A brief history of ultrasound in rheumatology: where are we going

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Received on January 22, 2014; accepted in revised form on January 27, 2014.

Clin Exp Rheumatol 2014; 32 (Suppl. 80): S106-S110.

Key words: ultrasound, Doppler, technology, standardisation

Competing interests: none declared.

ABSTRACT
Musculoskeletal ultrasound is an evolving technique widely used in rheumatology thanks to the numerous advances and the improved work on standardisation. This article deals with the new developments in terms of technology and validation.

In recent years, treatments of chronic inflammatory musculoskeletal diseases have increased in effectiveness due to the introduction of biologic therapies, and a more accurate use of existing drugs.

Two major areas of needs have been then highlighted: very early diagnosis of a chronic inflammatory disease, in order to prevent structural damage, and the need to objectively monitor the disease course for improving the cost-effectiveness of therapeutic decisions, leading to the concept of treat to target (1).

A more precise control of the disease process has also been achieved by the rapid development of imaging techniques. Among them musculoskeletal ultrasound has become a major subspecialty of diagnostic imaging in rheumatology thanks to the fast progression of its technology, which has facilitated its implementation in clinical and research practices.

An advance of note is the improvement of the probe technology. These include increased frequencies of transducers (for a detailed superficial work) in addition to broadband, compound and harmonic imaging, and improved sensitivity of Doppler (2). Of note the development of three dimensional ultrasound (3D) applied to musculoskeletal evaluation offers an interesting prospect for the volumetric assessment of tissues using both grey-scale and Doppler imaging (3).

The advantages of 3D should include an increased speed of image acquisition, an improved reliability and the potential for image quantification (4, 5). The saved images can be viewed in coronal, transverse, sagittal, axial planes and reconstructed 3D planes. However, current commercialised software is not completely applicable for superficial tissue evaluation due to the reduction in image quality (both grey-scale and Doppler) and consequent decrease of clinical information. Another advance of note is the development of elastography, which permits to study the elastic component of tissues (6-8).

It has been observed that normal tissues are relatively more flexible (elastic) than stiffer pathological ones. Essentially this technology measures the elastic properties of the tissue, providing an additional way of interrogating tissues which is particularly useful when the standard grey-scale and Doppler information, as well as other imaging techniques such as computed tomography (CT) scan or magnetic resonance imaging (MRI) are unhelpful or equivocal (9).

There are several techniques which are known as elastography. These include:

1. compression elastography (strain imaging)
2. transient elastography
3. vibration sonoelastography (10)

In compression elastography, ultrasound images are compared before and after the compression of the tissue in order to compute a 'strain map'. In transient elastography, a low frequency transient vibration is applied and the resulting tissue displacements are detected using ultrasound before and after echo-boundaries occur. In vibration elastography, the image vibration patterns are analysed following the application of a low frequency vibration (50–300 Hz).

In general medicine, elastography has been mainly applied to patients with liver disease and for the investigation of tumours in particular in the breast and prostate tumours (11, 12).

In musculoskeletal diseases has been mostly applied to the investigation of tendon and muscle pathologies or soft tissue mass lesions. In these conditions, it can be quite difficult to visualise very subtle pathological changes with respect to presence, absence or extent. Most published work relates to the rotator cuff, lateral epicondylitis and the Achilles tendons (7, 8, 13, 14). In rheumatology, it may potentially be useful in differentiating fibrotic from non-fibrotic pannus or assessing skin stiffness in scleroderma (15).

Another development relates to the capability to fusion different imaging techniques.

The concept of fusion imaging describes the simultaneous mapping of one type of image modality onto another pre-acquired image modality. (16). In this way, for example, a live ultrasound examination, using global position sensors can be directly compared and potentially mapped on to a pre-acquired 3D multi-planar re-slice (MPR) CT or MR volume dataset (17).

There are obvious theoretical advantages to using fusion technology. However, whether it provides added value for a clinical setting is uncertain.

Our experience of the technique is that it is time consuming and requires a considerable amount of skill and spatial awareness. It involves 'registering' exact anatomical points seen using each technique.

Another development is the use of contrast agents. To improve the capability of ultrasound to evaluate the perfusion, the use of contrast agents can be helpful. The use of bubble contrast agents has steadily grown in recent years although they are not in routine use in most musculoskeletal imaging centres. There are several different types of bubbles used which have evolved over time (18). They have a number of potential advantages such as increasing the sensitivity of conventional colour and Power Doppler particularly for evaluating low and slow flow vessels seen in inflammatory tissues such as synovitis or enthesitis (18-26) .

The rate or peak level of uptake of bubble enhancement can be measured offering a means of quantifying vascularity. The disadvantages include its invasiveness, its potential exacerbation of existing medical problems involving the heart, relative short window of opportunity for scanning joints due to their short half-life, and its cost effectiveness. Although it has been shown that the use of micro bubbles increases the degree of Doppler signal detected in inflamed joint as well as the number of joints with synovitis in RA patients, we do not know at this time how this information can improve the management of those patients. The value of contrast however may be more visible when applied to the deeper joints such as the sacro-iliac joints or doubtful images as in superficial enthesitis (22, 23, 25). What can be of interest is their development in the field of molecular imaging with the potential to label bubbles with specific markers to either identify regions of interest or to deliver drugs. This has been pioneered in oncology fields but may have applications in rheumatology.

Despite the improvement in the technology and the large possibility of applications, ultrasound is considered as the most operator-dependent imaging modality. The relatively long learning curve and the lack of standardised training criteria are the main obstacles. Because of the rapid evolution of technologies, where the performance of a particular technique is continually developing with possible consequent improvement in efficacy, the standardisation is a challenge and can be difficult to achieve due to the absence of an adequate comparator (27).

In addition, conceptual difficulties can be pointed out: how does one relate outcome to the effect of a diagnostic technique when other factors such as therapy or medical opinion are involved?

In this context a hierarchical evaluative framework was suggested by Fineberg *et al.* in 1977 (28).

This original concept has since evolved into a five-stage framework which has gained widespread acceptance (29).

These five categories are:

1. Technical performance
2. Diagnostic performance
3. Diagnostic impact
4. Therapeutic impact
5. Impact on health.

In 1994 Thornbury *et al.* added a 6^{th} level of evaluation which includes medico-economic consideration which is called social impact (30). This evaluation in stages implies that it is possible for an imaging technique to perform well at one level but not at the next. This means that excellent technical performances not automatically mean good diagnostic performance. In recent years efforts have been put in to validate musculoskeletal ultrasound in rheumatology in order to use this imaging modality both as a clinical and as a research tool. According to the clinical trials the main purpose may be the evaluation of the diagnostic ability of the modality or the ability to measure changes over time often during treatment. Therefore the credibility of definitions of pathology and optimal machine settings must be determined. The inter- and intra-observer reliability must be established in respect to pathology and grading including image acquisition and interpretation should be clearly evaluated. In longitudinal studies the chosen scoring systems must be validated in relation to their sensitivity to change and in relation to clinical outcome.

Technical performance

In musculoskeletal ultrasound, as in other imaging modalities, the first step of standardisation includes the documentation of definitions of normal anatomy and pathology. The ability to do so is indeed linked to the quality of the machine regarding sensitivity and resolution. Therefore, information about machines, settings, post-processing and other technical specifications used to acquire and deliver the images, the positioning of patients, scanning conditions, like room temperature, and other subject-related sources of variability are of great importance. These different aspects have been addressed in several studies (31-35) including a publication on standard reference values for musculoskeletal ultrasound (36). However, the development of software is so rapid that the results regarding technical performance may change over time.

Diagnostic performance and diagnostic impact

Besides the improvement in technology other aspects of the validation process are important such as the diagnostic performance and the diagnostic impact. The quality of research studies in diagnostic imaging can be considered influenced by the methodology chosen and the possible biases in the overall design. These biases can arise in the selection of patients, the choice of the reference standard, and the measurement and interpretation of the results. This is particularly true for musculoskeletal ultrasound which is still considered highly operator dependent when compared to other imaging techniques such as magnetic resonance imaging, computed tomography scan or standard radiography.

To overcome these possible biases a group of experts in musculoskeletal ultrasound created an OMERACT (Outcome Measure in Rheumatology) Ultrasound Group in 2004 (later to become known as the EULAR (European League Against Rheumatism)/OMERACT Ultrasound Task Force). Composed of internationally recognised expert sonographers, the group is working on standardisation of US in as outcome instrument using an established framework for evaluating outcome measurement tools in clinical trial known as the OMERACT filter (37).

This filter is composed of three frameworks: Truth (validity), Feasibility and Discrimination. This resulted in a systematic review that highlighted a number of deficiencies in the validation including lack of ultrasound defined pathology definitions as well as a lack of criterion validity and reliability measures (38).

As a result, the group developed the first consensus derived definitions of ultrasound pathologies (39) which, since then, have ensured a more homogenous research approach in the described pathologies, and the evaluation of the discrimination of the technique was considered a priority of the group (40). Subsequently a number of mainly European-based projects were undertaken to assess the reliability ultrasound in inflammatory arthritis, in order to develop validated scoring system for the most common elementary lesions (*i.e.* synovitis, enthesitis, tenosynovitis, erosions, dactylitis and crystal-related lesions) (41-43). Numerous studies have demonstrated the diagnostic capability of ultrasound with regards to synovitis detection in RA, however the credibility and responsiveness of ultrasound in the context of clinical trials is an ongoing work (43). In particular, data about its added value over standard clinical measurements are under evaluation. The main questions at the moment are the appropriate number of joints to scan according to the purpose (*i.e.* diagnosis or follow-up evaluation) and the minimal level of activity (*i.e.* the threshold between normal and minimal abnormal findings). A recent study has suggested that ultrasound is at least comparable with clinical examination when evaluating joints prospectively. (44, 45). However, a systematic review of scoring systems and number of joints to scan showed that even though it has the potential of measuring inflammatory activity it needs further evaluation in term of homogeneity before it can be used to guide clinical decisions or used as an end-point in clinical trials (46).

Therapeutic impact and impact on health

There is only one single study evaluating the therapeutic impact of applying ultrasound in daily clinical practice. The study evaluates the impact of using ultrasound on the clinical decision to treat with local corticosteroid injections in inflammatory conditions in the foot. The study found that ultrasound frequently changed the diagnosis and consequently the treatment (47), and may also improve the short-term outcome. Further studies are warranted in this area. Regarding the impact of ultrasound on health, no published studies exist.

How to move from validation to clinical practice

In this process, ultrasound education has a prominent place. Only by ensuring high quality courses it is possible to ensure knowledge on anatomy and scoring systems which permits to implement a correct and standardised use of ultrasound in daily practice.

In rheumatology, the decrease in price of equipment has in fact resulted in facilitating the distribution of machines in the departments and the high image resolution and soft tissue contrast has improved the interpretation of ultrasound images themselves. This widespread use has led to an increasing demand for training and for the development of educational resources such as courses. At country and European level several approaches have been developed for that purpose, and different curricula have been suggested for rheumatologists who wish to learn ultrasound (48). Most of them have proposed a core set of competencies required for a beginner, intermediate and expert sonographer in rheumatology (49). This kind of approach, associated with a standardisation of teaching, represents the basis of EULAR sonography courses which have been running yearly since 1998. A set of EULAR recommendations for the content of ultrasound courses was recently published by the EULAR /OMERACT group (50).

Conclusion

Improvements in ultrasound technology have contributed greatly to the widespread use of this tool in rheumatologic practice increasing enormously the fields of its application. However the process of developing acceptable, standardised outcome measures requires effort and is often not achieved in medicine. This is particularly true in case of imaging (especially ultrasound) because of the rapid development of the technique. Since 2000 several efforts have been made for assessing the credibility, the reliability, and the discrimination (including diagnostic performance and reliability) of musculoskeletal ultrasound. These aspects have been globally established, the evaluation of diagnostic and therapeutic impact still needs further work.

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