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Research article

Feasibility of photoacoustic/ultrasound imaging of synovitis in finger joints using a point-of-care system

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ABSTRACT

We evaluate a portable ultrasound and photoacoustic imaging (PAI) system for the feasibility of a point-of-care assessment of clinically evident synovitis. Inflamed and non-inflamed proximal interphalangeal joints of 10 patients were examined and compared with joints from 7 healthy volunteers. PAI scans, ultrasound power Doppler (US-PD), and clinical examination were performed. We quantified the amount of photoacoustic (PA) signal using a region of interest (ROI) drawn over the hypertrophic joint space. PAI response was increased 4 to 10 fold when comparing inflamed with contralateral non-inflamed joints and with joints from healthy volunteers ($p < 0.001$ for both). US-PD and PAI were strongly correlated (Spearman's $\rho = 0.64$, with 95% CI: 0.42, 0.79). Hence, PAI using a compact handheld probe is capable of detecting clinically evident synovitis. This motivates further investigation into the predictive value of PAI, including multispectral PAI, with other established modalities such as US-PD or MRI.

1. Introduction

In rheumatoid arthritis (RA), imaging of synovitis with ultrasound power Doppler (US-PD) and magnetic resonance imaging (MRI) can predict disease progression and bone erosion [1–3]. In clinical remission, detection of subclinical synovitis indicates disease progression and increases the risk of disease flare [4–7]. US-PD has gained a place in the clinical workflow based on these qualities. However, US-PD has inherently high operator dependency and suboptimal reproducibility [8,9]. Specific complications of US-PD are its dependency on the angle between the flow vector and the sound beam, and the disturbance of the blood flow by the probe pressure. MRI is rather costly, specificity is modest and it requires contrast agents [10]. Optical imaging methods were studied in recent years as potential alternatives. Optical spectral transmission (OST) for example, has shown fair performance at detecting synovitis while being presumably low in cost [11–13], however, sensitivity and specificity are modest and the low spatial resolution limits differentiation between synovitis and tenosynovitis. Fluorescence optical imaging [14–17] appears to have higher performance than OST, but also has low resolution and in addition requires injection of contrast agents.

Photoacoustic imaging (PAI), a hybrid optical-and-ultrasound imaging technique, may offer a good balance in features, combining the sensitivity to haemoglobin of optical techniques with the resolution of clinical ultrasound [18–21]. To form a PA image, short laser pulses are shone on the skin and subsequently enter the tissue, where the light is scattered by cells and becomes diffuse. The light pulse is then absorbed by dark tissue constituents such as haemoglobin and melanin. The absorption slightly heats structures containing these constituents which leads to a small pressure build-up, generating sound waves that can be picked up by ultrasound transducers. PAI is therefore similar to sonography, except that the ultrasound is generated within tissue, instead of reflected ('backscattered') by it.

PAI differs significantly from US-PD in three aspects. First, movement of erythrocytes is not required for signal generation, since the generation of PA signals relies only on the presence of haemoglobin (or other chromophores) [19]. Second, there is a larger concentration of haemoglobin within vasculature than in surrounding tissue, leading to more signal generation, whereas in US-PD, erythrocytes reflect comparatively *less* signal than the surrounding tissue [22,23]. A wall filter is therefore not required in

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PAI, and 'flash' artefacts or motion clutter are not present. These properties imply that slow blood flow in synovial microvasculature poses no problem to PAI. As a result, we expect PAI to be particularly sensitive to subclinical synovitis. Finally, the PAI signal is less affected by the orientation of the blood vessel than US-PD.

PAI has been investigated in other medical areas involving angiogenesis, for instance in clinical studies into mammography [24–27]. PAI has also been investigated in pre-clinical studies of synovitis [28–31], and several setups have been proposed for human finger joints [32–37]. In addition, a few early feasibility studies have been performed with RA patients [38,39]. However, these studies used large lasers, not suited for routine clinical application, let alone point-of-care imaging.

In order to bring PAI to outpatient clinics, a handheld PA/US probe was developed [33], which in this study is investigated for possible use in assessing synovitis. The objective of this study is to investigate whether this PA/US probe can detect clinically evident synovitis and to compare the results with US-PD.

2. Methods

2.1. Patient inclusion

Patients undergoing care in the Ziekenhuisgroep Twente hospital were asked by their rheumatologist to participate in this study. Healthy volunteers were recruited in person or via flyers at the University of Twente.

Patients aged over 18 years with rheumatoid arthritis fulfilling 6 or more ACR/EULAR criteria (ACR/EULAR = American College of Rheumatology/European League Against Rheumatism) were included [40]. Specific inclusion criteria were: swelling of at least one proximal interphalangeal (PIP) joint, 2, 3 or 4 joints with at least grade 1 power-Doppler signal on US examination. Test subjects (healthy or patient) were excluded from participation if they had clinically significant bone deformation and/or osteoarthritis in the joint of interest. All subjects received written information and gave informed consent, resulting in a delay of 3 to 8 days between the inclusion by a rheumatologist and time of measurement.

2.2. Imaging system

The imaging study is performed using a dual modality photoacoustic/ultrasound system. The system relies on a probe that houses both a small diode laser together with ultrasound transducers (see Fig. 1). The diode laser is pulsed to generate photoacoustic waves, which are then detected by the ultrasound transducers. These transducers are also used to transmit ultrasound to generate high-quality b-mode ultrasound images. The probe in this study is a second generation prototype developed from the probe described earlier in detail [33]. The original probe contained diode lasers producing 130 ns pulses at a 805 nm wavelength and a pulse energy of 0.56 mJ. As will appear, the main change is a doubling of the pulse energy.

The diode laser source (Quantel Laser, les Ulis, France) is controlled by a short pulse laser driver (Brightloop Converters, Paris, France) and generates 1 mJ pulses of 120 ns duration. The pulses are formed into a rectangular shape of 2.2 mm by 17.6 mm ($1/e^2$) by a diffractive optical element (SILIOS Technologies, Peynier, France), after which the light exits the probe under an angle via a prism. The laser emission is at 808 nm, which corresponds to the isosbestic point of oxy-haemoglobin and deoxy-haemoglobin, which leads to PA signal amplitudes independent of the blood oxygenation.

The ultrasound detection is based on an ESAOTE SL3323 probe. Transducers are placed in an array of 128 elements. Each element has a bandwidth from 2.5 MHz to 10 MHz with a 7.5 MHz centre frequency. An acoustic lens (focal length: 24 mm) is placed in front of the transducers to moderately focus the detection in the elevational plane.

The probe is connected to a MylabOne ultrasound scanner (ESAOTE Europe), which can be used in two modes. In the first it transfers the collected time-pressure data from the middle 64 elements directly to a laptop. This mode is used to acquire photoacoustic data. In the second mode the scanner operates regularly and is used to acquire b-mode ultrasound using all 128 elements in a line-by-line transmission and acquisition scheme.

The US-PD examination is done using an identical MylabOne scanner (in the second mode as described above) in combination with a 14 MHz centre frequency linear array (SL3116, ESAOTE). The PRF was set at 750 Hz, and the wall filter at its lowest and the sensitivity at its highest setting.

2.3. Scan protocol

Per subject examination, a minimum of two PIP joints were scanned: one clinically inflamed joint and an uninflamed joint – preferably the same joint contra-lateral. A complete examination of one subject included a series of longitudinal images using power Doppler ultrasound for each applicable joint and another series using the PA/US system. Both examinations took place with the subject's arm placed in a water bath fitted with supports for the arm, hand and the finger to be scanned (see Fig. 1). The water temperature was controlled to 29–31 °C during the examination. During measurements there was no contact of the PA/US and US-PD probes with the skin in order to avoid pressure artefacts. In addition, the PA/US probe was placed 4–5 mm from the skin such that the laser beam intersects with the ultrasound elevational plane at the skin surface.

For the PA/US examination the PA/US probe was placed on a motorized stage for better control of the measurement. The probe

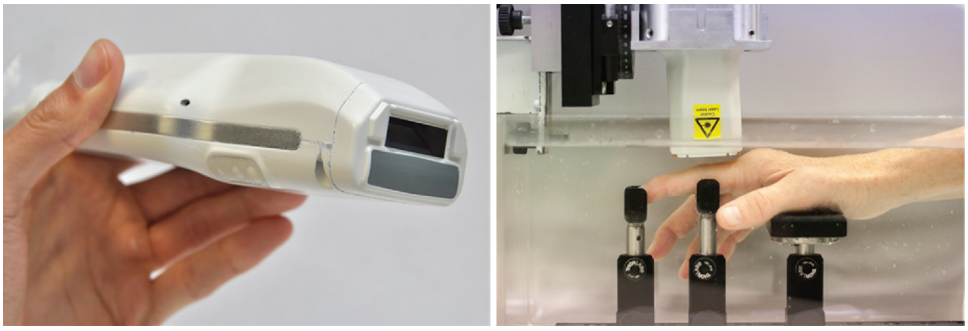

Fig. 1. The PA/US probe (left) with view of the front end showing the light delivery window (dark aperture) and acoustic lens in medium gray. The patient's hand is submerged in water (right) where it rests on a series of supports. The probe is mounted on a 2-axis motorized stage and positioned above the joint.