Doppler ultrasonography for assessing rheumatoid arthritis

Doppler ultrasound is able to visualize blood flow by the change in frequency (Doppler shift) of sound waves that are reflected by moving blood cells inside the vessels (Doppler effect). Since hyperemia caused by vasodilation and angiogenesis can be the earliest detectable pathologic changes in the beginning of synovitis, Doppler ultrasonography can be used to assess inflammatory activity. In addition, several studies demonstrate a strong correlation between MRI as well as histological findings (blood vessel density) and Doppler sonographic visualization of synovial perfusion. To achieve this goal, equipment settings must be adapted to slow blood flow in very small blood vessels to reach an appropriate imaging quality. Color and power Doppler ultrasound depict different grades of intra-articular and peritendineous blood flow, which allows an estimation of inflammatory activity and is a helpful tool for the monitoring of rheumatic diseases during follow-up.

KEYWORDS: color Doppler ultrasonography ▪ musculoskeletal ultrasound ▪ power Doppler ▪ synovitis

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Learning objectives

Upon completion of this activity, participants should be able to:

- Describe the role of Doppler ultrasonography in diagnosing patients with early rheumatoid arthritis
- Describe the role of Doppler ultrasonography in determining the prognosis of patients with early rheumatoid arthritis
- Describe the role of Doppler ultrasonography in monitoring of treatment response in patients with early rheumatoid arthritis

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Musculoskeletal ultrasound in rheumatology

Musculoskeletal ultrasound has become an established imaging technique in the diagnosis of patients with rheumatic diseases. It is commonly used for the detection of fluid collection in joints and tendon sheaths, as well as in the assessment of soft tissue, cartilage, tendons and bone surface. Technological improvements during recent years have resulted in higher resolution and made the assessment of synovial proliferation as well as early bone erosions possible [1,2].

In rheumatoid arthritis (RA), hyperemia caused by vasodilation is one of the earliest detectable pathologic alterations at the beginning of joint inflammation, and angiogenesis, as one of the key prerequisites for pannus formation, plays a crucial role in the initiation and perpetuation of synovitis [3]. Both processes result in an increased intra-articular perfusion at the microvascular level, which can be visualized by Doppler ultrasonography (DUS) [4,5].

The recent introduction of potent joint-protective therapies for the management of patients with RA created new demands for the sensitivity and precision of predicting and monitoring synovitis and erosive damage [6]. Since intra-articular synovial hyperemia indicates active inflammation, DUS is a useful imaging method to detect and determine early arthritis and to assess and monitor arthritic activity during the course of disease [7,8]. Moreover, new data indicate that the initial amount of Doppler activity is a prognostic parameter for the development of subsequent bone destruction [9].

Doppler ultrasonography

Technical principles

The Doppler effect, named after the Austrian mathematician Christian Doppler, is a change in frequency of a wave that is transmitted from a moving transducer or which is reflected at a moving surface. DUS working with high-frequency sound waves (MHz) uses moving blood cells (mainly erythrocytes) inside the vessels as reflectors which generate a change in frequency (Doppler shift). Color DUS provides an estimate of the mean velocity of flow within a vessel by color coding the change in frequency and displaying it superimposed on the grayscale image. The flow direction is indicated by the colors 'red', which means flow towards the transducer, and 'blue', which means flow away from the transducer. Power DUS encodes the amplitude of the spectral density of the Doppler signals, which allows the detection of low-velocity blood flow at the microvascular level at the expense of directional and velocity information [10].

Validity

Proving the validity of DUS requires evidence that this method is measuring actual tissue (synovial) vascularization. Some studies demonstrate a correlation between the blood vessel density, which was evaluated by histology ('gold standard'), and DUS scores in affected joints [11–13]. Most studies examining validity compared DUS scores with other measures that are indirect biomarkers or clinical markers of inflammation such as acute phase reactants (erythrocyte sedimentation rate, C-reactive protein) or joint swelling and tenderness [14–17]. Another approach was the comparison of DUS with other imaging methods, which are able to visualize tissue perfusion, such as contrast-enhanced MRI [18,19]. Whereas the correlations between clinical signs of inflammation and Doppler sonographic findings were only weak to moderate, the correlations between intra-articular Doppler flow and vascularization demonstrated by histology and contrast-enhanced MRI, respectively, were strong.

Reliability

The reliability of a test result is its ability to be reproduced between different investigators (interobserver) and at different time points by one investigator (intraobserver). In ultrasound this is a critical issue because of the subjectivity as well as the experience and duration of training of the individual examiner. Moreover, it is influenced by the image quality, which depends on the technical equipment of the ultrasound machine.

Of note, different studies that investigated the inter- and intraobserver reliability of musculoskeletal ultrasonography findings revealed a broad range of agreement, but the results varied with respect to the investigated joints and the findings. In general, the values for exact agreement were higher for the assessment of power Doppler signals (80 to >90%) compared with grayscale findings [20–22].

Practical guidelines for the use of DUS

Machine settings

The additional information of DUS is overlaid on the B-mode (grayscale) ultrasound image to give a dynamic view of vascularization. The grayscale image of the typical hypo- and anechoic area, which represents joint effusion and synovitis and which is equivalent to the intra-articular region, is the basis for the interpretation of DUS at the joints, because it is very important to evaluate only Doppler activity that is localized inside the inflamed synovium (Figures 1 & 2). After activation of the Doppler function, a 'color box' indicates the area in which the DUS investigation is conducted. The color box should cover the region of interest of the examined joint and it should be set to the upper margin of the grayscale image. Typically, joint ultrasound is performed with a linear array transducer operating from 7.5 to 15 MHz, depending on the depth of the investigated joint. Most importantly, only minimal pressure should be exerted with the probe on the skin of the patient to avoid compression and collapse of blood vessels. Moreover, the examined joint should be in a relaxed position and abrupt movements of the ultrasound probe need to be avoided because it can produce artifacts [23,24]. The 'gain' is the overall sensitivity to flow signals. It should be set to obtain a good signal for flow and to minimize the signals from surrounding tissue (Figure 3).

During recent years the rapid development of ultrasonographic techniques has yielded more efficient and sensitive ultrasound machines and probes that make possible the visualization of very small structures and blood flow with low velocity at the microvascular level. In some older ultrasound machines only power Doppler could be used for the investigation of intra-articular hyperemia, whereas today using a high-end machine there is no difference between conventional color Doppler or power Doppler.

Doppler ultrasonography in general uses pulsed wave (PW) ultrasound, which means that ultrasound waves are transmitted in pulses at a given sampling frequency, which is known as the 'pulse repetition frequency' (PRF). The PRF should be standardized to between 500 and 1000 Hz, because a low PRF allows the detection of low-velocity blood flow at the microvascular level inside the joints. For the same reason the 'wall filter' should be set as low as possible, and the 'Doppler frequency' must be adapted to the depth of the region of interest. High Doppler frequencies give better sensitivity to low flow and have better spatial resolution, whereas low frequencies have better penetration [25].

Artifacts

Movement of the patient or the probe may produce false-positive color signals, especially because of the very low PRF used. A high gain can cause 'background noise', which fills the whole Doppler box with color. Moreover, it can lead to a 'blooming', which means that the color signals reach beyond the vessel into the adjacent area.

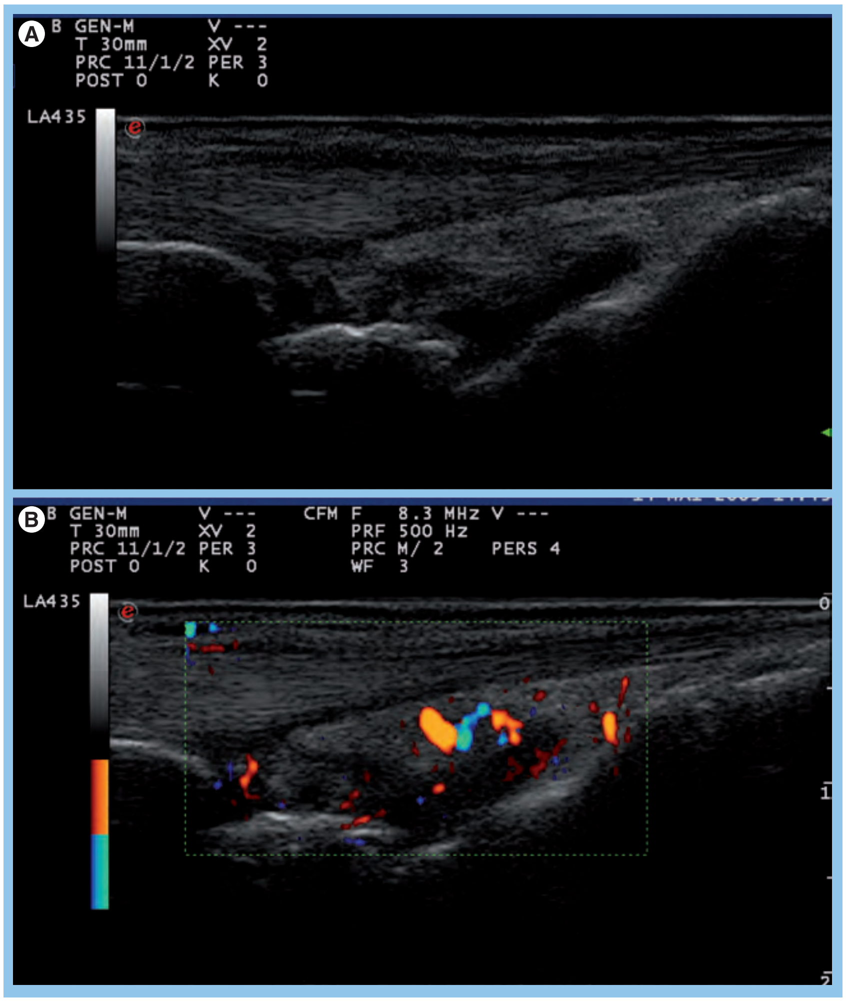

Figure 1. Dorsal longitudinal view of a wrist. (A) Grayscale and **(B)** Doppler sonographic image of wrist arthritis in a patient with rheumatoid arthritis.

High pressure of the probe on the patient's skin must be avoided because it decreases the blood flow in the underlying vessels, which is known as a 'blanching effect' [24].

'Reverberation' means the repetition of a superficial Doppler signal in deeper layers of the tissue that may be located inside the joint area, which does not reflect real blood flow. To avoid this, the Doppler box must cover the upper margin of the grayscale image. At very strong echogenic surfaces such as bone, 'mirroring' may lead to color signals under the bony surface that are not consistent with blood flow [25].

In general, during musculoskeletal ultrasonography every joint can be examined by DUS, but the use of DUS is more effective at superficial joints and structures such as wrists, finger joints, superficial tendons and bursae in contrast to deep joints such as the hip and shoulder. The reason for this is the low blood flow velocity in the very small synovial vessels, which only produce a weak Doppler signal that cannot always reach the transducer from deep layers of the tissue.

Clinical indications of DUS in the assessment of RA

In patients with RA, remission is regarded as the optimal therapeutic target to prevent joint damage and disability. Rates of remission are increasing with more effective drug treatments and with modern therapeutic strategies, which assume early diagnosis of the disease and a tight monitoring of disease activity, before structural damage could occur. Current methods used to diagnose RA and to evaluate disease activity rely on composite scores based on clinical and laboratory assessments such as the Disease Activity Score (DAS) or the American College of Rheumatology (ACR) criteria.

Imaging techniques such as ultrasonography (including DUS) are capable of directly visualizing and objectively quantifying synovial inflammation. Since hyperemia is an early sign of inflammatory activity that shows a rapid decrease under successful anti-inflammatory treatment, DUS is an ideal assessment tool to provide an early diagnosis and a more accurate measure of disease activity during treatment. Moreover, the level of imaging-detected synovial inflammation by DUS has been shown to correlate with subsequent bone damage and functional outcome. These advantages are the basis for the three major indications for the use of DUS in patients with RA:

- Early diagnosis
- Monitoring of disease activity
- Risk assessment with regard to developing destruction (individual prognosis)

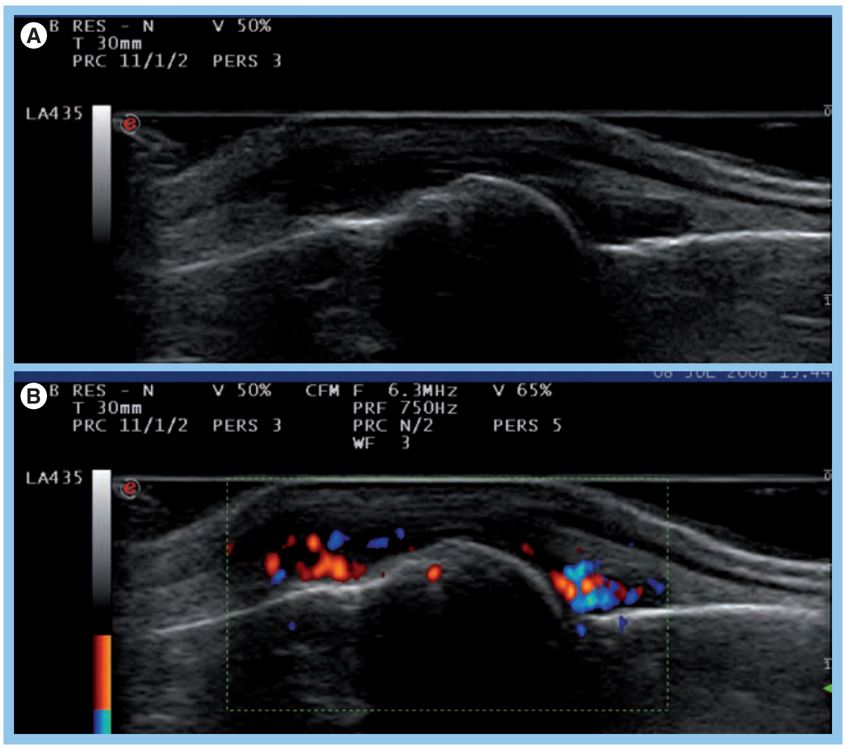

Figure 2. Dorsal longitudinal view of a metacarpophalangeal joint. **(A)** Grayscale and **(B)** Doppler sonographic image of arthritis of a metacarpophalangeal joint of a patient with active rheumatoid arthritis.

Early diagnosis

Recently, a collaborative initiative of the ACR and the European League Against Rheumatism (EULAR) developed new classification criteria for RA [26]. The reason for the development of new criteria was the lack of sensitivity of the criteria from 1987 in patients with early RA. In the glossary of definitions, an 'involved joint' is defined by swelling and tenderness and it is mentioned that "additional evidence of joint activity from other imaging techniques (e.g., MRI or ultrasound) may be used for confirmation of the clinical findings". Thus, for the first time, ultrasound including DUS was taken into consideration for the classification of early RA, because of its significant value for the detection of early inflammatory changes in the joints.

A number of studies have reported the ability of DUS to detect synovial hyperemia in patients with confirmed RA [13–16]. Moreover, when compared with contrast-enhanced MRI as the gold standard, the sensitivity of DUS was 89% and the specificity was 98%. However, there is still a lack of prospective diagnostic studies that try to answer the question of whether DUS can distinguish patients with and without RA among patients in whom it is reasonable to suspect that the disease is present (Phase III diagnostic study described by Sackett [27]). In this context it should be noted that intra-articular Doppler signals are not specific for RA, but indicate inflammatory driven synovial hyperemia in general, independent of the underlying disease. Since septic arthritis, psoriatic arthritis, arthritis in gout and others show similar Doppler sonographic activity to arthritis in RA, this method plays a potential role in the early detection of arthritis in general, but is not very helpful in the differentiation of the various inflammatory arthritides.

Monitoring of disease activity

During recent years, several longitudinal studies have investigated the feasibility and usefulness of Doppler sonographic assessment of synovitis under different anti-inflammatory treatments, such as intra-articular steroid injection or therapy with biologic agents (e.g., anti-TNF-α antibodies) [28–32]. The results revealed the substantial potential of DUS for an improved evaluation of RA response during treatment.

A still persisting problem of DUS is the lack of a consistent quantification of the synovial Doppler flow and the subsequent difficulties in reproducibility and comparability of this method which, however, is crucial for the evaluation of a treatment response. Usually a semiquantitative four-step grading is used (0 = no flow, 1 = mild flow, 2 = moderate flow, 3 = intense flow), which was first described by Newman *et al.* [7]. Other approaches such as a computerized analysis of the number of color pixels and the use of the resistance index have been reported as helpful tools to measure synovial hyperemia [33,34].

Risk assessment

Since the level of Doppler activity in patients with RA has been shown to correlate with subsequent bone damage in the course of the disease it can be used as a prognostic factor [9,35]. Moreover, a recent study found an increased intra-articular Doppler flow in 43% of asymptomatic patients with RA who were in clinical remission [36,37]. This subclinical inflammation may explain the observed progression of structural damage in patients who have achieved remission criteria (silent progression), and it indicates the necessity for a more accurate evaluation of disease activity by means of imaging assessment such as DUS.

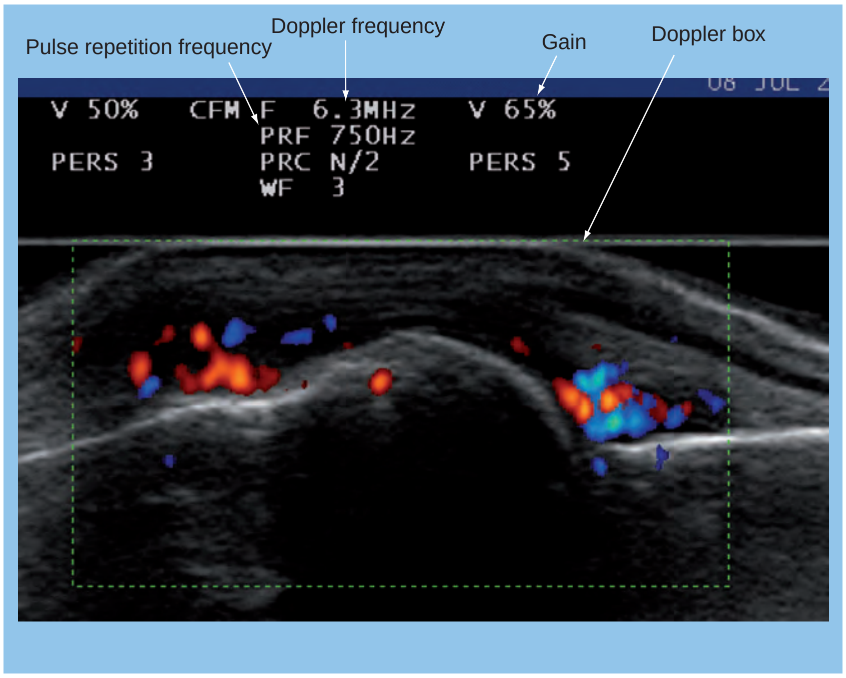

Figure 3. Doppler settings (dorsal longitudinal scan of a metacarpophalangeal joint).

Conclusion

The assessment of RA is based on clinical, laboratory and imaging findings. During recent years radiologic evaluation of bone destruction (erosions) was the only imaging method that was routinely used. New imaging modalities such as high-resolution ultrasound and DUS make possible the direct visualization of the underlying inflammatory process (synovitis), which facilitates and improves the diagnosis and assessment of disease activity in patients with RA.

Future perspective

Since musculoskeletal ultrasonography has become a routinely available bedside method with high patient acceptability, the next task will be the implementation of advanced techniques such as DUS in daily rheumatologic practice for the assessment of RA. New ultrasound scores such as a 12-joint power DUS score or a novel seven-joint score that uses grayscale as well as DUS for the assessment of arthritis are promising approaches to achieve this goal [38,39].

Further evaluation of DUS as a diagnostic method by prospective diagnostic studies (Phase III studies described by Sackett [27]) is also urgently needed in order to improve the important role of this method as an assessment tool in clinical studies as well as an independent criterion for the classification of RA.

Executive summary

Technical principles

- Doppler frequency is a change in frequency (Doppler shift) of a sound wave that is transmitted from a moving transducer or which is reflected at a moving surface.
- Color Doppler provides an estimate of the mean velocity of flow within a vessel by color coding the change in frequency and displaying it superimposed on the grayscale image.
- Power Doppler encodes the amplitude of the spectral density of the Doppler flow rather than the Doppler frequency signal at the expense of directional and velocity information.

Machine settings

- The Doppler box is the area in which the Doppler investigation is conducted. It should cover the upper margin of the grayscale image and the whole region of interest.
- Gain is the overall sensitivity to flow signals. It should be set to obtain a good signal for flow and to minimize the signals from surrounding tissue.
- Pulse repetition frequency should be standardized to between 500 and 1000 Hz, because a low pulse repetition frequency allows for the detection of low-velocity blood flow.
- Doppler frequency should be set as high as possible and must be adapted to the depth of the investigated tissue.

Artifacts

- Background noise fills the whole Doppler box with color because of movement of the probe or of the patient.
- In cases of blooming, a high level of gain results in color signals that reach beyond the vessel into the adjacent area.
- Blanching is a decrease of blood flow because of high pressure of the probe on the patient's skin.
- Reverberation refers to the repetition of a superficial Doppler signal in deeper layers of the tissue.
- At strong echogenic surfaces such as bone, artificial color signals can arise under the bone surface; this is known as mirroring.

Clinical indications

- Diagnosis: since synovial hyperemia is one of the earliest detectable pathologic alterations at the beginning of joint inflammation, Doppler ultrasonography is a helpful diagnostic tool in early rheumatoid arthritis.
- Monitoring: Doppler ultrasonography can assess a decrease of intra-articular perfusion under treatment, which is a surrogate parameter for therapeutic efficacy.
- Risk assessment: the level of the initial amount of Doppler activity is a prognostic factor for the development of subsequent bone damage.

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1 Your patient is a 39-year-old white woman with knee pain and swelling thought possibly to be early rheumatoid arthritis. Based on the above review by Drs Strunk and Müller-Ladner, which of the following statements about the role of Doppler ultrasonography in her diagnosis is most likely to be correct?

- ☐ **A** Hyperemia occurs late in the development of synovitis
- ☐ **B** Doppler ultrasound can depict joint hyperemia caused by vasodilation and angiogenesis
- ☐ **C** Intra-articular Doppler ultrasound signals indicating hyperemia are specific for rheumatoid arthritis
- ☐ **D** Pulse repetition frequency should be standardized to 1500 Hz

2 Your patient undergoes Doppler ultrasonography, but some artifacts are observed. Based on the above review, which of the following statements about the prognostic value of Doppler ultrasonography in your patient is most likely correct?

- ☐ **A** The level of the initial amount of Doppler ultrasound activity helps predict the development of subsequent bone damage
- ☐ **B** During clinical remission, increased intra-articular Doppler flow has not been observed in asymptomatic patients
- ☐ **C** An artifact known as mirroring refers to the repetition of a superficial Doppler ultrasound signal in deeper layers of tissue
- ☐ **D** An artifact known as reverberation refers to artificial color signals arising under the surface of bone or other strong echogenic surface

3	Your patient is started on intra-articular steroid injection for rheumatoid arthritis, and repeat Doppler ultrasonography is planned to monitor her response. Based on the above review, which of the following statements is most likely to apply to performance and interpretation of this test?	
☐	**A**	Doppler ultrasound findings are unlikely to correlate with MRI and histology findings
☐	**B**	Equipment settings should be adapted to slow blood flow in very small blood vessels
☐	**C**	Color and power Doppler ultrasound are unlikely to be helpful
☐	**D**	It is not necessary to consistently quantify synovial Doppler flow