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Laser Imaging Techniques for Follow-up Analysis of Joint Inflammation in Patients with Rheumatoid Arthritis

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Summary

Rheumatoid arthritis (RA) is the most frequent chronic inflammatory arthropathy that often leads to joint destruction. Essential for the progress of the disease are both an early diagnosis and a sensitive follow-up of synovitis. In this paper, we present new laser based imaging techniques for the transillumination of small finger joints.
The "Laserscan" technique allows the transillumination of small finger joints using red laser light with a wavelength of 675nm. The laser is positioned above the finger joint and a CCD camera detects the scattering distribution below the joint. After processing the data through a statistical machine learning method, we could show in a preliminary clinical study that it was possible to correctly classify the inflammatory status of 62 of 72 joints from 22 patients with RA compared to precise clinical examination. Sagittal optical tomography is a further development of "Laserscan". In this technique, a red laser is moved in sagittal plane above the proximal interphalangeal finger joint while a detector underneath the joint measures the scattered light distribution in the same plane. Using model-based iterative image reconstruction algorithms, sagittal cross-sectional images are obtained based on the acquired data. These images reflect the distribution of scattering and absorption properties within and around the joint cavity of a first healthy volunteer.

Key words
Rheumatoid arthritis, synovitis, finger joint, imaging methods, laser transillumination

Introduction

Rheumatoid arthritis (RA) is a chronic, progressive disease that often leads to early disability and joint deformity. Early in the disease course, people may notice general fatigue, soreness, stiffness and aching. Pain and swelling may occur in the same joints on both sides of the body and will usually start in the hands or feet. RA affects the wrist and many of the hand joints, but usually not the joints that are closest to the fingernails; joints most often affected are the proximal interphalangeal (PIP) and metacarpophalangeal joints. Recent studies have suggested that this devastating disease might well be prevented, or at least delayed, by early diagnosis and consequent treatment. Given the widespread availability of effective therapeutic ap-

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proaches, early diagnosis and sensitive follow-up could change the quality of life for many RA patients.

Until now, conventional radiography has been the standard method of identifying destructive arthritis. This method, however, routinely overlooks early erosive lesions. While other imaging procedures, such as musculoskeletal sonography or magnetic resonance imaging (MRI), offer possible alternatives for uncovering early evidence of arthritis and its progression, they have definite downsides. MRI is costly in terms of unit price, maintenance and contrast media; ultrasound is time consuming and both techniques require a trained examiner. 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 to rapidly, objectively, and reproducibly assess joint swelling are needed to supplement clinical assessment and radiology (22).

Transillumination imaging has been performed in different medical fields, e.g. otolaryngology for diagnosing acute sinusitis (4, 15). Diaphanoscopy has also been applied as diagnostic tool in gynecology for detecting breast cancer (8, 17, 21), ophthalmology (6, 9) and for caries diagnosis in dentistry (2, 24). Diaphanoscopic modalities in the field of rheumatology have first been discussed by Beuthan et al. (3) who found out that inflammatory rheumatic diseases of the finger joints correlate with significant tissue-optical changes. This has been confirmed by supplementary results achieved by this research group. First in-vitro examinations on the influence of inflammatory tissue on light scattering were performed by Prapavat et al. (19, 21) using a phantom finger model. They found out that joint tissue such as bone, cartilage and synovia show significant differences in the optical characteristics of normal and pathological tissue. The first experimental setting for clinical examination of joints was described by Prapavat et al. (18). Based on these studies, an improved diaphanoscopic laser-based imaging technique of clinical value was developed for proximal interphalangeal finger joints (22).

In this paper we present the clinical data of the diaphanoscopic imaging technique "Laserscan" described earlier by our research team (22). In a next step we will give an outlook to another laser based imaging technique, the sagittal laser optical tomography (SLOT) and present first images of a healthy volunteer.

Laser imaging ("Laserscan")

Patients and Methods

Patients and Clinical examination

22 patients (20 women and 2 men) with rheumatoid arthritis according to the classification criteriae of the American College of Rheumatology (1) were included in the study. All patients were recruited from the rheumatological outpatient clinic (Georg-August University of Göttingen) and had clinical involvement of the finger joints. A total of 72 inflamed PIP joints were examined at baseline and during a follow-up visit. At both time points, clinical signs of synovitis, circumference and degree of pain were assessed for each PIP joint in order to determine the clinical degree of inflammation. For every joint examined, data for each parameter from baseline and follow-up visit were compared and changes were rated as improvement, worsening or no change. Results from the clinical examination and from the laser-based optical joint analysis were then correlated to each other.

"Laserscan" technique and image analysis

All PIP joints of the 2nd to 5th fingers of both hands were examined clinically. We only included those 72 PIP joints of the 176 joints from patients with RA with definite signs of inflammation. The study was performed with the "Laserscan" technique developed by the Department of Medical Physics and Laser Medicine at the Free University of Berlin in cooperation with Siemens Medical Solutions (Erlangen, Germany). "Laserscan" allows the transillumination of finger joints using laser light at a wavelength of 675 nm with an output power of 2 mW. Each finger was positioned in a specially designed holder to ensure the same positioning during baseline and follow-up examination. By using a diode laser which is positioned above the finger joint and a CCD camera that visualizes the scattered light distribution below the joint (Fig. 1), optical characteristics of normal and inflamed joints can be detected. The acquired images undergo pre-processing, where different features are extracted from the laser images taken at baseline and follow-up. These features are in turn processed through machine learning methods that compute the change in inflammatory status. In Scheel et al (22), a neural network (NN) was used to find the change in

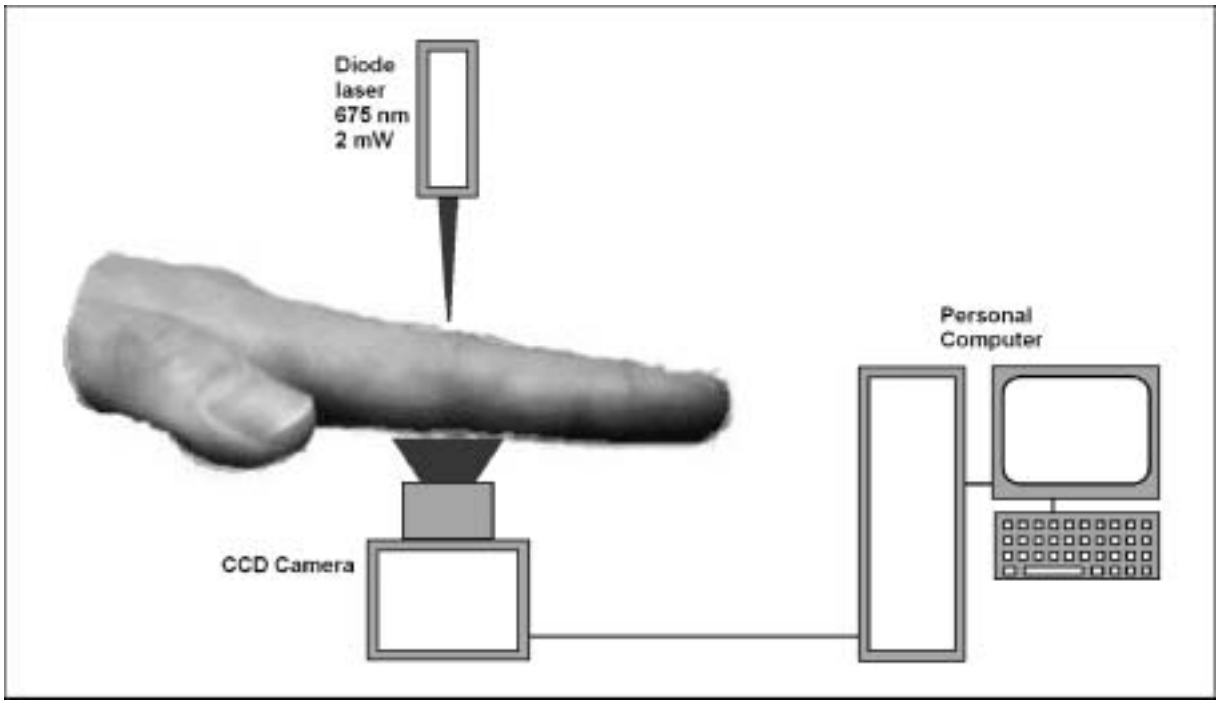

Fig. 1. Set-up for "Laserscan" examination. The personal computer is connected to the CCD camera which is placed below the finger joint. The CCD camera records the transillumination data which can be evaluated with the picture processing software.

inflammatory status. Further improvements on the results were achieved using a statistical machine learning method, as described in Schwaighofer et al. (23). Details on data acquisition, evaluation and technical details are given in the respective articles (22) and (23). In the following section, we always refer to the results achieved with the statistical machine learning method (23).

Clinical and "Laserscan" Results

At baseline, 72 PIP joints from the RA patients showed clinical signs of inflammation. At follow-up, 45 PIP joints showed an improvement as compared to the first visit. A constant degree of inflammation of the examined PIP joints between the two visits was seen in 13 joints, whereas 14 PIP joints showed worsening of the disease activity.

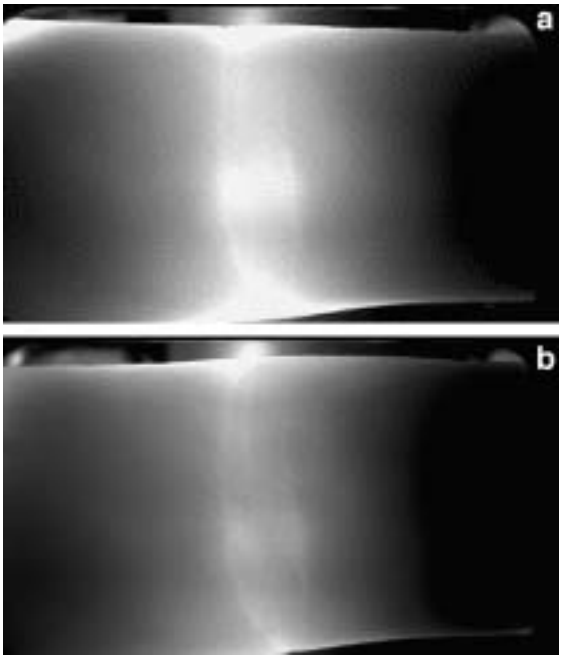

Fig. 2. Images taken from the CCD camera after transillumination with laser light. The first image (**a**) shows a proximal interphalangeal (PIP) joint from a healthy volunteer with no active inflammation. The white area in the middle of the image represents the joint cavity with information about the inflammatory status. The second image (**b**) shows a laser image of an inflamed PIP joint of a patient with rheumatoid arthritis. The area in the middle of the image is darker and rather fuzzy compared to the healthy joint.

In "Laserscan" examination, PIP-joint cavities could be seen as a longish area in a rather diffuse image of high signal intensity (Figs. 2a, b). Fig. 2b shows an actively inflamed PIP-joint which seems to be – compared to the healthy joint (Fig. 2a) – rather fuzzy and darker. In order to compare pictures intra-individually, the fingers had to be positioned for the second examination in exactly the same way as they were positioned the first time.

The inflammatory status of 62 of the 72 RA joints examined were classified correctly by laser examination and joint circumference determination, giving a sensitivity of 80%, a specificity of 89% and an accuracy of 86% in detecting inflammatory changes in affected joints (23). Our first results show that "Laserscan" allows the transillumination of PIP joints and – compared to precise clinical examination – provides information about the inflammatory status of the joint after processing through a statistical machine learning method (22, 23). The data of this study indicate that laser imaging may especially prove useful in assessing the follow-up of acute joint inflammation.

Images from this laser-based imaging technique only show transmitted light intensities and don't provide tomographic cross sections of optical properties. The images represent a conglomerate of scattering and absorption detected by the CCD camera. A better sensitivity to changes in optical properties can be expected if cross-sectional images of the joint are generated. This would allow to better localize optical properties. Therefore we have developed a novel imaging system, termed Sagittal laser optical tomography (SLOT). Numerical simulations of this technique showed promising results to distinguish between inflamed and non-inflamed joints (16). We now give an outlook to the technical set-up of the new imaging technique SLOT and describe preliminary reconstructed images of a healthy volunteer.

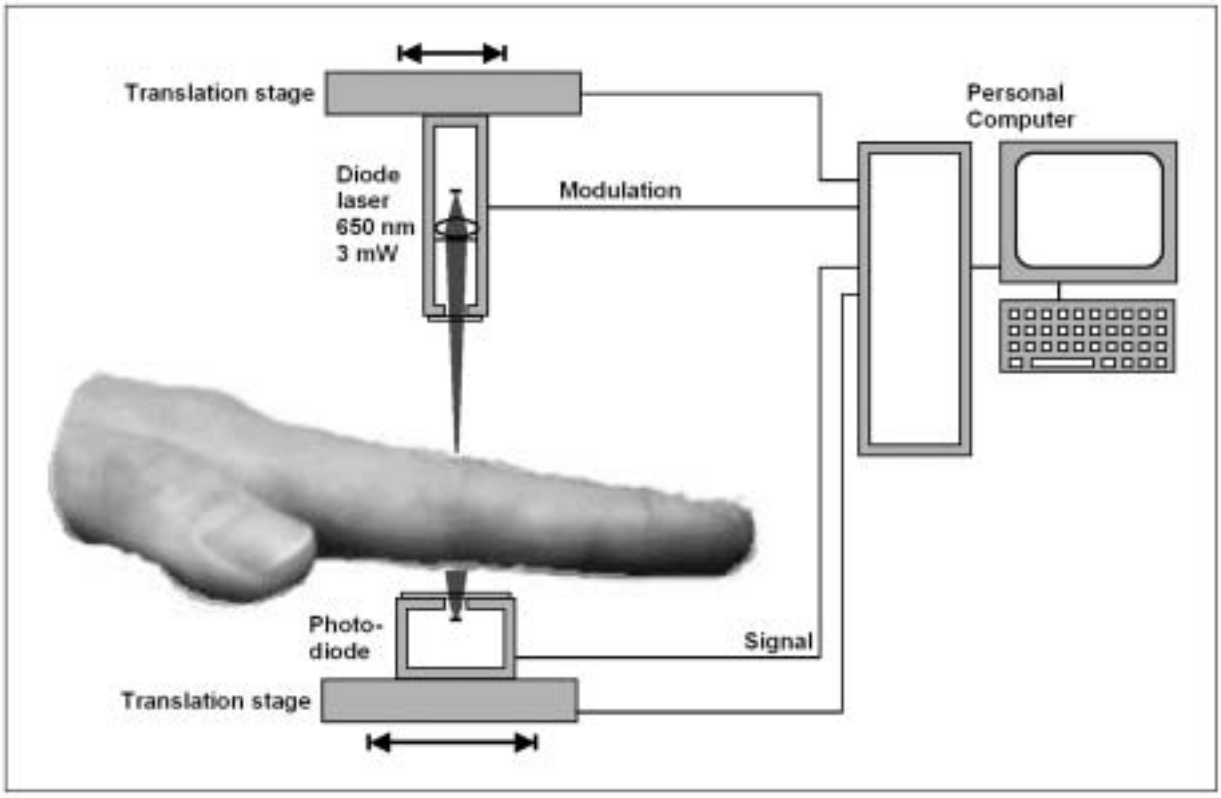

Fig. 3. Experimental set-up of sagittal laser optical tomography. The laser is arranged above the finger joint. Mounted on a stepping motor-driven translation stage, the laser is capable of scanning the joint in sagittal plane. Below the joint, a detector is similarly arranged. Both, the laser and the detector are connected to the control box, which, in turn, is connected to the PC.

Sagittal Laser Optical Tomography (SLOT)

SLOT Material and Methods

In **SLOT,** PIP joints are transilluminated with laser light (650 nm) in the sagittal plane in various positions and the scattered light distribution is detected (Si pin photodiode) underneath the joint (Fig. 3). To apply a lock-in technique for suppressing any broadband noise and any interference of ambient light, the diode laser is operated with an additional sinusoidal intensity modulation of 3.4 kHz. Using a lock-in amplifier card, the signal is directly read into a measuring computer. By means of a model-based iterative image reconstruction software, the measured data are then processed to form a cross-sectional image. For SLOT examination, the patient has to put the finger in a special holder to ensure correct positioning of the joint. The dorsal view of the finger is subject to sagittal laser point illumination. The detector acquires the scattered light distribution by point-to-point scanning of the palmar side of the finger for every laser position (Fig. 4a). From these scattered light distributions an image in the sagittal plane through the joint can be reconstructed. The iterative image reconstruction (AHH, ADK) based on the equation of radiative transfer (5) provides images through the finger joint, with the contrast being presented by spatial distribution of scattering or absorption coefficients. The complete reconstruction scheme is described in detail by Klose and Hielscher (11, 12, 13, 14). The healthy individual (male, 32 years old) underwent SLOT examination twice at two different timepoints.

SLOT Results

The experimental setup for SLOT (Fig. 3) makes diaphanoscopic measurements on PIP joints possible. As shown in Fig. 3, the scattered light distribution at

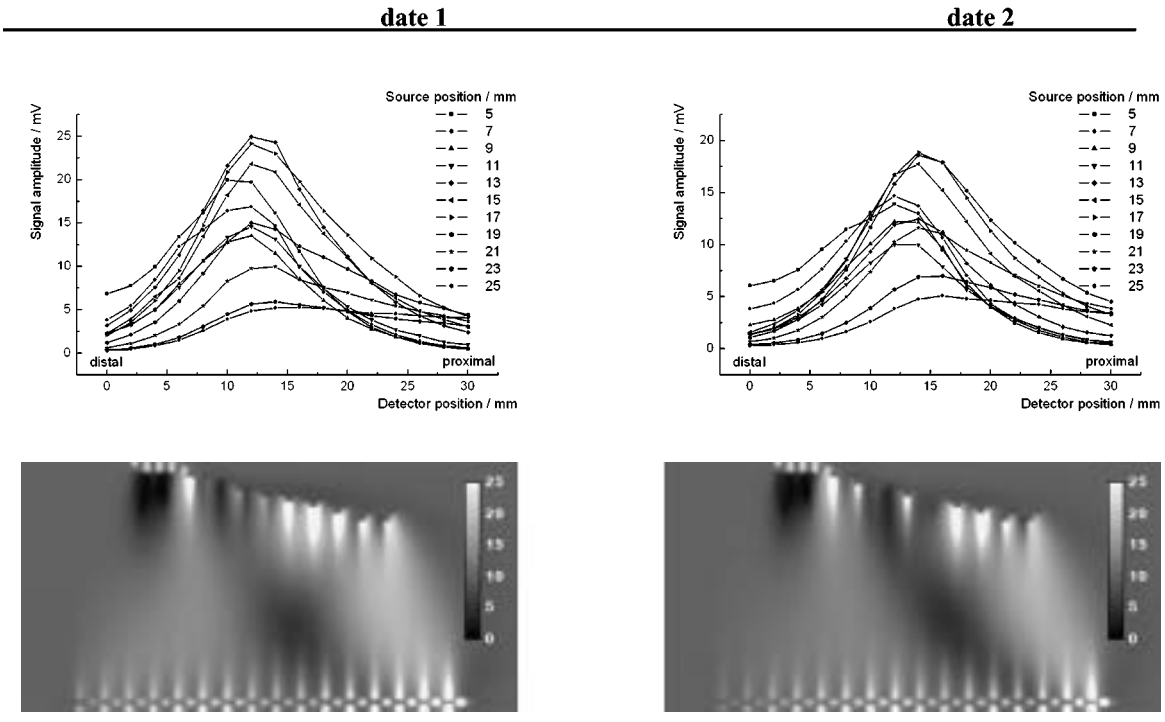

Fig. 4. Sagittal laser optical tomography (SLOT) images of proximal interphalangeal (PIP) joint II of a healthy volunteer. Fig. 4a shows unprocessed data provided by sagittal laser optical tomography at two different examinations of the same individual within 12 hours. Each curve plotted in the diagram corresponds to a laser position; the x-axis represents the diode positions in mm, while the y-axis displays the signal amplitude in mV. Fig. 4b shows typical reconstructed SLOT images (reduced scattering coefficient μ_s' in units of 1/cm) computed from the data of a healthy volunteer (male, 32 years).

each position of the laser diode is measured by the detector in the sagittal plane along the examined joint and leads to curves documented in the diagram.

The curve shape of a scattered light distribution mainly depends on the thickness of the transilluminated layer, i.e. on finger thickness, on distance between the light source and the detector, and on spatial distribution of the optical density inside the finger, which is represented by the scattering and absorption coefficient. Considering that –due to finger anatomy- the distal part of the finger is thinner than the proximal part, the light transmittance decreases from distal to proximal. Thus, the total light power, i.e. the area below the curve, is expected to decrease from distal to proximal. However, considering the optical properties of healthy joint tissue, the total light power is supposed to increase close to the joint since light is less scattered and less absorbed in this area as compared to the surrounding tissue. Thus, the curves of the scattered light distributions rise when the laser reaches the joint space (Fig. 4a).

Fig. 4b shows two sagittal laser tomographic images of a healthy volunteer (data was obtained from two different examinations of the same volunteer within 12 hours) that was reconstructed from the curves according to the method described by Klose et al. (11). The reconstructed images are presented using a linear grey scale. Areas plotted white in the image reveal high scattering, while dark areas signify low scattering coefficients. The dark areas in the center of the images correspond to the low scattering synovial fluid inside the joint cavity. The two adjacent lighter areas reflect zones of higher scattering, which correlates with the bone endings. The streaks at the edges of the finger are most likely imaging artefacts; a problem that needs to be addressed in future studies. By visual evaluation, both images have nearly the same characteristics indicating a good reproducibility.

Discussion

Imaging techniques are important for diagnosis and follow-up analysis of RA patients. Once the final diagnosis RA is made, an early treatment with disease modifying antirheumatic drugs should be started. Thus, an early diagnosis and sensitive follow-up is necessary to prevent or at least delay joint destruction in RA joints (7, 10, 25). Ultrasonographical and MRI examinations are suitable for early diagnosis in the detection of synovitis, while conventional X-ray examinations can only detect osseous changes at a later stage. The MRI technique, however, requires a considerable technical effort and is expensive. In addition, both the aforementioned techniques depend on the expertise and experience of the examining physician. Therefore, new methods to sensitively assess and objectively quantify inflammatory soft tissue changes in early rheumatoid disease which are non-invasive, of low cost, examiner independent and available in daily practice are needed to supplement clinical assessment and radiology (22).

In recent studies, a laser based imaging technique **(“Laserscan”)** for in vivo transillumination of finger joints has been developed (22). In this preliminary study, we could show that it was possible to receive a reproducible diaphanoscopic image of the PIP joint by using laser light for transillumination. After processing the image data through a statistical machine learning method, it was possible to sensitively detect changes of the inflammatory joint status receiving a sensitivity of 80% compared to precise clinical examination. The “Laserscan” technique might even be useful in making an early diagnosis of an inflammatory process, once an initial laser image of the finger joint has been taken. “Laserscan” may especially be useful for a sensitive follow-up analysis of joint inflammation, and therefore may provide important information about the response to antirheumatic medication. The technique has many advantages to the conventional imaging techniques since it is non-invasive, inexpensive and without side-effects. The automatic evaluation through a machine learning technique even makes the system examiner independent. Of course, additional studies wit a larger patient cohort and a comparison to other established imaging techniques (e.g. MRI and ultrasound) have to be carried out.

A further development, **sagittal laser optical tomography or SLOT**, as an experimental setting shall enable the examining physician to quantify and localize inflammatory changed tissue (synovitis) in more detail. The acquired data can be used within a model-based iterative image reconstruction algorithm to generate sagittal cross-sectional images of the PIP joints. Contrary to conventional laser scanning (22),

SLOT images should permit statements on the spatial distribution of scattering and absorption inside and around the examined joint. The reconstructed images (Fig. 4 b) reflect functional rather than pure morphological images of the joint. Comparing the images of a healthy volunteer, high scattering can be seen at the anatomical sites of the bone endings whereas low scattering (dark area, Fig. 4 b) represents the area of joint cavity. Since it is possible to receive reproducible images of SLOT at two consultations, considering preliminary simulation data of SLOT of inflamed joints (16) and promising results of the "Laserscan" technique (22), we now plan further studies for evaluating and optimizing this imaging method.

In particular, a detailed study will compare both laser techniques to ultrasound and MRI in a patient cohort suffering from early-stage RA with PIP joint swellings. As the previous study (22) has shown, this new laser imaging technique may have the potential to objectively quantify synovitis. The technique is also free from side effects and may prove useful for determining treatment efficacy. If these results are reconfirmed, further studies on other joints may be possible.

Lasergestützte bildgebende Verfahren zur Verlaufskontrolle von Gelenkentzündungen bei Patienten mit rheumatoider Arthritis

Die rheumatoide Arthritis (RA) ist die häufigste chronisch-entzündliche Erkrankung, die unbehandelt das Gelenk zerstört. Für den Verlauf der Erkrankung sind eine Frühdiagnostik und eine genaue Verlaufsbeurteilung der Synovitis wichtig. In der vorliegenden Arbeit stellen wir neue bildgebende Verfahren zur Durchleuchtung von kleinen Fingergelenken vor.

Bei dem „Laserscan"-Verfahren handelt es sich um eine Methode, bei der ein roter Laser mit einer Wellenlänge von 675 nm oberhalb des zu untersuchenden Gelenkes positioniert ist und eine CCD Kamera die Streuungsverteilung unterhalb des Gelenkes detektiert. Nach Evaluierung mit einer statistischen Klassifikations-Methode konnten wir in einer ersten klinischen Studie im Vergleich zu einer genauen klinischen Untersuchung zeigen, dass das Laserverfahren im Verlauf den Entzündungsstatus bei 62 von 72 Gelenken bei 22 Patienten mit RA korrekt einschätzen konnte. Bei der sagittalen laseroptischen Tomographie handelt es sich um eine Weiterentwicklung des Laserscan Verfahrens. Ein roter Laser fährt hierzu in sagittaler Ebene über das zu untersuchende Gelenk, während ein Detektor unterhalb des Gelenkes ebenfalls in derselben Ebene die Streulichtverteilung aufnimmt. Aus diesen Daten werden mittels modell-abhängiger, iterativer Rekonstruktionsverfahren Schnittbilder erzeugt, an denen man die Verteilung der optischen Streu- und Absorptionseigenschaften innerhalb des Gelenkes an einem ersten gesunden Probanden lokalisieren kann.

Schlüsselwörter
Rheumatoide Arthritis, Synovitis, Fingergelenk, bildgebende Verfahren, Laser-Durchleuchtung

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