Potential Clinical Applications of Photoacoustic Imaging in Arthritic Lesions: A Postprint

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Abstract

The incidence of arthritic diseases is gradually increasing, imposing a tremendous socioeconomic burden, and their early diagnosis and treatment are of significant importance. Photoacoustic imaging is a rapidly emerging novel optical imaging modality that combines the advantages of optical excitation and ultrasound detection, enabling simultaneous morphological, microvascular, and functional imaging of joints, as well as molecular imaging through exogenous contrast agents. Over the past decade, numerous research teams have developed a series of photoacoustic imaging instruments, including standalone tomography systems and multimodal imaging systems integrated with commercial ultrasound devices, and have conducted animal and human experiments for arthritis disease diagnosis. Preclinical studies have demonstrated the role of photoacoustic technology in arthritis diagnosis, among which the integrated PA/US system equipped with a handheld photoacoustic probe offers promising prospects for clinical translation.

Full Text

Preamble

The Potential Clinical Application Value of Photoacoustic Imaging in Arthritic Joint Disease

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Abstract

This decade has witnessed a growing prevalence of chronic arthritis worldwide. Early diagnosis of arthritis is essential for timely treatment and improved prognosis. Photoacoustic (PA) imaging (PAI), a multi-functional imaging technique, has been applied to visualize the morphological structures of peripheral joints and microvasculature in small joints. Blood oxygenation and other perfusion indices can also be calculated by PAI, enabling functional evaluation of joint tissues. Exogenous PA contrast agents, targeted to specific molecular biomarkers, facilitate molecular imaging using PA modalities. Several photoacoustic computed tomography (PACT) modalities have been developed for joint imaging, including dual-modality systems that integrate PA with other imaging methods. Leveraging the stability and maturity of commercial ultrasound units, co-registration of PA and ultrasound (US) systems with a portable probe represents an essential step for future clinical translation and widespread adoption. Currently, researchers are making efforts to eliminate reflection artifacts and enhance the quality and speed of PA image acquisition.

Keywords: joint imaging, inflammatory arthritis, photoacoustic imaging, photoacoustic effect, ultrasonography

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1. Overview of Joint Diseases

In recent years, the global incidence of joint diseases has increased significantly, particularly chronic non-traumatic inflammatory joint diseases including osteoarthritis (OA) and rheumatoid arthritis (RA). Chronic inflammatory joint disease is the most common cause of non-traumatic activity limitation and disability [1-2]. A 2005 U.S. population survey showed that approximately 8.6

million adults with impaired motor function had these two joint diseases as their primary condition [3]. Studies have demonstrated that early application of disease-modifying antirheumatic drugs (DMARDs) can effectively prevent deterioration of arthritic lesions and partially control subsequent functional limitation and disability [4]. However, early inflammatory joint lesions present with subtle clinical symptoms [5], and conventional imaging modalities have suboptimal diagnostic sensitivity and limited ability to predict prognosis or guide treatment. Therefore, applying novel imaging technologies for higher-resolution imaging of small joints to enable diagnosis and prognostic assessment of arthritic diseases will facilitate earlier clinical intervention, precision treatment guidance, and improved overall outcomes [6].

2. Conventional Imaging Evaluation Methods for Arthritic Diseases

Currently, commonly used imaging modalities for chronic arthritis diagnosis and assessment include conventional radiography (CR), computed tomography (CT), and magnetic resonance imaging (MRI), which are primarily employed to evaluate OA and RA-affected joints [7]. Imaging features of arthritis arise from pathological changes, such as joint space narrowing, subchondral sclerosis, and soft tissue ossification in OA, and synovial inflammation (including synovial thickening and hyperemia), tendon and peritendinous inflammatory lesions (tenosynovitis, peritendinitis), bursitis, and bone erosion in RA. Pathological manifestations vary according to disease type and stage, with corresponding imaging changes facilitating differential diagnosis [8-9]. Conventional radiography demonstrates high accuracy for diagnosing bone damage, and the 1987 American College of Rheumatology guidelines considered CR the gold standard imaging modality for RA diagnosis and classification [10]. However, limited resolution restricts its application in early diagnosis of arthritic diseases.

CT is not commonly used for arthritis diagnosis but serves as an adjunctive tool to display subchondral damage, soft tissue calcification, and bone erosion through multiplanar visualization [11-13]. MRI, with its high soft tissue resolution, is the most widely used imaging modality for clinical joint disease [14]. Through multi-sequence, multiplanar joint tissue imaging, MRI can reveal early arthritic changes, with sensitivity further enhanced after contrast agent injection [15]. High-frequency ultrasound can display periarthritic soft tissue changes, including synovitis, tenosynovitis, peritendinitis, bursitis, and enthesitis, and can also assess joint effusion and bone erosion commonly seen in arthritic diseases. Semi-quantitative scoring of inflammatory activity using grayscale ultrasound has been applied in some studies [16-17]. With Doppler technology, ultrasound' s diagnostic value for arthritis has improved; displaying blood flow in inflamed joints enables semi-quantitative assessment of disease activity [18-19].

Recently, with advances in imaging technology, novel modalities have been applied clinically, offering new hope for early diagnosis of arthritic diseases. These include optical imaging techniques such as diffuse optical imaging (DOI), flu-

orescence, and bioluminescence imaging [20-21]. Multi-wavelength DOI can calculate oxyhemoglobin and deoxyhemoglobin content to indicate functional changes in diseased joints, such as hyperemia, neovascularization, and hypoxia [22]. Contrast-enhanced ultrasound (CEUS) is a recently widely promoted ultrasound technique with many studies investigating its role in joint inflammation diagnosis. Research has demonstrated that CEUS can detect synovial inflammatory lesions and enable quantitative and semi-quantitative evaluation of disease activity; it can also facilitate molecular imaging of arthritis [20,23-25].

These conventional and novel imaging modalities enable morphological, microvascular, and functional imaging of joints with good accuracy and sensitivity. However, no single non-invasive method simultaneously achieves high-resolution small joint imaging with morphological, microvascular, and functional capabilities. Photoacoustic imaging technology promises to address this gap by enabling non-invasive, high-resolution small joint imaging with structural and functional quantitative analysis on a single platform. This article focuses on the feasibility and potential clinical value of photoacoustic imaging in joint diseases.

3. Principles and Imaging Systems of Photoacoustic Imaging Technology

Photoacoustic imaging (PAI) is a novel non-invasive optical imaging technology based on the photoacoustic effect—the conversion of optical signals to acoustic signals within a tunable range [26-27]. First described by Alexander Graham Bell in 1886 [28], the photoacoustic effect occurs when tissue irradiated by short-pulsed laser experiences temperature rise, producing thermoelastic expansion and pressure deformation that generates broadband ultrasound waves. These ultrasound waves are received by piezoelectric ultrasound probes and converted into photoacoustic images through image reconstruction and post-processing [27-29] [Figure 1: see original paper]. Photoacoustic imaging combines the advantages of optical imaging and ultrasound, reflecting tissue optical properties while achieving considerable depth and spatial resolution.

A typical photoacoustic system consists primarily of a laser emitter, light delivery path, and ultrasound signal reception/processing unit [30]. Q-switched neodymium-doped yttrium aluminum garnet (Nd:YAG) lasers and optical parametric oscillators (OPO) are commonly used as multi-wavelength imaging light sources [31]. Light-emitting diodes (LED) can also serve as ideal light sources for photoacoustic imaging [32]. Light delivery systems comprise various optical lenses and fibers combined in specific configurations, varying by instrument design [33]. Ultrasound signal reception commonly uses conventional piezoelectric elements or more sensitive capacitive micromachined ultrasonic transducers (CMUT) [34]. The main instrument types include photoacoustic computed tomography (PACT), photoacoustic microscopy (PAM), and photoacoustic endoscopy (PAE) [35]. Among these, PACT is a relatively mature technology that converts photoacoustic signals into 2D and 3D images through probe arrangement/rotation patterns and complex image processing. Numerous animal and

preclinical studies on PACT have been conducted in breast cancer and other fields [36-37]. PA systems can also be integrated with other imaging modalities to form multi-functional platforms, such as US, DOI, OCT, and MRI [33,38-40].

By displaying endogenous photoacoustic contrast agents, photoacoustic imaging can simultaneously achieve anatomical and functional imaging [41-42]. Endogenous contrast agents include oxyhemoglobin, deoxyhemoglobin, melanin, water, and lipids [43]. Multi-wavelength PAI displaying oxy- and deoxyhemoglobin enables calculation of functional parameters such as blood oxygen saturation [43]. Photoacoustic imaging also shows promise for melanoma diagnosis and treatment [44-45]. Using exogenous contrast agents loaded with specific molecules enables molecular photoacoustic imaging [46-48]. Research on exogenous photoacoustic contrast agents has increased in recent years, with main types including indocyanine green (ICG) [49-50], gold nanoparticles [51], and single-walled carbon nanotubes (SWNTs) [52-54].

4. Development of Photoacoustic Imaging Technology in Joint Imaging

Over the past decade, research on PAI applications in joint imaging has gradually increased. PAI offers both high spatial resolution and imaging depth, making it suitable for joint imaging, particularly small joints. Photoacoustic imaging can display not only joint anatomical structures but also quantitatively measure functional parameters, demonstrating good clinical translation prospects.

4.1 Photoacoustic Computed Tomography (PACT)

Table 1 summarizes recent independent PACT systems developed by international teams for joint imaging and corresponding animal, phantom, and human preclinical experiments. In 2006, a University of Michigan team first developed a dedicated 3D PACT system for joint imaging and tested it on rat tail joint models and human cadavers [55]. Using an Nd:YAG laser and a broadband ultrasound probe rotating in an arc around the joint, this system produced 3D images clearly displaying periarthritic tissues including skin, fat, muscle, blood vessels, synovium, and bone, while reflecting hemoglobin distribution [56]. Researchers quantified photoacoustic signals in arthritic rat ankle joints and found increased local photoacoustic signals [57].

Another research team from the University of Florida developed a quantitative 3D PACT system during the same period and conducted phantom and human in vivo experiments [58-60]. An ultrasound probe connected to a robotic arm rotated to achieve 3D imaging of finger joints, with studies showing consistency between photoacoustic 3D joint images and MRI. The team later improved the system with a semicircular ultrasound transducer array for better human joint imaging [61].

These studies demonstrated that PACT can effectively display periarthritic tis-

sue morphology, including tendons and synovium. Research has also confirmed that photoacoustic imaging can visualize intra-articular cartilage and bone that are difficult to detect with conventional ultrasound [62]. Most studies emphasize PACT' s high sensitivity for microvasculature and neovascularization, a crucial feature for joint disease diagnosis.

Peter Van Es et al. designed a PACT system with a semicircular ultrasound transducer array for imaging finger joint vasculature [63]. Vessels in the nail bed, skin layers, and subcutaneous soft tissues around interphalangeal joints were clearly visualized, ranging from linear capillaries to 1.5 mm diameter vessels, consistent with histology. Sergey Ermilov also developed a PACT system for joint microvascular imaging [64]. Using an arc-shaped probe with 360° rotation for 3D imaging, this system achieved high resolution for joint microvasculature and could display thermoregulatory responses in small vessels through rapid photoacoustic imaging.

4.2 Integration of Photoacoustic and Ultrasound Imaging–Dual-Modality PA/US Imaging Systems

Since both photoacoustic and ultrasound signals are received by ultrasound transducers, simultaneous imaging results from both modalities can be obtained through post-processing, with photoacoustic images superimposed on grayscale ultrasound images to achieve PA/US dual-modality imaging. This multi-modality approach is currently a hot topic in photoacoustic joint imaging research, with relevant studies summarized in Table 2 .

4.2.1 PA/US Tomography A research team from the University of Macau integrated PACT and ultrasound computed tomography (USCT) into a single imaging platform, forming a PACT/USCT dual-modality system that obtains microvascular and anatomical functional information through multi-band PACT and ultrasound overlay images [65]. Milan Oeri et al. applied the same principle to design a PA/US tomography system suitable for human finger joint imaging, enabling multi-modality imaging of finger joints and internal microvasculature [66].

4.2.2 Integration with Commercial Ultrasound Instruments Due to ultrasound' s high cost-effectiveness and portability, it is widely used globally. However, standalone photoacoustic imaging systems often consist of bulky, complex, and expensive equipment, limiting clinical application. To facilitate clinical translation, several research teams have integrated photoacoustic technology into commercial ultrasound systems, constructing novel integrated PA/US dual-modality imaging platforms. These systems integrate photoacoustic signals into ultrasound grayscale images, using ultrasound guidance for photoacoustic signal analysis and quantitative assessment, while maintaining the stability advantages of commercial ultrasound systems. Such dual-modality systems have been used

for breast cancer and metastatic lymph node evaluation, with studies also validating their application in joint imaging.

Wang et al. first integrated photoacoustic imaging into a commercial ultrasound instrument [67] and applied this dual-modality system to perform dual-wavelength (1064 nm and 532 nm) examination of arthritis model mouse ankles, detecting significantly elevated photoacoustic signals in inflammatory lesions [68]. The team also investigated its role in arthritis treatment monitoring [69]. Photoacoustic signals in treated arthritis mice decreased significantly, consistent with microPET and histology results. The team further modified the system for human joint imaging and obtained clear photoacoustic images of human finger joints [70].

4.2.3 Integrated PA/US Imaging Platforms with Handheld Photoacoustic Probes Integrating the optical delivery system directly into the ultrasound probe to form a portable, integrated PA/US probe better conforms to physician usage habits and offers greater potential for clinical translation and promotion. Therefore, integrated PA/US probes have become a recent research focus for multi-functional PA/US imaging systems. K. Daoudi and P.J. van den Berg et al. developed a simplified ultrasound probe integrating a photoacoustic system in 2014 [71]. Using a series of adjusted cylindrical lenses and diffractive optical elements integrated into the probe, the laser beam was shaped into a rectangular form matching the probe surface. This system simultaneously obtained clear ultrasound and photoacoustic images, with photoacoustic images added to ultrasound images in pseudo-color to clearly display microvessels and bone surface structures within joints.

To further demonstrate the clinical potential of this handheld probe system, researchers conducted preclinical studies [72]. The system was used to examine finger joints in 10 arthritis patients and healthy controls, with quantitative assessment of intra-articular photoacoustic signals. Results showed significantly increased PA signals that were statistically consistent with power Doppler ultrasound (PDUS) semi-quantitative scores.

A University of Michigan team developed a dual-modality PA/US imaging system with a handheld photoacoustic probe based on their previous work [73]. Researchers used the system to image finger joints in arthritis patients and healthy controls with 580 nm single-wavelength and 532 nm/1064 nm dual-wavelength imaging. Single-wavelength imaging at 580 nm displayed hemoglobin distribution in metacarpophalangeal (MCP) joints, while dual-wavelength imaging provided blood oxygen saturation information. The study found significant differences in blood flow and oxygen saturation between arthritis patients and controls, demonstrating the system' s ability to quantitatively diagnose functional changes in inflamed joints such as hyperemia and hypoxia [74]. The team further modified the dual-modality PA/US system using LEDs as the light source, successfully obtaining real-time integrated PA and US images with high signal-to-noise ratio. This system could display finger microvessels up to 5 mm in

diameter and obtain quantitative blood oxygen results. Compared to expensive, high-energy laser systems, LEDs are more cost-effective and suitable for clinical application, making this achievement valuable for promoting clinical PAI application in arthritis [75].

Since 2015, the ultrasound department of Peking Union Medical College Hospital, in collaboration with Peking University and Mindray, has focused on developing a multi-functional PA/US imaging platform with a handheld photoacoustic probe. The photoacoustic system was integrated into a clinical high-end ultrasound imaging probe (L9-3U, Mindray Bio-Medical Electronics Co., Ltd., China), using a clinical high-end ultrasound diagnostic instrument to simultaneously detect photoacoustic and ultrasound signals and obtain overlaid images [Figure 2: see original paper]. This imaging platform has successfully completed preclinical validation studies for thyroid and breast nodule diagnosis [76]. Currently, our research team has initiated clinical studies on rheumatoid arthritis, with preliminary results showing that this PA/US multi-modality imaging system provides good visualization of microvasculature in synovial tissue of small joints and demonstrates good correlation with clinical scores [Figure 3: see original paper]. Comprehensive evaluation of small joints in RA patients using this system is expected to have significant clinical value in disease activity assessment, post-treatment follow-up, and prognosis prediction.

4.3 Multi-Modality Imaging Systems Combining Ultrasound and Other Medical Imaging Technologies

In addition to ultrasound integration, photoacoustic technology can be combined with diffused optical tomography (DOT) on the same platform due to their shared optical imaging nature. Xi L et al. established an integrated PACT and DOT optical imaging platform, using transducer arrays to receive photoacoustic signals and finite-element image reconstruction to process diffused optical signals, achieving simultaneous PA and DOT imaging. Testing on human joints showed that periarthritic tissues and bone could be visualized by both PACT and DOT, suggesting the system' s potential application in assessing joint inflammation [77].

4.4 Application of Exogenous Photoacoustic Contrast Agents in Joint Imaging

Beyond instrument development, some researchers have employed exogenous photoacoustic contrast agents to extend photoacoustic joint imaging to the molecular level [78]. One study conjugated the anti-TNF targeted drug Etanercept to gold nanoparticles as an exogenous photoacoustic contrast agent and injected it into rat tail joints for photoacoustic imaging at 600 nm wavelength. The experimental group showed significantly higher intra-articular signal intensity than the control group without contrast agent, suggesting that molecular imaging with gold nanoparticle-based PAI can monitor intra-articular drug concentration.

Seminaphthorhodafluor (SNARF-5F) is a special pH-sensitive dye that can be combined with nanoprobes to detect local tissue pH values. This molecular probe can also be applied to photoacoustic joint imaging [79]. After injecting the molecular probe complex into local joint tissues, photoacoustic signals can be calculated to obtain local pH values, offering auxiliary diagnostic value for arthritic diseases.

Another approach involves labeling near-infrared fluorophores with polyanionic dendritic polyglycerol sulfate (dPGS) to form L-selectin/P-selectin-specific complexes for targeted monitoring of inflammatory responses. When this inflammation-specific probe was locally injected into knee and ankle joints of arthritis model mice, photoacoustic imaging revealed significantly higher PA signal intensity than in healthy mice, consistent with contrast-enhanced MRI and histology results [80].

Another study found that Clofazimine (CFZ), an anti-inflammatory drug for arthritis treatment, has high optical absorption at 450 nm, making it suitable for photoacoustic imaging [81]. CFZ accumulates in macrophages, potentially enabling cell-specific diagnosis and treatment monitoring. The study first confirmed CFZ' s applicability to photoacoustic molecular imaging using photoacoustic microscopy, then successfully obtained satisfactory photoacoustic signals from CFZ-injected models, animal models, and cadaveric finger joints using a dual-modality PA/US system, suggesting that photoacoustic technology can monitor CFZ treatment for arthritis.

5. Outlook for Photoacoustic Joint Imaging Technology

Integrating photoacoustic technology into commercial ultrasound systems is more suitable for clinical translation, leading to increasing research focus on multi-modality PA/US imaging platforms, particularly instruments with handheld portable photoacoustic probes. Photoacoustic microvascular imaging and multi-wavelength oxygen saturation measurement may assist in diagnosing early pathophysiological changes and monitoring drug efficacy in joint diseases, representing current research priorities.

As a novel imaging modality, various PAI systems currently have lower resolution than highly refined clinical imaging modalities such as MRI, requiring further optimization and improvement [82]. Beyond enhancing signal-to-noise ratio and resolution, artifact elimination is crucial for improving image quality and diagnostic capability. For example, ultrasound signals reflected from bone surfaces within joints may affect photoacoustic image reconstruction and create artifacts, though studies have applied special post-processing methods to identify such artifacts [83].

Currently, clinical studies on photoacoustic imaging in arthritic diseases are limited and have shortcomings. First, most studies are in early stages with small patient cohorts, providing insufficient evidence for clinical value. Additionally, comparative studies with other modalities are lacking, with research

only demonstrating consistency with other methods without discussing relative advantages and disadvantages. Further comparative studies are needed between photoacoustic imaging and power Doppler, contrast-enhanced ultrasound, and recent novel ultrasound microvascular flow imaging techniques (such as Superb Microvascular Imaging, SMI). A major advantage of photoacoustic imaging is functional imaging for blood oxygen saturation measurement, requiring larger sample sizes to validate its diagnostic value for arthritic diseases.

6. Conclusion

Photoacoustic imaging is a novel non-invasive medical imaging modality whose potential in joint imaging has been demonstrated by relevant studies, including structural imaging, functional imaging, and molecular photoacoustic imaging using exogenous contrast agents. It holds clinical value for early diagnosis, treatment monitoring, and drug therapy monitoring in arthritic diseases. Photoacoustic imaging is suitable for integration into commercial ultrasound instruments for multi-modality imaging, enabling acquisition of more effective diagnostic information through comprehensive image analysis. Combining photoacoustic imaging instruments with handheld ultrasound probes represents an important direction for future clinically translational imaging devices. With continuous optimization and improvement of photoacoustic imaging technology and equipment, clinical translation and widespread application in joint disease diagnosis and treatment are expected to be realized.

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Figure Captions

Figure 1. The PA/US multi-modality imaging system developed by our research team integrated into a high-end commercial ultrasound instrument. In this system, optical fiber transmission and reflection prisms are placed at specific angles within two metal boxes sized to match the ultrasound probe. Integration of the light delivery system and ultrasound probe is achieved by attaching the metal boxes to both sides of the probe, creating an integrated PA/US probe.

Figure 2. Real-time PA/US multi-modality imaging of an active RA patient' s MCP joint. The MCP joint synovium is markedly thickened, with the yellow-outlined area indicating significantly thickened synovial tissue above the MCP joint bone surface. 2A: Color Doppler ultrasound (CDUS) showing abundant internal blood flow signals; 2C, 2D: PA dual-wavelength imaging showing corresponding photoacoustic signals; 2B: PA dual-wavelength imaging with overlaid SO relative values, where PA signals appear in red pseudo-color indicating relatively high blood oxygen content.

Figure 3. The PA/US multi-modality imaging system developed by our research team integrated into a high-end commercial ultrasound instrument. In this system, optical fiber transmission and reflection prisms are placed at specific angles within two metal boxes sized to match the ultrasound probe. Integration of the light delivery system and ultrasound probe is achieved by attaching the metal boxes to both sides of the probe, creating an integrated PA/US probe.

Tables

Table 1. Summary of PACT-Related Research

Research Team	Imaging System	Ultrasound Transducer Mode	Imaging Target	Key Findings
Xueding Wang (2006, 2007)	3D PACT	Arc-rotating ultrasound probe	Mouse, arthritic mouse, human cadaver	Clear visualization of peri-arthritic tissues and hemoglobin distribution; increased PA signals in arthritis
Yao Sun	3D PACT	Arc-rotating ultrasound probe	Finger phantom, human fingers	3D joint imaging consistent with MRI
Yao Sun	3D PACT	Circular ultrasound transducer array	Human fingers	Improved system for human joint imaging
Sergey Ermilov	PACT for microvasculature	Arc-shaped transducer array	Human fingers	High-resolution microvascular imaging with thermoregulation display
Huang N	PACT	Arc-shaped transducer array	Human fingers	-
Peter Van Es	PACT	Semicircular transducer array	Human fingers	Clear visualization of vessels from capillaries to 1.5 mm diameter

Table 2. Summary of Dual-Modality PA/US Imaging System Research

Research Team	Imaging System	Key Features	Imaging Target	Main Results
Yubin Liu	PACT/USCT	Multi-wavelength display of finger joint structures	Human fingers	Simultaneous microvascular and anatomical imaging
MILAN Oeri	PACT/USCT	Real-time finger imaging	Human fingers	Multi-modality imaging of joint structures and microvasculature
Xueding Wang	PA system + commercial L10-5 probe	Dual-wavelength (1064/532 nm)	Arthritic mouse tail joints	Significantly elevated PA signals in inflammatory lesions; treatment monitoring capability
Xueding Wang	PA system + commercial L10-5 probe	Modified for human imaging	Human finger joints	Clear visualization of joint structures and microvasculature
Daoudi (2014)	Handheld PA/US probe	Integrated optical elements	Healthy and arthritic human finger joints	Clear PA/US images; PA signals correlated with PDUS scores

Research Team	Imaging System	Key Features	Imaging Target	Main Results
Jo J	Handheld PA/US probe	580 nm single-wavelength and 532/1064 nm dual-wavelength	Arthritic human finger joints	Quantitative microvascular imaging and blood oxygen saturation measurement; significant differences between arthritis patients and controls

Note: Figure translations are in progress. See original paper for figures.