Review

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Contrast-enhanced ultrasonography in inflammatory arthritis

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Abstract

The degree of inflammation is the keystone of therapy management in rheumatoid arthritis and other arthritides. The assessment of synovial perfusion using power Doppler ultrasound is an important point in the quantification of the joint inflammation but it is limited by the subjectivity of the vascularization grading and incapacity to detect flows in very small vessels. Contrast agent improves the ultrasound ability to depict and quantify blood flows in synovitis. Contrast-enhanced ultrasonography (CEUS) better differentiates synovitis from collection and distinguishes the active synovitis from inactive fibrotic or necrotic pannus. Quantitative assessment of inflammation is possible analyzing the time-intesity curves and by the correct measurement of the synovial thickness. The additional informations and the diagnostic value of CEUS in arthritides are still controversial but its excellent imaging of synovial vessels open the way for further clinical applications. This review aims to discuss the actual knowledges of CEUS in inflammatory arthritis.

Keywords: contrast agents, ultrasonography, arthritis, synovitis

Rezumat

Aprecierea gradului inflamaţiei articulare este un moment important în decizia terapeutică la pacienţii cu poliartrită reumatoidă şi alte artrite. Examenul power Doppler este folosit cu succes pentru cuantificarea inflamaţiei, dar această metodă este limitată de subiectivitatea gradării hipervascularizaţiei şi de incapacitatea de a detecta fluxuri foarte lente în vase foarte mici. Utilizarea substanţei de contrast creşte sensibilitatea ecografiei de a vizualiza şi cuantifica fluxurile vasculare la nivelul sinoviei. Ecografia cu substanţă de contrast diferenţiază mai bine sinovita de colecţie şi, de asemenea, deosebeşte sinovita activă de fibroză sau necroză. Analiza curbelor timp-intensitate şi măsurarea corectă a grosimii sinoviei permite o evaluare cantitativă a inflamaţiei. Valoarea diagnostică a ecografiei cu substanţă de contrast în artrite este controversată, dar capacitatea ei excepţională de a vizualiza vasele sinoviale lasă speranţa unor aplicaţii clinice ulterioare.

Cuvinte cheie: agenţi de contrast, ecografie, artrită, sinovită

Introduction

The experience of the past 20 years has shown that ultrasound is superior to clinical examination and, in the majority of the cases, similar to magnetic resonance imaging (MRI) in evaluation of joint inflammation. Intraarticular fluid collection, synovial thickening, synovial hyperemia, and bone erosions are identified by ultrasound with a high sensitivity. The color Doppler and power Doppler evaluation of neovascularization and flow changes in synovitis is an important moment in diagnosis. In rheumatoid arthritis (RA) and other types of inflammatory arthritis, the intensity of the color signal is a good indicator for disease's activity and a negative prognostic factor, being associated with the destructive evolution of arthritis. Aggressive biological treatments used in inflammatory arthritis should be carefully monitored. The evaluation of changes in the color signal during treatment helps define favorable response, the lack of response, and remission. Ultrasound contrast agents significantly enhance the signal in vessels, so contrast-enhanced ultrasound is expected to increase the diagnostic value of ultrasound in inflammatory arthritis [1-3].

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Technique

The contrast-enhanced ultrasonography (CEUS) of joints is performed with linear probes, with a mechanical index less than 0.1. The mean frequency used by these probes, corresponding to the resonance frequency of microbubbles, does not allow obtaining perfect resolution images, sometimes the identification of the region of interest being difficult. The intrasynovial microvascular tracts cannot be clearly anatomically delineated [4,5].

The first published studies used 7-15 ml Levovist, a contrast agent of the first generation, in a concentration of 300-400 mg/ml, administered as a bolus [6,7], in rapid one minute perfusion [8], or in slow 15-20 minute perfusion [9]. Recent studies use SonoVue, a contrast agent of the second generation, 4.8 ml [10-15] or 2.4 ml [16-18]. There is a high variability of the time interval from injection to the appearance of microbubbles in the joints. The bolus administration determines the appearance of microbubbles in articular and periarticular tissues after approximately 20 seconds. This time is characteristic for the inflamed synovium in small joints. In normal articular and periarticular structures in the hand and the foot, the contrast agent frequently appears later, after up to 30 seconds, due to the very small caliber of the vessels at this level. In the inflamed synovium of the large joints (knee for example), the presence of microbubbles is frequently detected 15 seconds after contrast agent administration. In old, largely fibrosed synovial pannus, vessels can be visualized in gray scale, sometimes only 1-2 minutes after the contrast injection. These are probably vessels that open belatedly and have a reduced flow.

In the case of the bolus administration, the examination window is of 3-5 minutes. The slow 15-20 minutes intravenous perfusion allows the examination of the joints throughout this time period. This technique provides an increase in uniform contrast over a longer time period and allows for the examination of a greater number of joints [9]. It is useful when the aim is the intensification of the color Doppler signal and the grading of hypervascularization in compound scores at the level of several joints. Slow perfusion administration allows the microbubbles to penetrate the smallest vessels, diminishes the blooming effect of the color signal that occurs after bolus administration, and avoids the consequences of the important and rapid destruction of the bubbles by power Doppler [19]. Using the bolus administration technique, one or maximum two joints can be examined. However, this technique is easier to standardize and allows the quantification of inflammation, analyzing the time-intensity curves. This is an important objective of arthritis CEUS – monitoring of the disease evolution and therapeutic response. The dose of 2.4 ml or 4.8 ml is still under debate.

The mean duration of an examination is about 20 minutes. The analysis of the digitally recorded images is frequently performed after examination, at the work table. The use of specialized computerized programs for the analysis of time-intensity curves shortens the time allocated to a patient.

The normal aspect

The ultrasonographic detection of vascularization in normal joints depends on the quality of the ultrasound machine, its optimal setting, the accuracy of the image acquisition technique, the examined joint. Using high performance equipment and an optimal examination protocol, more than 50% of the metacarpophalangeal joints expressed a color signal on contrast enhanced power Doppler [7]. In normal intrasynovial vessels, the contrast agent does not alter the resistance index [7]. Two previous studies [6,9] reported no color signal before or after contrast administration in the small hand joints of healthy subjects. In large joints, in which the synovium is at a greater distance from the transducer, the color signal is recorded much more rarely. In another study [13], none of the six healthy knees examined presented a color signal before or after the administration of the contrast substance. Contrast enhanced power Doppler records no color signal in the Achilles enthesis in healthy individuals and visualizes only some of the small nutrition vessels around the tendon and the enthesis [20].

In an arthroscopically controlled study [21] in the knee, contrast enhanced power Doppler was found to have a higher sensitivity but a lower specificity than unenhanced power Doppler in identification of the pathologically hypervascularized synovial areas. The lower specificity might result in an overdiagnosis of synovitis.

The differentiation of the normal aspect from the pathological aspect of intraarticular and periarticular vascularization is mandatory for the diagnosis of early arthritis and for the differentiation of active arthritis from inactive arthritis. Further studies are required in order to establish the threshold between normal and pathological findings in various joints, using standard equipment and examination techniques.

Contrast-enhanced ultrasound findings in arthritis

The contrast agent in the inflamed joints produces signal enhancement of the hyperemic synovium, an intensification of the color signal (fig 1), and differentiates more clearly active synovitis from collection, necrosis or

fibrosis (fig 2). CEUS identifies with a high sensitivity inflammatory vascular changes in the intraarticular synovium, bursae (fig 3), tendons (fig 4), entheses and bone erosions (fig 5).

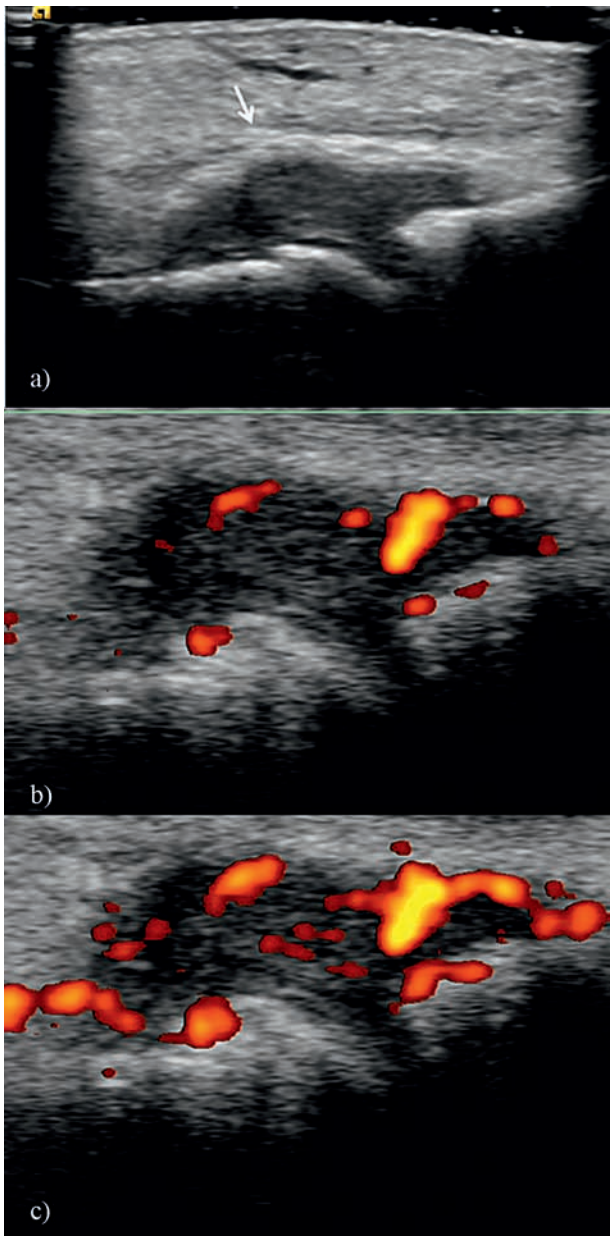


Fig 1. a) Longitudinal dorsal gray-scale ultrasound of the second metatarsophalangeal joint, showing a hump (arrow) of hypertrofic synovitis in a patient with rheumatoid arthritis; b) unenhanced Power Doppler demonstrates pathologic color signal; c) power Doppler signal enhances after intravenous contrast agent injection, at least one grade. Note new vessels visible in the middle of the pannus.

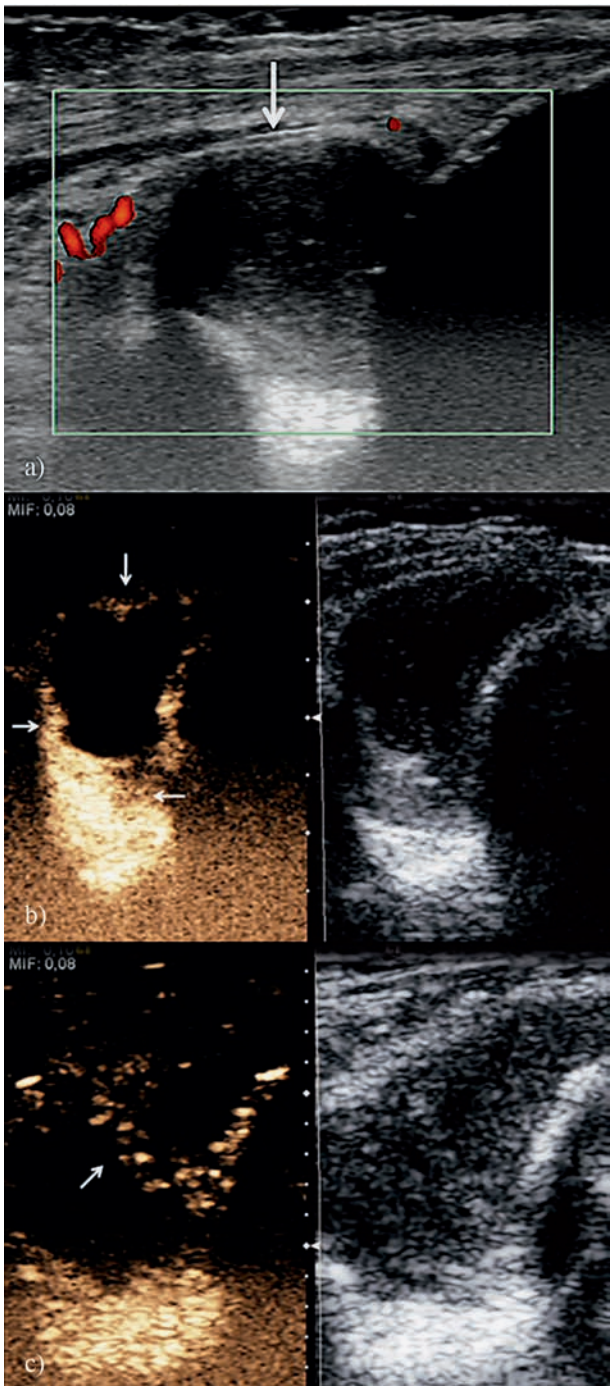


Fig 2. a) Residual pannus (arrow) in the elbow of a treated rheumatoid arthritis patient. The absence of power Doppler signal suggests inactivity; b) 20 seconds after contrast agent injection a rim of enhancement (arrows) is detected proving still active disease; c) two minutes after injection a new vessels (arrow) is detected in the middle of fibrotic pannus. These are small slow-flow vessels that open belatedly.

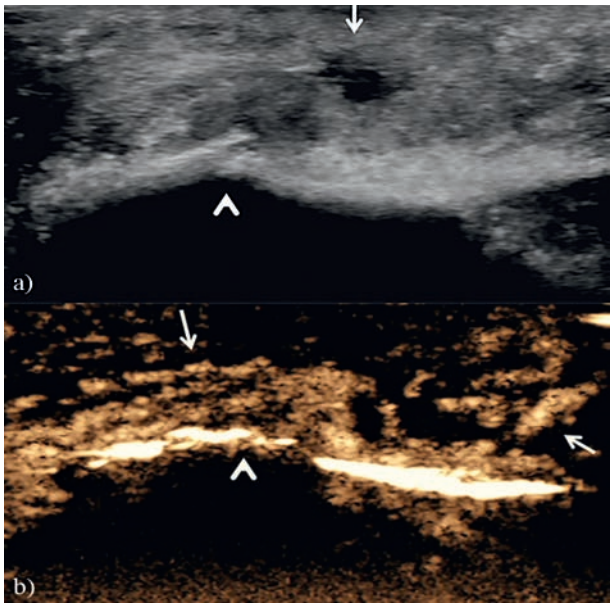


Fig 3. Olecranon bursitis: a) a small collection (arrow) is visualized inside the bursa close to the olecranon bone surface (arrow head). Inflamed synovium cannot be differentiated from surrounding fat tissue; b) CEUS clearly depict the folds (arrows) of synovitis.

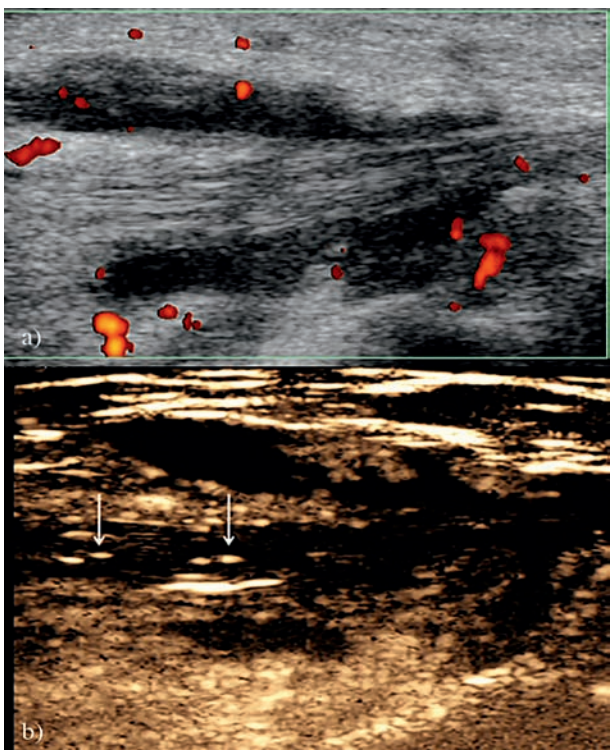


Fig 4. Posterior tibial tenosynovitis: a) power Doppler shows color signal in the hypertrophic synovium surrounding the tendon.; b) after contrast agent injection there is an enhancement in the inflamed tendon sheath. Moving microbubbles (arrows) inside the tendon prove neovascularization.

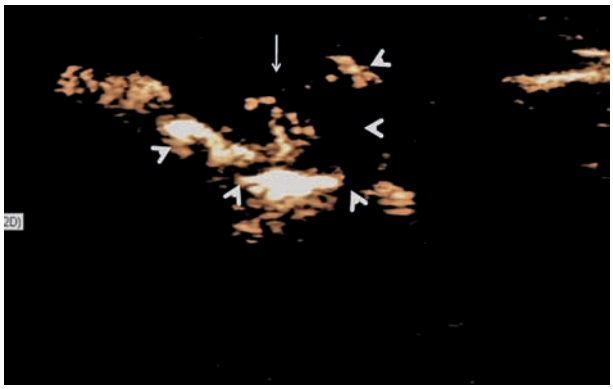


Fig 5. Large erosion (arrow heads) in a metacarpal head. CEUS perceives two erosive vessels (arrow) in the bottom of the bone erosion.

A number of studies have appreciated the contribution of contrast enhanced power Doppler compared to unenhanced power Doppler in the characterization of vascularization in the inflamed synovium. The majority of of the studies, performed by patients with RA, have shown that the use of the contrast agent increases the detection of the color signal, better evaluates the extension of intraarticular vascularization and improves the differentiation of synovia from collection [9,11,22].

Using MRI as control, in a study including 40 patients with various rheumatoid disorders found that contrast enhanced power Doppler had a significantly higher value compared to the same technique without a contrast agent, contrast enhanced power Doppler results being in accordance with MRI results in all cases [23]. When the synovitis in painful knee osteoarthritis was evaluated a higher sensitivity of contrast enhanced power Doppler compared to MRI in the characterization of inflammatory changes of the suprapatellar recess was demonstrated [13].

Not all studies have confirmed the contribution of contrast agents to the increased capacity of ultrasound in identifing and grading the synovial vascularization. In a study that used MRI as a gold standard, the power Doppler ultrasound of the shoulder with or without contrast agent had a low sensitivity in the identification of synovitis and its differentiation from collection of the subacromial bursa, the axillary recess, and the glenohumeral joint [24]. Another study, also having MRI as a reference, found that the use of the contrast agent did not add information to the power Doppler examination of rheumatoid metacarpophalangeal joints. The joints without a pre-contrast color signal inside also showed no color signal after Levovist administration [6]. Similar results were obtained by Platzgummer et al in comparing CEUS to the semi-quantitative power Doppler score. The area

under the curve was correlated with the power Doppler score, the authors questioning the real benefit of contrast-enhanced ultrasound in current practice [14].

The differences in the results of the studies regarding contrast enhanced power Doppler sensitivity can be explained by the small number of examinations, the quality of the equipment used, the technical image acquisition accuracy, the normal-pathological differentiation criteria, the examined joint, or the joint disease.

An important contribution to the contrast agent in the arthritis management is the possibility of evaluation of the thickness of the inflamed synovium (fig 6). The amount of synovitis is correlated with its aggressive, erosive behavior. The exact measurement of the thickened synovium is also important in therapy monitoring. Active synovitis is difficult to differentiate from collection, necrosis, fibrosis or blood clots by B-Mode and power Doppler ultrasound. A multicenter study demonstrates that contrast-enhanced power Doppler better characterizes active synovitis in both large and small joints. The thickness of synovitis is greater after contrast administration than before it [10].

Analyzing the time-intensity curves in a region of interest offers an opportunity for quantitative quantification of the inflammation (fig 7), a permanent goal in rheumatology. Area under the curve, the slope of the ascending and descending curve, the possibility to calculate the flow rate, vascular volume and mean velocity are promising tools to quantify inflammation. Reproducibility is not verified.

The contrast agent increases the ability of the ultrasound in detecting the vascularization of the sacroiliac joints. After contrast administration there is a significant improvement of power Doppler sensitivity in identifying active sacroiliitis by showing color signal into the sacroiliac joints. The signal is not detectable in inactive joints of patients or controls [12,25]. One study obtained excellent results verifying CEUS sensitivity to detect sacroiliitis. Gray scale contrast enhancement was present deep into the sacroiliac joint only in active patients, unlike the superficial enhancement under the joint capsule, which can be found in healthy controls or asymptomatic patients [18].

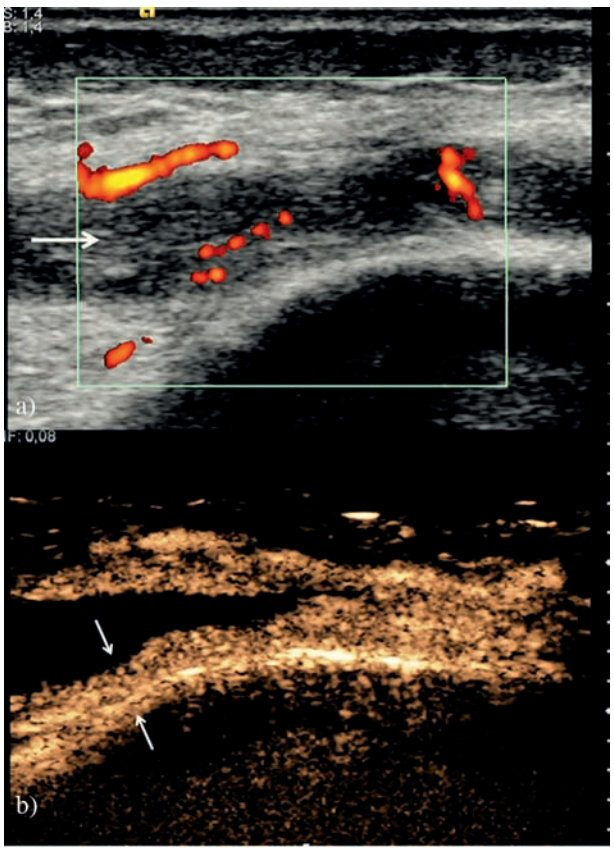


Fig 6. Lateral recess of the knee in an active rheumatoid arthritis patient: a) gray-scale and power Doppler cannot distinguish the nature of the echogenic structure (arrow)- synovitis, collection, necrosis, or clots; b) CEUS clearly identify synovitis (arrows) that can be correctly measured.

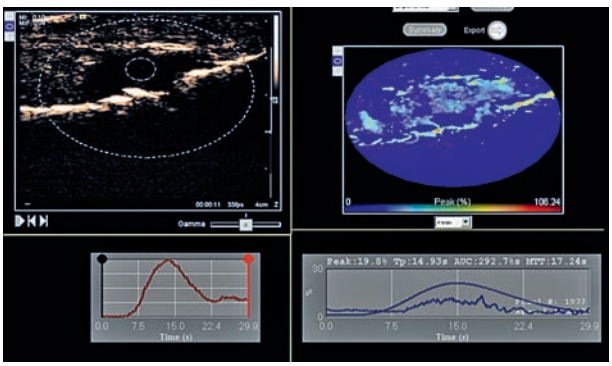


Fig 7. Analysis of the time-intensity curve. Region of interest is selected (top of the screen) and the curve is computerized generated and analyzed (bottom of the screen).

Correlations with histopathology

While searching for correlations between CEUS features and histopathological findings in animals with induced arthritis, it was found that the density of microvascularization in the inflamed synovium was correlated with the intensity of the color signal on post-contrast, but not pre-contrast power Doppler [26]. The analysis of the time-intensity curves showed that the ascending curve, but not the descending curve, and the area under the curve were correlated with the vascular endothelial growth factor determined in histopathological specimens [27]. Also, all these parameters were higher in severe arthritis compared to mild arthritis. In another animal mod-

el study [28], which monitored at close time intervals the histopathological and ultrasound changes in sepsis and chemically induced arthritis, the contrast enhanced power Doppler was the most sensitive imaging modality for evaluating the increase of blood flows, followed by unenhanced power Doppler and color Doppler. Moreover, contrast enhanced power Doppler showed the presence of vascular flow in early stages of the disease as compared with the other ultrasonography techniques. This variability between ultrasonographic findings depending on the time period from the onset of the disease were also obtained in a study monitoring with CEUS the flow parameters in arthritis induced in rabbits [29]. In the early stages of arthritis the signal has high velocity and low amplitude, while in the late stages of synovial inflammation the signal has low velocity and low amplitude. These parameters can be more accurately recorded using contrast agents. Thus, contrast-enhanced ultrasound plays an important role in the early diagnosis of inflammatory arthritis.

These efforts emphasize the importance of CEUS in understanding the behavior of vascularization in the inflamed synovium. The analysis of ultrasonographic parameters could establish certain types of pathological synovial vascularization that might differentiate the types, stages and prognosis of inflammatory arthritis.

Diagnostic, prognostic and therapy monitoring value

The published studies have evaluated CEUS in patients with RA [6,9,10,11,14,16,24], juvenile arthritis [30], spondyloarthropathies [12,15,18,25] and osteoarthritis [13,31]. In early arthritis, CEUS may evidence before power Doppler intraarticular hyperemia. However, the differentiation from normal intraarticular vessels is necessary. The threshold between normal and pathological findings is not yet clearly defined. In established arthritis, CEUS contributes to the assessment of the activity of the disease and its grading. Differentiation between active synovitis and inactive remaining pannus is important for therapeutical decision. The exact evaluation of the thickness of synovitis and the quantitative assessment of hyperemia by measurement of the area under the curve in the analysis of time-intensity curves, allows for a more accurate ultrasonographic evaluation of the disease activity. The use of power Doppler scores after contrast administration is questionable. The increase in the power Doppler vascularization grade after contrast administration, even from 1 to 3 [16], poses interpretation problems. The monitoring of treatment using CEUS is another perspective. The administration of intraarticular or oral cortisone determines a significant reduction of the area under the curve [8,17]. The monitoring of biological therapies in inflammatory arthritis is a challenge for contrast-enhanced ultrasound. The administration of the contrast agent allows the selection of active synovitis areas during the ultrasonographically guided synovial biopsy.

Limits

There are several common and specific limits of contrast-enhanced ultrasound in arthritis assessment: microinvasiveness of the method, minimal risk of contrast agent administration, cost and prolongation of the examination and interpretation time. The main specific limitations are the small number of joints, usually one, that can be once examined, the blooming artifact after injection, the lack of definition of normal joint flows, so slightly increased flows are undefined also. The diagnostic value and the precision of the method in arthritis follow-up are not well established. All these drawbacks limit the day-to-day use of the method.

Conclusion

CEUS provides additional informations for the evaluation of intraarticular vascularization but its place and benefits in arthritis management are not yet clearly established. It has a higher sensitivity compared to color Doppler ultrasound in the identification of abnormal vascularization in joint inflammation. The exact measurement of active synovitis and the analysis of time-intensity curves allow a quantitative assessment of inflammation, which is very important for staging and follow-up work. The method should be standardized and its diagnostic, prognostic and therapy monitoring value should be verified in subsequent studies. However, we believe that the tremendous improvement in depicting the intraarticular vessels consistently support the role of CEUS in arthritis management.

Conflict of interest: none

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