Sonographic synovial vascularity of synovitis in rheumatoid arthritis

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Abstract

RA is a condition of multiple synovitis. Abnormal synovial vascularity (SV) is evident with the onset of joint inflammation. The idea of estimating the level of joint inflammation by sonographic SV was conceived with the advancement of US. The ideal treatment strategy, called treat to target (T2T), requires early diagnosis and assessment of RA. Detection of positive SV can be useful for proving the presence of synovitis and finally diagnosing RA. In the assessment of RA, US-based global scores aimed at assessing overall disease activity have the potential to be useful for the achievement of T2T because US can directly detect changes in synovitis. Remaining SV in local joints increases the risk of structural deterioration. RA requires both improvement of overall disease activity and the disappearance of local SV for remission. The evaluation of SV provides various information and contributes to the clinical treatment of RA.

Key words: rheumatoid arthritis, ultrasound, power Doppler sonography, synovitis, synovial vascularity, treat to target.

Introduction

Today, why are rheumatologists enthusiastic to evaluate synovial vascularity (SV) in patients with RA in daily practice? RA is a condition of multiple cryptogenic synovitis characterized by expansion of soft tissue and destructive bone invasion at various joint sites that results in systemic musculoskeletal dysfunction. The pathogenesis of rheumatoid synovitis has been strongly associated with SV (Fig. 1).

Pathological explorations have tried to discover the characteristic pathogenesis of rheumatoid synovitis, and in recent years it has become apparent that with the onset of inflammation, abnormal vascularization is evident in the synovium due to vasodilation or angiogenesis [1-5]. A close relation between SV and synovitis has been confirmed. Presently SV is one of the hottest topics in rheumatology clinics.

Various factors such as the variety of afflicted joint sites or the diversity of disease progression may affect evaluation of the disease activity of RA. Composite scoring, which comprises clinical findings such as tender or swollen joint counts, has been established to evaluate the overall disease activity of RA. Clinical composite scores such as the 28-joint DAS (DAS28), the Simplified Disease Activity Index and the Clinical Disease Activity Index have been proven to be useful by various clinical trials [6, 7]. Although these clinical composite scores assess overall disease activity, they do not satisfactorily alert the clinician to changes in local joints due to their dichotomous judgment for each joint. To achieve deep remission of RA and to halt all abnormal joint destruction, the focus must be on detecting changes in local joint inflammation.

Progress in digital technology has resulted in US systems that produce high-quality images that enable observation of small joints. The novel idea of estimating the level of joint inflammation by sonographic SV was conceived with advancements in power Doppler US (PDS). Newman et al. [8, 9] first reported the use of PDS to detect abnormal SV, and Szkudlarek et al. [10] compared PDS with dynamic MRI to assess synovitis in finger joints and showed equivalency with both techniques.

With advancements in treatments for RA, early diagnosis and treatment have come to the forefront [11-14]. In response to this, new ACR/ European League Against Rheumatism (EULAR) classification criteria were introduced in 2010 [15, 16]. These criteria specify that patients with probable synovitis are first screened according to...
Assessment of SV

PDS is essentially a flexible and sonographer-dependent examination. Although PDS is useful for the assessment of SV, reproducibility is a major problem [17]. Settings of US machines and the scanning technique of the sonographer can greatly influence the visualization of SV, which affects reproducibility. Among the various US machine settings, US parameters such as pulse repetition frequency influence the quality of PDS imaging. Further, deterioration of the US transducer can adversely affect PDS imaging. Thus appropriate machine settings and maintenance are critical to ensure stable and reproducible PDS imaging. To minimize problems of the scanning technique, standardization of joint scanning has been studied by the EULAR [18, 19]. Education of the sonographer and proficiency in scanning are important for stable PDS imaging and improves reproducibility.

To measure SV by PDS, a semi-quantitative scoring system has been described [20] that comprises four scoring categories (0, none; 1, mild; 2, moderate; 3, severe) determined by the area of SV and grossly scored from the PDS images. This simple method has the advantage of no requirement for additional devices or special software, but reproducibility and reliability are problematic. Several clinical trials, most performed by members of the EULAR, have addressed these issues [21–24]. These studies found that appropriate training in scanning technique and reading of PDS images could improve and stabilize the reproducibility and reliability of scoring. However, this semi-quantitative scoring system might not be satisfactory to assess joint inflammation because it includes only four scoring categories. Therefore quantitative methods were established to measure SV in more detail [25–27]. Several groups reported a quantitative method to measure pixel counts of SV in the region of interest, which was located at in synovial tissue. Quantitative measurement could show the level or changes of SV numerically.

Because US is fundamentally a two-dimensional (2D) assessment, the images reflect a cross section of volumetric synovial tissue. Therefore the question of a discrepancy between sonographic assessment and the level of practical inflammation always exists. Recently three-dimensional (3D) PDS has been developed that enables assessment of SV at a volumetric level [28, 29]. This method may have several advantages, including image reproducibility and fewer training requirements for scanning joints or reading images. Naredo et al. [30] reported that 3D PDS showed repeatability such that it could be used in multicentre cohort studies of RA.

Abnormal SV in the early diagnosis of RA

Because abnormal SV is strongly associated with the pathology of synovitis, logically, detecting abnormal SV at symptomatic joints may be useful for proving the presence of synovitis and in finally diagnosing RA. We previously reported that when the sum of the levels of SV at the finger joints in each undiagnosed patient exceeded a certain level, the patient was ultimately diagnosed as having RA [31]. This result indicated the potential for detection of SV to become a first-stage screening test for RA. Importantly, diagnosis of RA requires not only detection of synovitis, but also systemic evaluation including serological or clinical tests.

The new 2010 ACR/EULAR classification criteria for RA were introduced with the aim of diagnosing RA earlier than with conventional methods [15, 16]. Attempts to combine the 2010 ACR/EULAR classification criteria with detection of synovitis by US to improve diagnostic power were reported from several groups [32–34]. Kawashiri et al. [33] reported that positive signs of sonographically abnormal SV in patients with undefined arthritis were a stronger prognostic factor for developing RA than were MRI findings or the presence of sonographic synovial hypertrophy. Nakagomi et al. [34] reported that US findings, including positive SV, had the power to confirm the presence of synovitis and increased the accuracy of the classification criteria. Thus, in the early diagnosis of RA, detection of abnormal SV has the potential to be used as a screening test or to confirm clinical findings.

Change in SV for assessment of overall disease activity in RA

Estimation of SV can be useful for assessment of disease activity in RA [35]. Although the semi-quantitative scoring system comprises only four categories, and thus is inadequate to assess changes in local joints, it could be useful for assessment of overall disease activity in combination with US estimation at several joints. US-based global scores aimed at assessing overall disease activity consist of the synovial hypertrophy score and SV score. These
methods are expected to be more accurate and sensitive than the clinical composite score, with numerous basic studies in this area [36, 37]. However, this method may have the disadvantages of high cost or being time consuming in practical use. Several research groups have produced unique US-based global scores that targeted limited joint sites to prove these disadvantages [38–44]. At present, there is no consensus as to which score should be used for clinical trials or in daily practice [45]. Additional and confirmatory trials are required to establish a US-based global score. Of note, Backhaus et al. produced a unique US-based composite score called the US7, which targets seven joints to reflect disease activity. They reported results of several trials and have steadily progressed in their study of this score [43, 44].

Treat to target (T2T) is a concept of ideal treatment of RA that has become widespread internationally [46]. It emphasizes that RA must be treated in the early phase and tightly controlled by appropriate measurement of disease activity so that patients will receive maximum therapeutic impact and achieve the goal of remission. The US-based global scores have the potential to be useful for the achievement of T2T because US can directly detect changes in synovitis. The various US-based composite scores mentioned here are now in the evaluation process, and additional detailed analyses are anticipated.

Change in SV for assessment of local joints in RA

In our investigation focusing on local joints, we reported that remaining SV at local joints increases the risk of structural deterioration, despite the fact that anti-rheumatoid therapy achieved low disease activity (LDA) clinically at 8 weeks [25, 47]. Interestingly, these joints tended to show improvement in clinical signs such as joint pain or swelling and thus clinical composite scores also showed improvement. Similar findings were reported by another group [48]. Subclinical synovitis and sonography were first reviewed by Bresnihan et al. [49], and Brown et al. [50, 51] reported that detailed sonographic observation detected subclinical synovitis in patients with long-term clinical remission. These joints with a poor prognosis were asymptomatic or mildly symptomatic but showed positive SV at the local level. Joints with remaining SV might be related to subclinical synovitis. Further longitudinal observation may clarify this relation.

We also reported that joints with a disappearance of SV with simultaneous overall disease improvement showed an improvement in joint prognosis [52]. Dougados et al. [53] reported a similar conclusion in their multicentre prospective trial. These results indicate that RA requires both an improvement in overall disease activity and the disappearance of local SV for remission and achievement of T2T. Remaining SV at a local joint indicates ongoing structural alteration. Recently the EULAR published recommendations for the use of joint imaging in RA [54] in which monitoring of inflammatory activity and prediction of response to treatment by imaging were discussed. Although PDS was considered useful for these purposes, more detailed data are needed for PDS to become an established examination tool. We have focused on the response of SV to treatment that may predict structural deterioration in local joints. Multicentre studies are necessary to establish the mechanism of response of SV to treatment.

In RA, accumulation of inflammation leads to the progression of joint damage and, logically, time-integrated SV consequently relates to a change in structural alteration. Naredo et al. [55] showed that in the body overall, time-integrated joint counts with positive SV are related to the change in total Sharp score. We also reported that local joints showed poor prognosis when SV remained despite achievement of LDA clinically. However, changes in structural alteration of the joint are not related to time-integrated quantitative SV [52]. The reason for this unexpected result is unknown. We speculated that local synovitis might change to heterogeneous inflammation in a condition of LDA that is neither that of simple reduction of acute inflammation nor of prolonged recovery. Further studies are needed to confirm these results.

In daily clinical practice, joints with remaining SV are often detected by PDS, however, there are no definitive methods to treat them. Although these asymptomatic or mildly symptomatic joints with poor prognosis, namely those showing subclinical synovitis, need to be treated, it is unclear whether systemic intensive therapy or topical therapy are effective. Recently a research group called the Targeted Ultrasound Initiative started a multicentre international study called Targeted Ultrasound in RA to investigate the effect of corticosteroid injection in joints with remaining positive SV [56]. T2T emphasizes optimizing treatment by appropriate disease assessment, and clinical composite scores reflecting systemic disease activity are mostly used at present. The use of local assessment with US will help to achieve T2T.

Conclusion

Why should rheumatologists evaluate SV in RA? Early diagnosis and assessment of disease activity are at the heart of the T2T approach in RA. In the early diagnosis of RA, detection of SV to discover synovitis could be used as a screening test for entry into the ACR/EULAR classification algorithm. A US-based global score consisting of both the SV score and synovial hypertrophy score used to assess overall disease activity may be more sensitive and objective than the clinical composite score and thus may be useful as a guide for optimizing disease treatment. Also, changes in local SV have prognostic value for local joint destruction that may lead to meticulous control of inflammation. The evaluation of SV provides various important information and contributes to the clinical practice of RA (Fig. 2).
Abnormal SV is strongly associated with synovitis of RA. Detection of SV is useful for proving the presence of synovitis and diagnosing RA. RA remission requires an improvement of overall disease activity and disappearance of local SV.

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References


