons) developed using the software tool Simulation Environment for Neural Networks (Siemens, Mu-

nich, Germany). After training, the output value of the neural network classifier is a number between 0 and 1. An output of 1 indicates that the classifier assigns a data set to "class 1" (positive development, improvement) with certainty, while an output of 0 indicates that the classifier assigns the data set to "class 2" (negative development, worsening) with certainty, and an output of 0.5 indicates a high degree of uncertainty about the classification result. Finger joints were classified as belonging to class 1 if the output of the neural network was above a specific threshold value; otherwise, they were classified as belonging to class 2.

The performance of the classifier can best be analyzed and visualized using a receiver operating characteristic (ROC) curve, as discussed by Metz (15). In an ROC curve, sensitivity is plotted against 1 minus the specificity by varying the threshold value. The terms "sensitivity" and "specificity" are defined as follows:

$$\text{Sensitivity} = \frac{\text{No. of true-positive changes (by laser and circumference measures)}}{\text{No. of actually positive changes (by clinical evaluation)}}$$

$$\text{Specificity} = \frac{\text{No. of true-negative changes (by laser and circumference measures)}}{\text{No. of actually negative changes (by clinical evaluation)}}$$

An ROC curve of a classifier that operates no better than chance will lie along the major diagonal (lower left to upper right). Curve points closest to the upper left corner represent the threshold that maximizes the number of true positive results and minimizes the number of false positive results. The accuracy of the classifier is defined as follows:

$$\text{Accuracy} = \text{Sensitivity} \times \frac{\text{No. of actually positive changes (by clinical evaluation)}}{\text{Total no. of subjects examined}} + \text{Specificity} \times \frac{\text{No. of actually negative changes (by clinical evaluation)}}{\text{Total no. of subjects examined}}$$

RESULTS

Patients with RA. *Clinical findings*. Of the 176 PIP joints examined at baseline, only the 72 joints which showed clinical signs of inflammation were evaluated further. Based on the changes in 3 clinical criteria (degree of inflammation as assessed by the examiner, pain as assessed by the patient on a VAS, and joint circumference) between baseline examination and followup visit, PIP joints were categorized as showing an improvement, being constantly active, or showing a deterioration as a result of the inflammatory activity.

At followup, 45 PIP joints showed improvement compared with the first visit. Thirteen PIP joints showed a constant degree of inflammation between the visits, whereas 14 PIP joints showed worsening of disease activity.

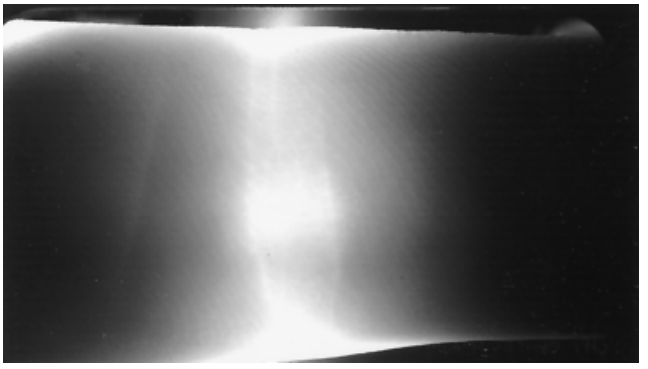

Figure 3. Laser light–transmitted image of a proximal interphalangeal joint of a healthy control, showing no active inflammation. The extended area in the middle of the image, built by the laser light that is transmitted through the joint, holds the information for the assessment of the joint's inflammatory status. The image was taken from the charge-coupled device camera.

The degree of clinically evident synovitis of the 72 PIP joints was rated between 0 and 3 at the first visit, with a mean ± SD degree of synovitis of 1.05 ± 0.63. At the second visit, the degree of synovitis ranged between 2.5 and 0, with a mean ± SD of 0.64 ± 0.69, indicating that there had been an improvement in the degree of arthritis between the visits. The difference in the degree of synovitis was a maximum of 2 and a minimum of –1.5, with a mean ± SD difference of 0.41 ± 0.79.

The patients rated their degree of pain of the PIP joints between 0 and 9 during the baseline visit, with a mean ± SD of 3.84 ± 2.60, while at followup they rated their pain lower, with a mean ± SD of 3.09 ± 2.06 (range 0–7). Thus, in the evaluation of pain as well, there was an overall improvement between the first and second visits. The difference in pain ranged between 7 and –7, with a mean ± SD difference of 0.75 ± 2.26.

The circumference of the PIP joints ranged between 45 mm and 78 mm during the first visit, with a mean ± SD of 62.21 ± 7.49 mm, whereas at the second visit the range was between 45 mm and 77 mm, with a mean ± SD of 61.67 ± 7.46 mm. The difference in circumference between the first and second visits ranged between 8 mm and –4 mm (mean ± SD difference 1.54 ± 2.71).

Laser-based imaging data. PIP joint cavities could be seen as an extended area in a rather diffuse image of high signal intensity (Figures 3 and 4). Figure 4 shows an

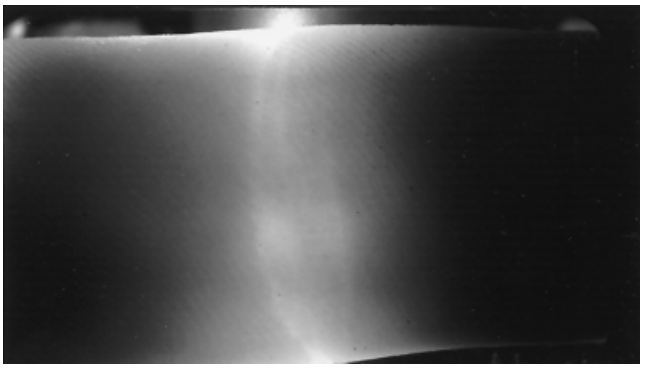

Figure 4. Laser light–transmitted image of an actively inflamed proximal interphalangeal joint of a patient with early rheumatoid arthritis. Compared with that of the healthy control (Figure 3), the extended area in the middle of the image appears to be darker and rather fuzzy due to altered optical characteristics of the inflamed joint. The image was taken from the charge-coupled device camera. The data taken from this and the other images were evaluated by the neural network as described in Patients and Methods.

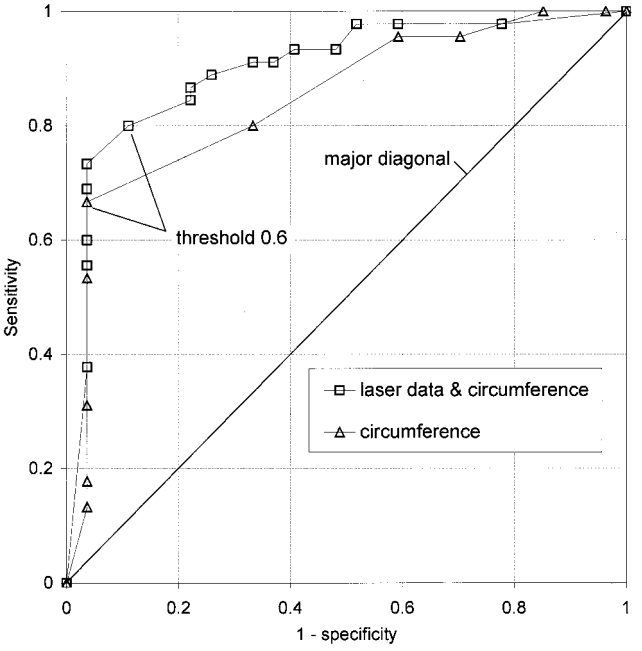

Figure 5. Receiver operating characteristic (ROC) curve of the sensitivity against the false-positive rate (1 – specificity) plotted across a range of thresholds. The line with squares represents results taken from the laser imaging device and joint circumference measurements. The line with triangles represents results taken only from changes in joint circumference. The major diagonal represents the ROC curve of a classifier that operates no better than chance, as described in Patients and Methods.

actively inflamed PIP joint, which seems to be rather fuzzy and darker when compared with the healthy joint shown in Figure 3. The pictures differed interindividually, making comparisons quite difficult. In order to compare pictures intraindividually, the fingers had to be positioned for the second examination in exactly the same way as they were positioned the first time. This was accomplished by directly comparing the previously taken picture with the live image of the finger being currently measured. This procedure reduces artifacts and results in a repositioning accuracy of <1 mm.

The data sets (2 features from the laser image and the circumference) for each pair of images were used as input parameters for the neural network classifier. The result of that classification was a number between 0 and 1, with 1 indicating improvement and 0 indicating worsening or no change. Since the output of the classification could be any number between 0 and 1, it was necessary to define a threshold in order to classify an output value above this threshold as representing "improvement" and an output value below the threshold as representing "worsening." We compared the PIP joints of patients with an improvement with PIP joints that had worsened as well as with PIP joints that showed a constant inflammatory status.

For finding the correct threshold, data are most usefully presented in the ROC curve. The ROC curve plots sensitivity against 1 minus the specificity over a range of thresholds (Figure 5). Points closest to the upper left corner indicate the thresholds that maximize the number of true-positive results and minimize the number of false-positive results. The sensitivity, specificity, and accuracy were calculated for the different thresholds (Table 1). The best results were obtained with a threshold of 0.6, in that laser and circumference data correctly described the joint status with a sensitivity of 80%, a specificity of 89%, and an accuracy of 83% (i.e., 60 of the 72 joints examined were classified correctly). At followup, 36 of 45 "clinically improved" PIP joints showed an improvement according to the laser imaging

Table 1. Sensitivity, specificity, and accuracy for the patient group, according to the algorithms by Metz (see ref. 15), at different thresholds from the receiver operating characteristic curve, including laser data and joint circumference*

Statistical quantity	Threshold					
	0.0	0.4	0.5	0.6	0.7	1.0
Sensitivity	100	89	87	80	69	0
Specificity	0	74	78	89	96	100
Accuracy	63	83	83	83	79	38

* Values are percentages. See Patients and Methods for explanations.

technique data. Moreover, 24 of 27 joints that were clinically worse or showed no change in inflammatory status were classified accordingly by the laser examination. Thresholds of <0.6 would lead to lower specificity and higher thresholds would lead to lower sensitivity. With a given threshold of 0, the sensitivity would be 100% and the specificity would be 0%. If the threshold was set at 1, the specificity would be 100%, but the sensitivity would be 0%.

Intensive data analysis, including comparisons of the results of "only circumference," "only laser data," and "laser data in combination with circumference," showed that the best results with the highest accuracy and sensitivity in detecting inflammatory changes could only be achieved by the combination of the laser imaging data with the change in circumference. However, an ROC curve representing the circumference only confirms that the changes in circumference of a joint play an important role in the diagnosis of inflammatory processes. By analyzing circumference changes alone, 56 joints (of 72) were classified correctly, of which 30 (of 45) showed an improvement and 26 (of 27) developed a worsening in inflammatory status. Given a threshold of 0.6, this results in a sensitivity of 67%, a specificity of 96%, and an accuracy of 78% (Table 2).

Control group. *Clinical findings*. None of the 64 PIP joints of the 8 healthy individuals showed any signs of synovitis. The changes in joint circumference between both visits were a maximum of ±1 mm, and the control group individuals rated the degree of pain for each PIP joint as 0 at both visits. The clinically evident degree of synovitis was rated 0, and there was no difference between the visits. The circumference of the PIP joints measured at the first visit ranged between 46 mm and 69 mm, with a mean ± SD of 59.83 ± 5.52 mm, and between 46 mm and 68 mm at the second visit, with a mean ± SD of 59.91 ± 5.55 mm.

Laser-based imaging data. For the control group, the accuracy was calculated for the different thresholds in the same way as for the patient group (Table 3). The laser data were evaluated by the same neural network classifier as those for the patient group. Using the same threshold of 0.6, laser data and joint circumference determination resulted in an accuracy of 85%; therefore, it was possible to receive a reproducible image of healthy PIP joints with the laser imaging technique in a high percentage of examinations.

However, comparison of data both from RA patients and from healthy controls revealed that it was not always possible to reliably distinguish inflamed from healthy joints only on the basis of laser data and joint circumference. Due to a high interindividual variability of joint structure and optical characteristics, there was a large overlap of data from both groups. While this novel technique was able to detect inflammatory changes of PIP joints with high sensitivity in intraindividual followup studies, information on the inflammatory joint status after a single laser examination was still limited.

Table 2. Sensitivity, specificity, and accuracy for the patient group at different thresholds from the receiver operating characteristic curve, including joint circumference only*

Statistical quantity	Threshold					
	0.0	0.4	0.5	0.6	0.7	1.0
Sensitivity	100	80	80	67	53	0
Specificity	0	67	67	96	96	100
Accuracy	63	75	75	78	69	38

* Values are percentages. See Patients and Methods for explanations.

Table 3. Accuracy for the different thresholds from the receiver operating characteristic curve, including laser data and joint circumference, for the healthy individuals*

Statistical quantity	Threshold					
	0.0	0.4	0.5	0.6	0.7	1.0
Accuracy	0	75	81	85	91	100

* Values are percentages. See Patients and Methods for explanations.

DISCUSSION

Imaging techniques play an important role in the diagnosis and monitoring of RA. Recent studies have convincingly shown that early treatment, and therefore an early diagnosis and sensitive followup, is mandatory for preventing or at least delaying joint destruction in RA (4,16,17). Thus, novel methods for sensitively assessing joint swelling and inflammatory soft tissue changes in early disease which are noninvasive, of low cost, examiner independent, and readily available in daily practice are needed to supplement clinical assessment and radiography.

We have invented a new imaging method which allows the in vivo transillumination of finger joints with laser light in the near-infrared wavelength range. Since biologic tissue is a highly scattering medium, the transmitted light distribution detected by the camera does not give the familiar sharp morphologic picture provided by other medical imaging techniques. Instead, it shows a more-or-less diffuse image of the joint cavity as an extended area of high signal intensity (Figures 3 and 4).

This is a functional rather than a pure morphologic image of the optical joint characteristics that correlate with the inflammatory status of the joint.

The data from the present preliminary study show that it is possible to receive a reproducible diaphanoscopic image of the PIP joint by using laser light for transillumination. Optical data had to be processed by a neural network and were supplemented by joint circumference measurements. Using an ROC curve plot and by defining a threshold of 0.6, this approach led to an accuracy of 85% in receiving reproducible images of the PIP joints of healthy individuals (Table 3).

In RA patients, the results for correctly detecting the course of joint inflammation showed an overall accuracy of up to 83% (Table 1). Again, a threshold of 0.6 appeared to be optimal, giving a sensitivity of 80%, a specificity of 89%, and an accuracy of 83% (Table 1). Analysis of laser imaging or joint circumference changes alone revealed that single parameters were not sufficient to assess arthritic changes (data not shown). The ROC curve (Figure 5), plotting improvement against worsening and steady active inflammation, showed that optical joint characteristics were significantly influenced by joint circumference. However, the combined analysis of the features extracted from the laser image calculated by a neural network and the change in circumference resulted in the most sensitive method for detecting a change in inflammatory joint status. These data provide strong evidence that laser imaging combined with measurement of joint circumference is a promising tool for assessing the inflammatory process in PIP joints. Since the procedure of measuring the circumference of each joint is very time consuming, an electronic method for measuring the joint circumferences while taking a laser picture would be a very helpful tool for the rheumatologist and is currently being evaluated.

The optical characteristics of PIP joints are determined by various factors. The optical changes detected that correlate with the degree of arthritis are most probably due to inflammatory processes in both synovial fluid and synovial membrane. Clouding of the synovial fluid and edema and cellular infiltration of the synovial membrane are likely to influence absorption and scattering of laser light (12,13,18). When all other factors are kept more or less constant, as they are in intraindividual followup studies, these inflammatory changes may be quantified by laser imaging. However, there are a number of other factors which influence the results of diaphanoscopic joint examinations. Changes in the moisture level of the skin, the skin color, the ambient temperature, dirt, or callused skin might affect scattering and, as a consequence, the results of the investigation. In order to avoid such artifacts, only white patients were included in the study and a constant room temperature was maintained. In addition, patients had to wash their hands and use a conventional moisturizing cream to give a reproducible skin surface. Nevertheless, there are still unchangeable individual differences in joint anatomy that significantly influence the laser imaging results and overlie the effects of arthritis. It is therefore not yet possible to definitely distinguish between a healthy and an inflamed joint in different individuals by laser imaging, whether or not the procedure is combined with circumference determination.

Taken together, the new laser imaging device might allow an early diagnosis of an inflammatory process if a corresponding initial image has been taken for a later comparison of both images. However, at this stage of the study, laser imaging is of only limited help for an individual diagnosis of early arthritis due to interindividual anatomic differences of the joint structures. Thus, laser imaging may be especially useful for a sensitive followup analysis of joint inflammation, and may therefore provide important information about the response to medication as well as for the objective quantification of the effectiveness of antirheumatic medication. The new laser imaging technique is easy to handle, noninvasive, and inexpensive. It therefore has many advantages over conventional imaging and provides new information about inflammatory joint status. Laser imaging may supplement our imaging armamentarium and help us to better assess our arthritis patients. However, additional studies with more patients and a comparison with other, established imaging techniques have to be performed before the overall usefulness of this new technique can be conclusively evaluated.

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