

Quantification of the synovial perfusion in rheumatoid arthritis using Doppler ultrasonography

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ABSTRACT

In the past decade, Power Doppler ultrasound (PDUS) has been established as a new imaging modality for the evaluation of synovial perfusion in the inflamed joints of patients with rheumatic diseases. Various studies have been dealing with the problem of a reproducible quantification method in PDUS as this still appears to be one of the main disadvantages in comparison with magnetic resonance imaging and also with contrast-enhanced ultrasound technique. The main studies addressing this problem are presented and compared to the recently described three-dimensional power Doppler ultrasound by outlining the advantages and the remaining difficulties in quantifying synovial vascularity with PDUS.

Introduction

Four years ago, Walter Grassi and his group addressed a striking appeal to the ultrasound world by describing the immense potential of power Doppler ultrasonography (PDUS) for the monitoring of therapeutic response in rheumatic diseases (1). In his article, three studies were discussed, which had been published until 2002, using PDUS as an imaging tool for the evaluation of rheumatoid arthritis (RA) treatment (2-4).

In the meantime, numerous studies have been dealing with PDUS not only for the monitoring of therapy (5-17), but also for diagnostic, clinical (18-21) and pathophysiological research (22-25). Several methodical papers have confirmed the potential of PDUS for the measurement of disease activity of RA (26-31). Still, its reliability requires further evaluation before a general usage of PDUS for individual clinical guidance or as an outcome measurement in

clinical trials can be recommended (32, 33).

One of the main reasons for this hesitation to allocate to PDUS a higher value as a primary imaging and monitoring modality, particularly in comparison with magnetic resonance imaging (MRI) and with conventional x-rays, appears to be the problem of a reproducible quantification method.

Internationally standardized scoring systems such as the defined Outcome Measures in Rheumatology Clinical Trials (OMERACT) RA scoring system (RAMRIS) and the well established, already modified van der Heide/Sharp Score have been developed for MRI images and plain radiographs assist in exact assessment of joint disease progression defined by early inflammatory and secondary erosive changes (34-36).

Some characteristics of PDUS imaging aggravate a reliable quantification. During US examination, the images have to be selected by the operator, which allows only a limited section of the complex dynamic examination. Furthermore, the outcome is essentially dependent on the skills and experience of the sonographer, as well as on the technical equipment. The EULAR ultrasound group has therefore focused on the evaluation of interobserver agreement values from the well-experienced ultrasound teachers showing moderate to good results for the pathologic findings compared to MRI (37) and moderate values for the Doppler findings due to the above mentioned varieties (38).

The following paper introduces the varying methods of Doppler ultrasound for the assessment of synovial vascularity. For each quantification method, a brief description is provided together with the review of the available data on reproducibility.

Technical principles

The *Doppler effect*, named after the Austrian mathematician and physicist Christian Doppler, is a change in the frequency of a reflected wave, resulting from motion of the source or of the reflector. *Doppler US* is used to detect and measure blood flow, the major reflector being the moving erythrocytes. *Colour Doppler US* provides an estimate of the mean velocity of flow within a vessel by colour coding the information and displaying it superimposed on the grey-scale image. The flow direction is arbitrarily assigned the colour red or blue, indicating flow toward or away from the transducer. *Power Doppler US* (PDUS) depicts the amplitude or power of Doppler signals rather than the frequency shift. This allows the detection of a larger range of Doppler shifts and thus better visualization of the low velocity blood flow in small vessels, but at the expense of directional and velocity information. PDUS is performed with a linear array transducer, operating from 7.5 to 15 MHz. The power Doppler image is optimised by adjusting the pulse repetition frequency (PRF), the wall filter and the sensitivity in order to fill in the entire vessel lumen without extension of colour signal outside the artery. The PRF should be standardised to between 500 and 1000Hz. A low PRF detects

low velocities but reduces the sequence of images. The colour box should cover the region of interest of the examined joint containing the intra- and periarticular area.

For the acquisition of a three-dimensional (3D) PDUS image, the transducer has to be mechanically moved in a predefined region of interest with high Doppler signal intensity in one direction (*free-hand sweep*) to obtain a sequence of 2D PDUS images. An online 3D power Doppler function provided by the vascular software of the US system is used to generate a 3D image of the peri- and intra-articular blood vessels in which grey-scale information of the surrounding tissue is already subtracted. The acquired data is digitally stored as a cine loop, in which the 3D blood vessels can be viewed as it rotates which provides a true 3D perspective.

Some possible artefacts are particularly important for the performance of the Doppler examination and for the correct quantitative analysis: the “bleeding” of colour signals from a vessel into an adjacent area without flow is due to an inappropriately high setting of the colour gain. In most of the studies, the gain is set as suggested by Rubin *et al.* (39): this setting requires the manual elevation of the power Doppler US gain level until the colour box is almost uniformly filled with the

first indication of colour and with only the minimum amount of the next highest signal just beginning to appear.

On the other hand, an increased transducer pressure can markedly reduce or obliterate the power Doppler intensity (‘blanching effect’) so that minimal probe pressure is necessary for the Doppler examination (40).

Quantification methods in Doppler ultrasound

1. Semiquantitative evaluation of Doppler flow

Several efforts of providing a quantification method, which can be commonly used and reproduced, have been undertaken. The internationally most frequently applied method is a semiquantitative scoring system in which the intensity of the synovial blood flow is graded in a four step scale defining the intensity of Doppler signals from 0: no Doppler signal / no blood flow; 1: single Doppler signals / mild blood flow, 2: various, confluent Doppler signals / moderate blood flow and 3: almost complete filling with confluent Doppler signals / intense blood flow (Fig. 1) (2). As the semiquantitative grading system is cheap and fast to apply, because it does not involve contrast-media or computer-assisted evaluation, it is used in many studies for diagnostic and therapeutic outcome evaluation (Table I). There are several modifications addressing specifically the intensity or the number of flow signals inside the synovial tissue. However, in all studies the main grading from 0-3 based on a semiquantitative assessment of the investigator is kept at the same level (12, 48).

Naredo *et al.* showed moderate to excellent interreader agreement values for all individual joint regions from 0.69 unweighted kappa (wrist) to 1.00 for glenohumeral, hip and talar joints (n = 44) but there is no information whether the latter values might result from finding no power Doppler signals in the corresponding joint regions. The interreader agreement data were obtained from saved images of one sonographer which then were read by a second blinded rheumatologist (20). In contrast to the repetitive reading of the

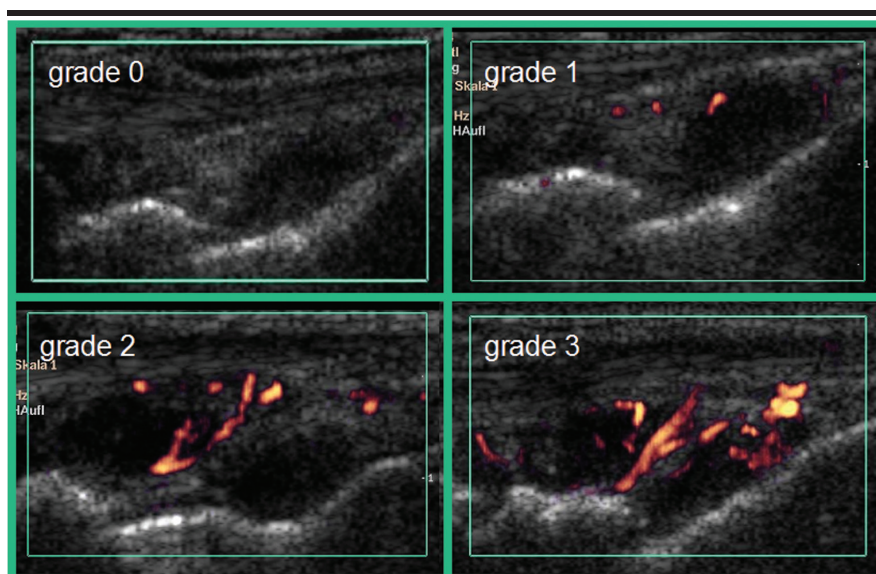


Fig. 1. Semiquantitative grading of power Doppler intensity with four levels: 0 = no flow / no Doppler signals; 1 = mild flow / single Doppler signals; 2 = moderate flow / many Doppler signals; 3 = intense flow / confluent Doppler signals covering the synovium.

Table I. Quantification methods of published articles from 1994 - 2007 using power or colour Doppler ultrasound.

Author	Journal	Key words	Year	Joints	Quantification method
1. Semiquantitative scoring					
Newman <i>et al.</i> (41)	Am J Roentgenol	Bursitis, Hyperemia, Synovial Cyst, Tendinopathy	1994	23 various	Score (PDUS)
Newman <i>et al.</i> (2)	Radiology	Antiinflammatory agents, Knee joint, Synovitis, Triamcinolone	1996	8 knees	Score (PDUS)
Breidahl <i>et al.</i> (42)	Am J Roentgenol	Exudates and Transudates, Muskuloskeletal Diseases, DUS	1996	39 various	Score (PDUS)
Breidahl <i>et al.</i> (43)	J Ultrasound Med	Tendons, Tenosynovitis, DUS	1998	26 various	Score (PDUS)
Schmidt <i>et al.</i> (44)	Clin Exp Rheumatol	OA, Knee, Synovitis, CDUS	2000	20 knees	Score (CDUS + PDUS)
Walther <i>et al.</i> (45)	Arthritis Rheum	RA, OA, Synovial Membrane, DUS	2001	23 knees	Score (PDUS)
Stone <i>et al.</i> (3)	J Rheumatol	RA, Synovitis, CDUS	2001	12 wrists	Score (PDUS)
Szkudlarek <i>et al.</i> (28)	Arthritis Rheum	RA, MCP joint, synovitis, DUS	2001	54 MCPs	Score (PDUS)
Walther <i>et al.</i> (46)	Radiology	RA, Hip joint, Osteoarthritis, Synovial Membrane, DUS	2002	24 hips	Score (+Pixels in a score, PDUS)
Ribbens <i>et al.</i> (5)	Radiology	Monoclonal Antibodies, RA, Finger joint, Synovitis, Wrist joint	2003	233 wrists, MCP, PIP	Score (PDUS)
Szkudlarek <i>et al.</i> (29)	Arthritis Rheum	RA, Finger joint, Toe joint, DUS	2003	150 MCP, PIP, MTP	Score (PDUS)
Weidekamm <i>et al.</i> (18)	Arthritis Rheum	RA, Finger joint, DUS, Wrist joint	2003	940 wrist, MCP, PIP	Score (PDUS)
Filippucci <i>et al.</i> (9)	Ann Rheum Dis	Antiinflammatory agents, Synovitis, Triamcinolone, DUS	2004	20 various	Score (PDUS)
Strunk <i>et al.</i> (23)	Rheumatology	RA, pathologic neovascularisation, VEGF	2004	21 wrists	Score (PDUS)
Fiocco <i>et al.</i> (12)	Ann Rheum Dis	PsoA, RA, Immunoglobulin, Knee Joint, TNF-receptors, Synovitis	2005	27 knees	Score (PDUS)
Naredo <i>et al.</i> (20)	Ann Rheum Dis	RA	2005	5640 various	Score (PDUS)
Filippucci <i>et al.</i> (14)	Ann Rheum Dis	Monoclonal Antibodies, Antirheumatic agents, RA, Synovial Fluid, Wrist joint	2006	48 wrists	Score (PDUS)
Koski <i>et al.</i> (33)	Ann Rheum Dis	Arthritis	2006	41 various	Score (PDUS)
Koski <i>et al.</i> (25)	Ann Rheum Dis	Synovitis, DUS	2006	44 various	Score (PDUS)
Strunk <i>et al.</i> (16)	Ann Rheum Dis	Glucocorticoids, Synovial Membrane, Synovitis	2006	8 various	Score (2D, 3D PDUS)
Strunk <i>et al.</i> (17)	Rheumatology	Arthritis, Cryotherapy, Synovial Membrane, Wrist joint	2006	13 wrists	Score (2D, 3D PDUS)
Bajaj <i>et al.</i> (24)	Skeletal Radiol	Erosive progression	2007	168 MCP, PIP, MTP	Score (PDUS)
Naredo <i>et al.</i> (61)	Arthritis Rheum	RA, US, PDUS	2007	1176 various	Score (PDUS)
2a. Pixel Count					
Hau <i>et al.</i> (26)	Arthritis Rheum	RA, MCP joint, US	1999	153 MCP, PIP	Pixels (CDUS)
Hau <i>et al.</i> (4)	Ann Rheum Dis	Antirheumatic agents, RA, Finger joint, Immunglobulin G, TNF receptors	2002	5 MCP	Pixels (CS/ROI, CDUS)
Taylor <i>et al.</i> (11)	Arthritis Rheum	Monoclonal Antibodies, Antirheumatic agents	2004	240 MCP	Pixels (sum score, PDUS)
2b. Resistance Index					
Teh <i>et al.</i> (6)	Br J Rheumatol	RA, Synovial membrane, Synovitis	2003	13 hand joints	Amplitude of signal (PDUS)
Terslev <i>et al.</i> (7)	Ann Rheum Dis	RA, Synovial membrane, CDUS	2003	51 joints	RI, Pixels (Colour Fraction, CDUS)
Terslev <i>et al.</i> (8)	Ann Rheum Dis	Antirheumatic agents, RA, Immunoglobulin Gelenk, TNF Receptors	2003	11 wrist, MCP	RI, Pixels (Colour Fraction, CDUS)
Ozgoemen <i>et al.</i> (48)	Joint Bone Spine	RA, bone density, DUS, MCP joint	2004	150 MCP	RI, PI
Terslev <i>et al.</i> (19)	Ann Rheum Dis	Finger joint, wrist	2004	324 wrist, MCP, PIP	RI, Pixels (Colour Fraction, CDUS)
Sato <i>et al.</i> (47)	Mod Rheumatol	RA, DUS	2005	42 knees	RI, PI, Score
Takahashi <i>et al.</i> (13)	Mod Rheumatol	RA, Monoclonal Antibodies, DUS	2005	12 knees	RI, PI, Score
Kiris <i>et al.</i> (30)	J Clin Ultrasound	RA, MCP joint, synovial membrane, wrist joint	2006	288 wrist, MCP	RI, PI, Score
Shio <i>et al.</i> (15)	Mod Rheumatol	Monoclonal antibodies, antirheumatic agents, RA, DUS	2006	60 MCP, knees	RI, Score

Table I continues

Author	Journal	Key words	Year	Joints	Quantification method
3. Contrast-enhanced					
Magarelli <i>et al.</i> (54)	Eur Radiol	Contrast media, image enhancement, MRI, synovitis, DUS	2001	40 various	CEUS (Levovist®; PDUS)
Qvistgaard <i>et al.</i> (27)	Ann Rheum Dis	RA, Finger joint, synovial membrane	2001	18 wrist, MCP, PIP	CEUS (Levovist®); RI, PI, pixel (CDUS, PDUS)
Carotti <i>et al.</i> (50)	Ann Rheum Dis	RA, knee joint, synovial membrane, synovitis	2002	42 knees	CEUS (Levovist®): time intensity/area under the curve (PDUS)
Klauser <i>et al.</i> (49)	Arthritis Rheum	RA, Contrast-media, finger joint, CDUS	2002	198 Finger joints	CEUS (Levovist®); Pixel (CDUS)
Fiocco <i>et al.</i> (22)	J Rheumatol	Arthroscopy, Contrast-Media, Synovitis, Ultrasonography	2003	18 knees	CEUS (Levovist®): Score (PDUS)
Szkudlarek <i>et al.</i> (51)	Eur Radiol	Arthritis, Contras-Media, Doppler, Rheumatoid, US	2003	15 MCP	CEUS (Levovist®): Score (PDUS)
Wamser <i>et al.</i> (52)	Skeletal Radiol	MRI, RA, contrast-media, DUS, shoulder joint	2003	24 shoulders	CEUS (Levovist®): Score (PDUS)
Salaffi <i>et al.</i> (10)	Clin Rheumatol	RA, contrast-media, knee joint, Synovitis, Triamcinolone	2004	18 knees	CEUS (Levovist®): time intensity curve (PDUS)
Klauser <i>et al.</i> (53)	Eur Radiol	RA, Image Enhancement, Joints, Synovitis	2005	113 various	CEUS (SonoVue®; PDUS)
Rees <i>et al.</i> (21)	Rheumatology	RA, Synovitis, US, PD, SonoVue	2006	40 MCP, PIP	CEUS (SonoVue®): Score (PDUS)
4. 3D Blood Vessel Count					
Strunk <i>et al.</i> (56)	Joint Bone Spine	RA, 3D Imaging, MRI, DUS, wrist joint	2006	9 wrists	Blood vessel count, 3D score (PDUS)
5. Voxel Count					
Strunk <i>et al.</i> (31)	Ultraschall Med	Angiogenesis, 3D, extremities, arthritides	2007	15 wrists	Voxels, blood vessels, pixels, RI, 2D, 3D score (PDUS)

DUS: Doppler ultrasound; PDUS: Power Doppler ultrasound; CDUS: Colour Doppler ultrasound; RA: Rheumatoid Arthritis; OA: Osteoarthritis; CEUS: contrast-enhanced ultrasound; MRI: magnetic resonance imaging; MCP: metacarpophalangeal; PIP: proximal interphalangeal; RI: resistance index; PI: pulsatility index.

same US images (= interreader agreement), two independent investigators (one experienced radiologist and one experienced rheumatologist) did the US examination by Szkudlarek *et al.* (= interobserver agreement), presenting a moderate intraclass correlation coefficient (ICC = 0.72), kappa value ($k = 0.55$) and overall agreement of 87% in $n = 150$ MCP/MTP joints for the presence and grading of power Doppler signals (29). Filippucci *et al.* reported on very high kappa values for interobserver data from two experienced US investigators ($k = 0.9$) for the power Doppler assessment in various joints ($n = 20$) (9). The interobserver agreement from one experienced and one unexperienced sonographer published by Strunk *et al.* was moderate ($k = 0.63$) for the wrist joint ($n = 75$) (31).

2. Quantitative measurements

a. Computer-assisted measurement of colour pixels

For the quantitative measurement of col-

our pixels, an exact region of interest (ROI) in which the colour pixels are measured needs to be defined by the sonographer (Fig. 2). This ROI should correlate with the intraarticular region inside the joint capsule. In the study from Hau *et al.*, the MCP joints were scanned longitudinally and transversely from the dorsal view. With a computer aided image analysis, intraarticular colour density was then quantified by counting the pixels in relation to the predefined ROI in both views, finally added to a pannus vessel index (sum of all colour pixels from both longitudinal and transverse scan (CS/ROI) (4). Walther *et al.* quantified the number of red-yellow pixels according to the calibration procedure described by Rubin *et al.* (39) and then graded the number of pixels on a semiquantitative score from 0-4, 0 representing 0-100 pixels, 0.5: 101-500 pixels, up to 4: more than 5.000 pixels. (46). Terslev *et al.* transferred digitally stored colour Doppler images in DICOM format to a

processing program. Then the number of counted colour pixels was expressed in relation to the total number of pixels in the ROI described as the colour fraction (7, 8). Taylor *et al.* subsumed a total vascularity score from the pixel count of 10 metacarpophalangeal joints in each patient (11).

The interobserver agreement for the computerized pixel count in the paper of Strunk *et al.* showed moderate correlations ($r_p = 0.65$, $n = 75$) between the two ultrasound investigators (31). A good interreader agreement ($r_p = 0.81$, $n = 75$) was described by Qvistgaard *et al.* but in this study, two investigators did the measurement of the pixel counting for the same pictures of one ultrasound examiner (27).

b. Resistance index and analysis of Doppler curves

To obtain a spectral Doppler curve, the sampling area can be placed over an intrasynovial artery. The US unit identifies the cardiac cycles as well as the

peak systolic and the end diastolic flow, which is used to calculate automatically the resistance index (RI) being defined as: maximum systolic amplitude – end diastolic amplitude; maximum systolic amplitude (Fig. 3). The values of the RI range are set between 0 and 1. Low RI values indicate a low blood vessel resistance in accordance with an increased tissue perfusion, whereas high RI levels correlate with a high resistance, indicating a subsequent decrease of perfusion. When spectral Doppler measurements cannot be done due to the lack of inflammatory activity, the RI can be defined as 1.00 assuming the resistance in the synovial arteries to be the same as in the extrasynovial musculoskeletal tissue (7). Because the intra-synovial vessels are very small, both the artery and its concomitant veins are often sampled simultaneously even with the smallest possible Doppler gate. A flow reversal during the diastole will then remain unnoticed because the reversed arterial flow will superimpose the venous signal. Therefore the spectral measurements should be limited to the arterial side of the Doppler line, defining 1.00 as the maximum for RI.

In the working group of Terslev *et al.*, a mean RI value obtained from three different synovial arteries was generated, if more than one synovial artery could be sampled (7, 8). Interobserver agreement was not tested for the RI measurement as the authors defined the RI being determined by the US system and not dependent on the experience of the investigator (7). But Strunk *et al.*, who used one intraarticular artery for the RI measurement, showed only a weak interobserver agreement between the two US investigators ($r_p = 0.53$, $n = 75$) (31). Kiris *et al.* obtained a mean RI calculated from 12 joints of each patient and compared the mean value to a cumulative flow signal score derived from the semiquantitative grading (30). Sato *et al.* calculated mean values of the longitudinal and transverse scanning whereas the area of colour signals obtaining the RI was randomly selected (47). Both studies demonstrated an inverse correlation between flow signals and RI. In these

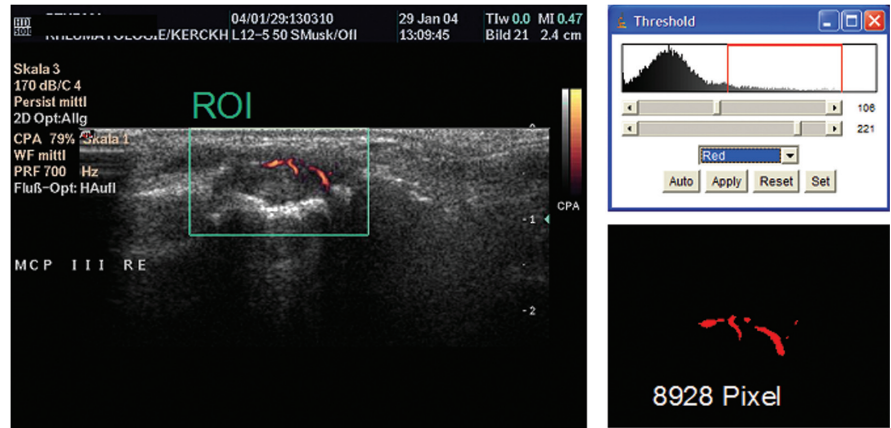


Fig. 2. Dorsal longitudinal scan of a metacarpophalangeal joint with synovitis. The colour pixels inside the region of interest (ROI) are counted after threshold settings using a public domain imaging analysis program (58).

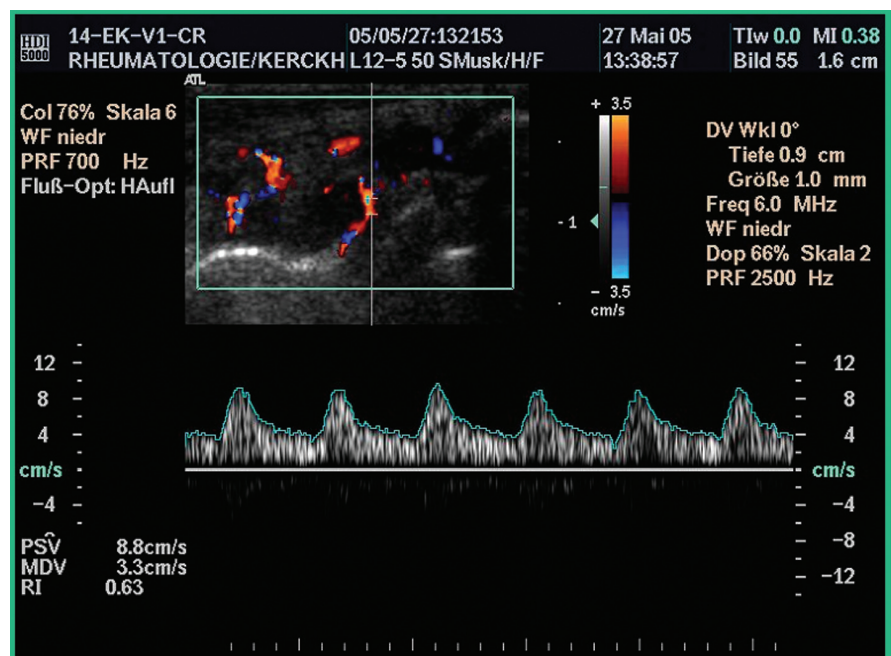


Fig. 3. Resistance index (RI) measurement in a small intraarticular artery at a dorsal longitudinal scan of the wrist. The Doppler velocity curve is shown with the peak systolic flow (PSV) and the minimal diastolic velocity (MDV).

studies, an interobserver agreement was not investigated.

3. Contrast-enhanced Doppler US with quantitative or semiquantitative evaluation

Contrast-enhanced ultrasound (CEUS) is using gas-filled microbubble contrast media in order to improve the flow-related sensitivity of colour signals. In contrast to MRI contrast medium, the US contrast agent stays inside the lumen of the vessel and does not diffuse in the extraarterial tissue.

The first type of US contrast agent was galactose palmitic acid (Levovist®). Levovist® has been used in most of the published studies (22, 49-52). An increased sensitivity to detect intra-articular blood flow was described by Klauser *et al.* with a loss in the specificity for detecting active RA (49). Szkudlarek *et al.* did not find an increased sensitivity in the assessment of synovitis in MCP joints by using a semiquantitative assessment method (51).

In the paper of Fiocco *et al.* concern-



Fig. 4. In the three-dimensional images of the synovial blood vessel signals inside a wrist joint, the number of the intraarticular blood vessels is counted after looking at the rotating blood vessel tree from all possible directions. A quantitative comparison is shown during three months of treatment with TNF-alpha inhibiting therapy presenting a significant rarification of intraarticular blood vessels.

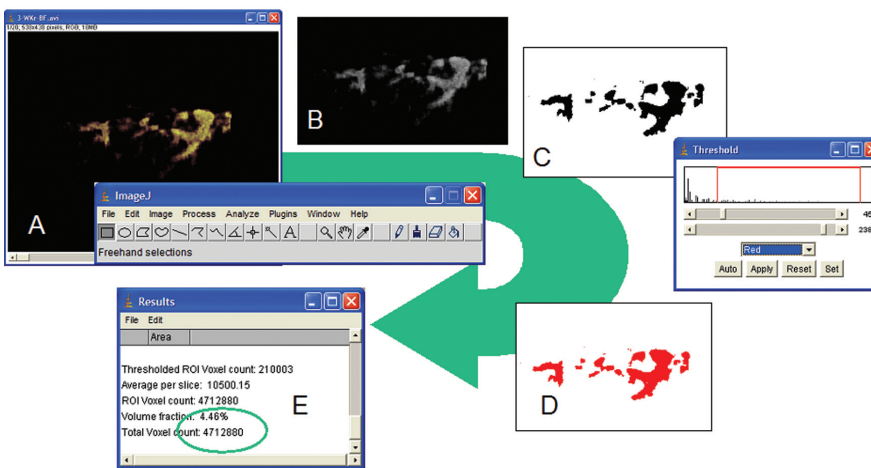


Fig. 5. The 3D movie of the synovial blood vessel tree consists of 15 single slides obtained by moving the probe in a longitudinal dorsal view over the wrist. After loading the .avi file to the image analysis program (A), it was converted to an 8-bit grey-scale stack (B), threshold values were set (C) and the volume pixels (= voxels) were counted in all 15 slides (D). Displayed is then the total voxel count as well as the average count per slice and the volume fraction (E) (58).

ing the validity of contrast-enhanced and non-enhanced PDUS, a flow signal score was used for power Doppler images and a vascular score in arthroscopic video recording. Reviewing the PD images prior to and after contrast medium by two experienced observers, they obtained an excellent interreader reliability (k -value = 1.0, $n = 18$) (22). Still, these parameters remain on the basis of a qualitative assessment.

A quantitative measurement can be done either by assessing the area under the curve for a defined amount of time (50), by performing a computerized pixel count at the peak contrast phase (27, 49) or by estimating the slope of

the time-intensity curve after the bolus injection (10).

The more recent type of US contrast agents consists of stabilised microbubbles of a sulphur hexafluoride gas (SonoVue®). They provide a higher sensitivity and allow the delineation of weak intraarticular blood flow. This method depicts the blood flow in a grey scale image that provides only inaccurate information on the anatomic structures around the perfused areas. In a multicenter study from the International Arthritis Contrast Ultrasound study group (IACUS), CEUS with SonoVue® was compared to grey-scale and PDUS showing an improved differentiation between active and inactive synovitis (53).

3D quantification methods

Three-dimensional power Doppler ultrasound (3D PDUS) has been proven to provide a good imaging reproduction of the synovial blood flow representing a complete vascular tree inside and on the verge of the synovial tissue (55). This method has already been used for the assessment of physical therapy treatment with local cryotherapy and after intraarticular steroid injection, confirming a reduction of blood flow in patients with RA (16, 17).

In opposition to 2D PDUS, 3D imaging enables a more extensive information about the volume of the dilated and increased number of blood vessels due to the addition of the single cross-sectional 2D images. Therefore, 3D imaging is predestined to generate a more precise quantification of the vascularity and thereby affords the benefit of detecting small changes in the acquired volume in the monitoring of clinical and therapeutic strategies.

4. Blood vessel count

In the 3D image of an intraarticular blood vessel tree, all of the blood vessels inside the region of interest (ROI) can be counted by looking at the rotating blood vessel tree from all directions (Fig. 4). By taking the advantage of 3D imaging, a consistent recognition allows the discrimination of all individual blood vessels within the ROI. It takes about 5 minutes to generate the 3D image of the blood vessel tree by free-hand sweep and another two minutes to count the blood vessels. In the paper of Strunk *et al.*, two observers generated their own 3D data sets for the vessel count. A significant decrease of blood vessels could be evaluated after anti-inflammatory treatment with a good interobserver reliability for this method ($r_p = 0.83$, $n = 75$) (31). The data sets for this study were acquired with a HDI 5000/Philips, using the online 3D Power Doppler function provided by the HDI 5000 vascular software. This is of further importance, because some of the other high-end US systems do not offer such a precise Power Doppler image of the blood vessels which is necessary for the discrimination of the individual vessel branches, instead,

PDUS signals tend to overlay the vessel lumen. It should be clarified that this method only describes the arrangement of the Doppler flow signals inside the region of interest, as the real blood vessel cannot be visualized in the Doppler image.

5. Voxel count

The three-dimensional quantification method is derived from the pixel counting of 2D PDUS and uses the acquired volume of the blood vessels in 3D imaging. "Voxel" is a short form for volume pixel and is obtained in the same region of interest as done before with pixel count in the cross-sectioned 2D image. A voxel-based registration of 3D PDUS images was already used in vascular imaging for the evaluation of the outcome of 3D PDUS and 3D MR angiographic images of carotid arteries (57). A single voxel represents the smallest distinguishable box-shaped part of a three-dimensional image. The volumes are initially thresholded to reduce noise signals, thereafter, a voxel counter which can be connected with the Image J Analysis program from the National Institute of Health in Maryland, USA, counts the thresholded voxels (58) (Fig. 5). As a result of acquiring the whole volume with 3D method, the outcome becomes independent from the selected area of the investigator in 2D method. Therefore, a high interobserver agreement between two blinded, one experienced and one unskilled sonographer, was achieved ($r_p = 0.85$, $n = 75$) (31). However, owing to the manual generation of the data, the 3D imaging remains elaborate and time-consuming. The performance of one examination including the calculation of the voxel count takes about 20 minutes for an experienced investigator.

New developments in Doppler ultrasonography

The development of 3D ultrasound technology allows independent readers to view almost identically the examination of the sonographer, which minimises the differences in interpretation between the sonographer and the second assessor.

4D probes, which provide a direct visualization of the third dimension, are already used in prenatal diagnosis in obstetrics and gynaecological ultrasound (59). The development of a 3D linear array broadband transducer for small parts and superficial tissue (for example RSP 6-12, General Electric, USA) might simplify the volume measurement of the articular blood vessels, because in contrast to the free-hand sweep, the performance of a volume scan is automatically done without movement of the probe. The probe has to be kept unchanged on the region of interest, the automatic volume scan takes less than one minute to generate a whole 4D block of the complete colour and grey scale information which can be adapted afterwards without the patients presence. The volumetric probe therefore provides automatic acquisition of a virtually infinite number of scanning planes which evokes its potential to minimise the operator dependence of US, simplifying the acquisition and interpretation of US findings (60).

By assembling the ultrasound software with an integrated self-acting voxel counting program, the volume measurement of the articular blood vessels could be standardised in future ultrasound systems so that an impartial quantification parameter could be easily accessed in a serial repetition of sonographic examinations during the process of inflammatory activity.

The high costs for the required hardware and software limit the 4D US performance at the moment only to research purposes.

Conclusion

The semiquantitative grading of intraarticular perfusion can be easily and rapidly performed in order to assess the inflammatory activity. Therefore, it is used in most of the clinical studies. However, the interobserver reliability shows only moderate results from different working groups and the outcome results stay on a qualitative basis. The pixel count and the spectral Doppler curve analysis are the first real quantitative measurements for 2D imaging. Both methods are considerably more

time consuming and need the knowledge of an experienced sonographer. The contrast-enhanced US requires the availability of high-end US equipment. It is more expensive and time-consuming and lacks the advantage of US as a completely non-invasive diagnostic tool. In contrast to other medical fields, in rheumatologic US, 3D PDUS is in the early stage of development and especially due to the high costs, every day use is still some way ahead, with quantitative measurements of PDUS and bedside-application methods being the next goals to achieve.

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