

# ULTRASOUND ELASTOGRAPHY IN CLINICAL DIAGNOSTICS AND IN SCIENTIFIC RESEARCH ON MUSCLES

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**Abstract** Ultrasound elastography is a revolutionary medical imaging technique, enabling a quantitative and qualitative evaluation of tissue stiffness. This paper presents, based on published evidence, a wide range of possibilities for this method in clinical trials and scientific research. The use of dynamic elastography avoids the undesired influence of force applied to the tissue by the elastograph probe on the information content of the obtained image. In clinical practice, elastography is used to identify and examine the pathological condition of soft tissues (including cancer lesions and tendonitis) and to diagnose neuromuscular diseases. It is also used in scientific investigations as a non-invasive method to study the structure of skeletal muscle, including muscle thickness, fiber length and pennation angle using standard ultrasonography mode; it is also possible to obtain information about physical properties such as stiffness. Ultrasound elastography could also be a useful tool for physiotherapists monitoring the rehabilitation process. Based on the results of these studies, advances in elastographic imaging technology, and progress in biomedical diagnostic methods, elastography is expected to become a common method used in clinical diagnostics and scientific research.

**Key words** diagnostic imaging, stiffness, skeletal muscles, neoplasm

## Introduction

Palpation is a basic diagnostic method. The earliest documented mentions of palpation are found in the Elebra Papyrus and the Edwin Smith Papyrus, from 1500 BC. In ancient Greece, Hippocrates was a main propagator of palpation. Nowadays, it is one of the basic examination methods used in medical practice (e.g. palpation of the abdomen and lymph nodes), in physiotherapy practice (e.g. palpation of muscle, ligaments, and bone structures), as well as by patients themselves (e.g. breast cancer prevention). During palpation, the investigator senses the position of organs, their ability to displace and their stiffness by applying pressure to the examined part of the

body. One should emphasize that this method has its limitations, i.e. it is subjective and requires an experienced investigator. Not all organs are suitable for palpation, e.g. the kidneys, and in addition the quality of examination depends on body constitution and body mass. Whereas massive and on the advanced stage pathological changes can already be quite well palpable, in many cases, small changes are impossible to examine. Taking the above limitations into consideration, ultrasonography (USG) is now routinely applied in medical practice. This method of imaging is based on phenomena associated with the propagation of mechanical waves with ultrasound frequency through tissues, which allows the examiner to observe very small structures. Initially, USG was used exclusively for the detection of defects in metals, but since the 1970s, it has been popular in clinical diagnosis. However, USG images do not contain any information about tissue properties such as stiffness, defined as displacement caused by an external force (Hooke's law). In medical practice, information about tissue properties could be helpful in cancer diagnosis. To address this problem, ultrasound elastography (UE) was developed the 1980s and 1990s as a USG method with the ability to map tissue stiffness (Wells, Liang, 2011; Gennisson, Deffieux, Fink, Tanter, 2013).

## **Imaging by ultrasound elastography**

Measuring stiffness by UE is based on Young's modulus, which defines the relationship between stress and deformation in a material. There are many advantages of UE, such as more precise detection of changes even at an initial stage of progression, which can lead to earlier implementation of a treatment. UE has become a valid tool in clinical practice, and is often called 'palpation imaging'. The main advantage of UE over palpation is its repeatability and the ability to examine deeper structures (Gennisson et al., 2013; Drakonaki, 2012).

## **Methods**

Assessment of stiffness is obtained as a result of the analysis of deformation caused by the impact of an external force of probe (the quasi-static method) or an internal force generated by a shear wave (the dynamic method) inside tissue.

### **The quasi-static method**

In the quasi-static method, often called strain imaging, Young's modulus is estimated based on deformation before pressure applied by the probe (pre-compression image) and after (post-compression image) (Szabo, 2004). In practice, the value of the force is unknown, which means that the result is not precise, so this method is mainly used for preliminary estimation (Gennisson et al., 2013; Ophir et al., 1999).

In contrast, the dynamic method utilizes forces, variable over time, that are generated in tissues as a result of the influence of ultrasound. In diagnostic practice, two kinds of waves are applied: shear waves and compression waves. Compression waves propagate very quickly at high frequencies while shear waves propagate slowly and at lower frequencies. The speed depends on the relationship between deformation and force, which is described by the shear modulus (Kirchhoff modulus). For most of human tissues, the value of Young's modulus is approximately three times greater than the shear modulus (Gennisson et al., 2013). The fundamentals of shear wave imaging (SWEI) that utilizes shear waves in clinical practice are described by Saravzyan and co-authors (Saravzyan, Rudenko, Swanson, Fowlkes, Emelianov, 1998). The main advantage of the dynamic method is that the results do not depend on the pressure of the probe.

In comparison to the quasi-static method, using shear waves allows for quantified measurements. However, imaging with both compressional and shear waves can cause interference waves as a result of simultaneous influences on tissues. Based on these restrictions, transient elastography depends on force generated in the form of an aperiodic impulse that reduces interference (Gennisson et al., 2013; Franchi-Abella, Elo, Correas, 2013).

### **Dynamic techniques used in ultrasound elastography**

In contrast to the quasi-static method that is performed only one way, the dynamic method encompasses several techniques. Vibro-acoustography, invented by Fatemi and Greenleaf (Fatemi, Greenleaf, 1998; 1999) is an extraordinarily sensitive high-definition imaging technique using low frequencies. It exploits two confocal waves that differ in frequency. Interference between these two waves causes the deformation of tissues. Based on the response of tissues to the vibration evoked by ultrasound and recorded by a hydrophone, images are created that show the amplitude of deformation. This highly sensitive technique can even detect microcalcifications of the carotid artery (Gennisson et al., 2013; Szabo, 2004).

Acoustic radiation force impulse imaging (AFRI) was developed by Nightingale and co-authors in 2001 (Nightingale, Palmeri, Nightingale, Trahey, 2001). In contrast to the vibro-acoustography, AFRI uses only one focal wave. The force of the radiation slightly displaces tissue around a focal spot and simultaneously with known, programmed time intervals images are recorded. Definitive images showing deformation of the examined area consists of particular images. This technique is similar to the quasi-static method, but it is more precise. Unfortunately, only assessing stiffness exclusively near a focal spot is possible (Gennisson et al., 2013; Szabo, 2004).

Transient elastography consists of generating impulses in tissues and registering shear wave propagation using a custom-constructed probe. This probe, the 1D transient elastography probe, was constructed at Institute Langevin in 1995 (Catheline, Thomas, Wu, Fink, 1999). This technique is becoming widely used in assessing chronic diseases of the liver and for quantifying hepatic or splenic fibrosis, reducing the number of biopsies by more than 50%. Since 2001, Echosens Co. has commercialized this technique and given it a trade name, FibroScan (Gennisson et al., 2013).

Supersonic Shear Imaging was also developed at Institute Langevin. The idea of analyzing shear wave acoustic radiation arose based on SWEI assumptions. This technique merges acoustic radiation and ultrafast ultrasound imaging. In clinical practice, it is used for the diagnosis of different organs, most commonly for breast examination (Gennisson et al., 2013; Szabo, 2004).

### **Ultrasound elastography in clinical diagnosis**

The application of ultrasound elastography allows for detecting changes in the stiffness of tissue, a sign of many diseases including neoplasia and fibrosis. This imaging technique facilitates diagnosis as well as the monitoring of disease and treatment course. Primarily, UE has been used in breast cancer prevention and to assess the progression of hepatic fibrosis. Currently, research is being conducted into the utility of UE in the assessment other tissues like the muscles, thyroid gland, or kidneys. In the case of breast examination, this technique is extremely useful, especially after detecting abnormalities during regular ultrasound examination (Balleyguier et al., 2012). The main mass of benign tumors is more able to deform in comparison to malignant tumors. Often, when examining a benign tumor, the lesion can be identified as a false positive, e.g. a fibrous fibroadenoma or scar tissue. Thus, UE is not an appropriate tool to monitor the recurrence of a tumor after treatment, since scar tissue

often develops after surgery or radiotherapy. In addition, complications can occur after breast implant surgery, such as capsular contracture, i.e. the formation of a capsule of scar tissue around the implants, so using UE may be difficult (Rzymski, Kubasik, Opala, 2011). In other cases, the results might be identified as a false negative, e.g. in the case of mucinous cancer, cancer with an inflammatory stoma, or lesions smaller than 5 mm in diameter. During the diagnostic process for cancer with an inflammatory stoma, ordinary USG is recommended, because the morphology can indicate the malignant characteristics of lesions. Examination with both USG and UE makes the diagnosis more reliable, since the methods are complementary. The advantage of using UE is the fact that it shows the local extension of cancer, which is not always seen in USG. The image received using UE is similar to size of changes in tissue confirmed histologically (Barr et al., 2012). In the case of breast cancer, it is important to determine whether the cancer has spread to the axillary lymph nodes. Metastatic axillary lymph nodes, considering their rich vascularization, have the tendency to be more resistant to deformation in comparison to inflammatory lymph nodes (Choi et al., 2011).

Another important benefit of UE is in the diagnosis, monitoring, and treatment of chronic liver diseases that lead to fibrosis, e.g. hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) infection, metabolic disease, autoimmune disease, and toxin exposure (e.g. alcohol). Comparatively 20 to 30% of patients with chronic liver disease evolve into cirrhosis. The degree of cirrhosis is described by the METAVIR score, developed by Bedossa and co-authors, members of the French METAVIR Cooperative Study Group (Bedossa et al., 1994). Until recently, liver biopsies have been the gold standard tool to assess liver disease, but now testing for blood serum markers using Fibrotest and UE assessments have become more common (Castera, 2012; Frulio, Trilluad, 2013).

During the UE examination, the patient is supine with the right arm in maximum abduction, in order to expand the intercostal spaces. One of techniques used is transient elastography. It has been described several times for liver diagnosis as it provides excellent repeatability and reproducibility (Fraquelli et al., 2007). It is recommended by the European Association for the Study of the Liver (EASL) (EASL, 2011). However, it has its limitations i.e. absence of ultrasound imaging, difficulties with examining obese people or people with narrow intercostal spaces (Frulio, Trilluad, 2013; Fraquelli et al., 2007). Another commonly used technique is ARFI. Unlike transient elastography, it allows for USG imaging of examined structures. Another advantage is the possibility of adjusting the wavelength depending on the position of the organs. Major drawbacks of ARFI include the very small measurement region and the lack of extensive validation (Karlas et al., 2011). The quasi-static method can be useful in assessing the liver in patients with ascites, but it is a non-quantitative and operator-dependent technique (Frulio, Trilluad, 2013). There has also been some research concerning the use of UE in the evaluation kidney fibrosis in chronic disease. However, due to the complicated morphology of the kidneys and their position, the analysis of the results can be more complicated in contrast to the liver, indicating the need for further research (Grenier, Gennisson, Cornelis, Le Bras, Couzi, 2013).

### **Ultrasound elastography in scientific research on muscles**

UE can be applied in scientific research on the muscles. This paper discusses published research on humans as well as animals, performed for the quantitative evaluation of muscle stiffness. Different methods are used to assess muscle stiffness, but they have some restrictions. They are often based on a qualitative not quantitative evaluation, and most measure the stiffness of a group of muscles responsible for movement at a joint, not individual muscles. Myotonometry can be used to assess the stiffness of individual muscle. The most common device for

this purpose is the Myoton (the most recent version is the MyotonPRO). It is a hand-held device that enables the examiner to perform a non-invasive measurement of the properties of muscles, tendons, and ligaments including stiffness, elasticity, muscle tone, creep, and relaxation time. It records the responses of tissues due to deformation caused by the movement of a small probe. Based on the dynamic function of muscle, it is important to perform the examination in real-time, providing a quantitative evaluation. Shear wave elastography seems to fulfill these conditions and has become a useful tool for diagnostic purposes.

In order to validate UE for assessing of skeletal muscle stiffness, studies have been conducted on the brachialis muscle dissected from female swine (Eby et al., 2013). The specimens were positioned in a material testing machine (model 312; MTS Minneapolis, MN) for tensile testing and UE. During testing, the force was measured by a load cell (model 3397; Lebow Products; Troy, MI) and deformation of muscle was assessed on the basis of changes in the cross-sectional area (CSA). Then, using Young's modulus, muscle stiffness was evaluated. Measurements were also conducted using the SWEI technique. The probe was placed in three positions according to the long axis: parallel, perpendicularly and at a 45° angle. There was correlation between the results obtained from Young's modulus and SWEI with the probe parallel to the long axis. The results showed an increase in muscle stiffness with a higher tensile load. The results obtained perpendicularly and at a 45° probe position were apparently different from Young's modulus. This was related to the fact that shear waves propagate more efficiently along muscle fibers in comparison to propagation across fibers. For this reason, it is important to investigate muscle morphology by USG before using shear wave elastography.

Another study (Takashima, Arai, Kawamura, Hayashi, Takagi, 2017) on use of UE assessed muscle stiffness caused by a disease or disorder of the joints or muscle system. It included people suffering from temporomandibular disorders (TMD) which manifest as myofascial pain and the appearance of trigger points sensitive during palpation. The diagnostic process of TMD is not objective, because it is based on a subjective assessment by the patient and the investigator. The masticatory muscles, including the masseter muscle, were examined by researchers in Japan with use of SWEI. They examined a group of women suffering from bilateral masseter pain and compared the results to a healthy, pain-free control group of women. It was found that women with TMD were characterized by two-times greater stiffness of the masseter muscle in comparison to the healthy group. These findings indicate the usefulness UE in masseter muscle evaluations.

In order to establish the optimal force applied during massage, muscle stiffness was also examined. TMD therapy can include massage, acupuncture, manual techniques used by physiotherapists, even meditation. Additionally, therapists use oral splints and occlusal adjustments. Information about masticatory muscle stiffness might facilitate the application of force during massage and assess therapeutic progress observed as a decrease in muscle stiffness compared to the initial examination. To obtain this information, a study was conducted by Y. Arij et al. (2009), it was performed on a healthy group of volunteers (men and women) and group of women with TMD. Measurements were taken by the same investigator, who placed the probe on the masseter muscle perpendicular to the ramus, 15 mm above the inferior border of body of the mandible. There were two measurement regions: the masseter muscle (region A; 100–125 mm<sup>2</sup>) and the subcutaneous fat covering the masseter muscle (region B; 20 mm<sup>2</sup>). The masseter stiffness index (MSI) was calculated. Temporomandibular joint therapy was conducted with the use of a specially constructed robot, i.e. the Waseda-Asahi Oral Rehabilitation Robot No. 1. (WAO 1). Massage was performed at different pressure forces: 1–2 N, 6–8 N, and 10 N. It was observed that patients with the lowest MSI chose most comfortable massage with 1–2 N of pressure, while those with a higher MSI chose 6–8 N and

patients with the highest MSI selected 10 N of pressure. The results showed that the evaluation of muscle stiffness by UE might help choose the optimal massage pressure and be useful in the estimation of therapeutic progress.

Another group of scientists from Korea (Park, Kwon, Kwon, 2018) evaluated the utility of UE in the examination of shortening or contraction of the sternocleidomastoid muscle (SCM) in infants with congenital muscular torticollis (CMT). Based on SCM thickness, participants were divided into two groups. Infants with an SCM thicker than 10 mm (group 1) were subdivided into two subgroups based on limitations in the passive range of motion (PROM) of neck rotation: 1S with severe and 1M with moderate limitation. Group 2 contained infants with an SCM thickness less than 10 mm. Measurements of SCM stiffness were conducted bilaterally with the ARFI technique. In group 1, the stiffness of the affected SCM was much higher compared to the unaffected one. The results showed greater stiffness of the SCM in group 1S in contrast to group 1M, with a positive correlation between muscle stiffness and PROM limitation. Furthermore, SCM stiffness in group 1 was higher than in group 2. These findings indicate that UE can be used to evaluate SCM stiffness in infants with CMT.

Although most studies use dynamic UE methods, a group from the USA (Gao et al., 2018) decided to conduct a study using strain imaging to estimate post-stroke spasticity in the biceps brachii muscle in healthy volunteers and stroke survivors. Changes in muscle length were induced by passive elbow extension (from 90° to 0° in healthy volunteers and maximally extended in stroke survivors without causing pain) and flexion, with the probe placed on the muscle belly. As an external force to deform the muscle, a 1 kg sandbag was attached to the probe. The results showed higher muscle stiffness in spastic muscles compared to non-spastic and healthy muscles. Moreover, impaired biceps brachii displacement was observed during passive extension of the elbow in spastic muscles in contrast with healthy and non-spastic muscles. This study provides evidence for the feasibility of strain imaging for estimating biceps brachii stiffness.

A recent report provided a comparison of two methods used to measure muscle stiffness, i.e. UE and myotonometry (Kelly et al., 2018). The study was conducted on three different muscles: the infraspinatus, erector spinae and gastrocnemius in healthy volunteers. Measurements were taken with the use of shear wave UE and MyotonPRO. The UE probe was placed parallel to the muscle fibers, and the MyotonPRO probe was placed in the center of the outline for the UE probe. Muscle stiffness was measured under three conditions: relaxed, 40% and 80% of maximum voluntary isometric contraction (MVIC) at a specific position for each muscle. The force of contraction was measured by a hand-held dynamometer (HHD, microFET2). In order to perform at the proper percentage of MVIC, participants observed their force biofeedback on a monitor. UE showed statistically significant differences between a contracted and relaxed erector spinae, but no significant difference between 40 and 80% of MVIC. Considering all conditions, there were no differences in the infraspinatus and gastrocnemius muscles. However, all measurements taken with MyotonPRO were significantly different. Despite the fact that the measurements were carried out by three different therapists, the intrarater reliability was good to excellent for all MyotonPRO measurements, in contrast to UE where it was generally lower. It is worth emphasizing that, in each studied muscle across all conditions, the scatter plots showed a positive correlation between UE and MyotonPRO.

## Conclusions

UE is a modern medical imaging technique that can provide a quantitative and qualitative evaluation of tissue stiffness. Although it is now routinely used in medical practice, further scientific studies are needed to provide evidence for the accuracy and reliability of this technique in assessing the properties of tissue as well as structures

and organs. Initially UE, was used as a diagnostic tool in the liver, kidney and breast, but it can now be utilized to estimate muscle stiffness.

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