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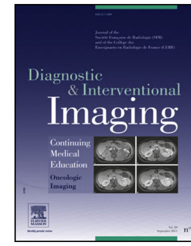

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Ultrasound elastography: Principles and techniques

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Impulse elastography;
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Abstract Ultrasonography has been widely used for diagnosis since it was first introduced in clinical practice in the 1970's. Since then, new ultrasound modalities have been developed, such as Doppler imaging, which provides new information for diagnosis. Elastography was developed in the 1990's to map tissue stiffness, and reproduces/replaces the palpation performed by clinicians. In this paper, we introduce the principles of elastography and give a technical summary for the main elastography techniques: from quasi-static methods that require a static compression of the tissue to dynamic methods that uses the propagation of mechanical waves in the body. Several dynamic methods are discussed: vibro-acoustography, Acoustic Radiation Force Impulse (ARFI), transient elastography, shear wave imaging, etc. This paper aims to help the reader at understanding the differences between the different methods of this promising imaging modality that may become a significant tool in medical imaging.

Ultrasonography is a widely used medical imaging technique with many clinical applications. Used in clinical practice for more than 40 years, it is highly regarded for its ease of use, real-time capability, portability and low cost. Based on the propagation of mechanical waves and more particularly on high frequency compressional waves aka ultrasound, it allows the construction of morphological images of organs, but lacks a fundamental and quantitative information on tissue elastic properties; indeed the bulk modulus that governs the propagation of ultrasound is almost homogeneous in the different biological tissues and does not depend on tissue elasticity [1]. Elastography, whose development started about 20 years ago, aims at imaging tissue stiffness, which provides an additional and clinically relevant information. Mapping the stiffness can either be estimated from the analysis of the strain in the tissue under a stress (quasi-static methods), or by the imaging of shear waves, mechanical waves, whose propagation is governed by the tissue stiffness rather than by its bulk modulus.

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From a physics point of view, elastography aims to quantitatively image the Young's E modulus, the physical parameter corresponding to the stiffness. This has two important advantages:

- the Young's modulus, noted E, exhibits important variations between different biological tissues, which makes it ideal for the characterization of different tissues with an excellent contrast [1];
- the Young's modulus characterizes the stiffness of a tissue, which is exactly the quantitative reproduction of a clinician's palpation and has relevant diagnostic value.

This simple and intuitive relationship between palpation and elastography calls for many applications of this ''palpation imaging'' such as breast tumor characterization and hepatic fibrosis staging where it was successfully been validated. Wherever palpation has been shown to have a clinical value, elastography can be seen as a relevant tool for diagnosis.

Moreover, although palpation requires a direct contact and can only be applied to superficial organs, many elastography techniques can also be applied to deep organs opening new possibilities of diagnosis.

To assess the Young's modulus of the tissue, all elastography techniques rely on the same basis: an external force is applied to the studied tissue and the resulting movements are then followed. The external force can be classified according to two means of excitation: the static methods (or the quasi-static method) and the dynamic methods.

The different methods

Quasi-static methods

In the case of quasi-static elastography, a constant stress is applied to the tissue. The displacement and the generated strain ε are then estimated using two-dimensional correlation of ultrasound images. The Young's modulus is then given via the Hooke's law ($\sigma = E.\varepsilon$), which links stress and strain in a purely elastic medium. In practice, since the applied stress is unknown, only the strain is displayed, this strain map is sometimes called the elastogram. This technique has the advantage of being easy to implement but the unknown stress distribution prevents any quantitative estimation of the local Young modulus in kilo-Pascal. Nevertheless, this method has been deployed on many commercial ultrasound diagnostic-imaging devices, as a simple yet indirect information on the tissue stiffness.

Dynamic methods

In dynamic methods, a time-varying force is applied to the tissue, it can either be a short transient mechanical force or an oscillatory force with a fixed frequency. A time-varying mechanical perturbation will propagate as mechanical waves which in a solid body can be compressional waves or shear waves (Fig. 1). The compressional waves propagate very quickly in the human body (~1500 m/s), and at high frequencies, these waves, also known as ultrasounds, can be used to image the body. Shear waves, which are only generated at low frequencies (10 Hz to 2000 Hz) due to absorption at higher frequencies, propagate more slowly, and their speed (~1—50 m/s) is directly related to the medium shear modulus ($\mu = \rho V_S$ 2), where ρ is the density of the area (~1000 kg/m^3).

In biological tissues, which are almost incompressible, the Young's modulus can be approximated as three times the shear modulus ($E = 3\mu$). The shear wave propagation speed can thus be used to map the Young's modulus quantitatively.

Dynamic elastography techniques, which rely on shear waves propagation, can produce quantitative and higher resolution Young's modulus map compared to quasi-static methods. The use of shear waves, however, requires a more complex system, able to generate the shear wave (mechanical vibrator or ultrasound radiation pressure) and to image the small displacements induced by the shear wave (ultrafast or stroboscopic ultrasound).

Comparison of the two approaches

Both static and dynamic methods use ultrasound to track the displacements in the tissue either due to a static stress or to the propagation of the shear wave. Both approaches are similar in that they apply an external stress and then monitor the induced strain, although the frequency range is very different: 0 Hz in static elastography and 50 to 500 Hz in dynamic elastography.

Quasi-static elastography cannot give a quantitative value for the Young's modulus since only the strain can be estimated and the applied stress is unknown. It is thus impossible to recover the Young's modulus using Hooke's law.

By using the wave equation of shear waves, dynamic elastography do not require to know the stress distribution

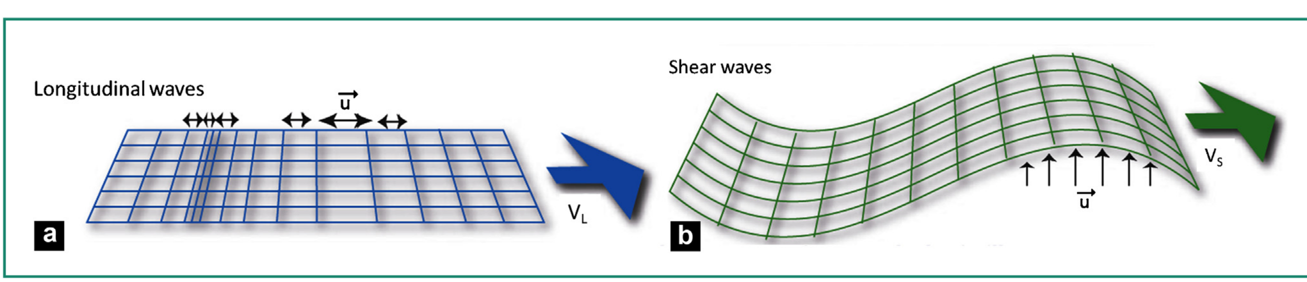

Figure 1. a: the longitudinal wave (P) spreads by successive volume variations of the medium. The displacement of the medium u is parallel to its propagation direction with a speed of VL. The ultrasounds used in ultrasonography are longitudinal waves. Sound is also a longitudinal wave in the range of audible frequencies; b: the shear wave (S) spreads by successive movements that are perpendicular to the direction of propagation with a speed of VS.

to estimate the local Young's modulus. However, this technique suffers from the presence of both compression and shear waves in the studied medium. Thus the overlapping waves require the use of tools that reduce the quality of the estimations. In addition, this technique is very sensitive to boundary conditions (the waves rebound at the interfaces and are mixed together), which makes it very difficult to distinguish between compression and shear waves.

Faced with these limitations, transient elastography was developed at the same time and provides several technological improvements. The main advantage of transient excitation is to naturally separate shear waves from compression waves, since shear waves are three times slower than compression waves. Thus measurements of the propagation speed become relatively more straightforward. The major difference in the different transient elastography techniques results in the mechanical source of excitation. By studying the propagation of only the shear waves induced by a specific mechanical excitation, it is possible to estimate the viscoelastic properties of the investigated tissues. Sarvazyan proposed an expression linking elasticity of tissues to the speed of transient shear waves induced by local and transient mechanical vibration.

Elastography techniques

Quasi-static method elastography

As its name indicates, this is a technique based on a quasi-static deformation ε of the medium: a compression is applied to the tissue and an image of the strain induced is extracted from the difference the reference image and the compressed image (Fig. 2). Most often, the displacement, which is relatively large, is calculated by 2D correlation of conventional ultrasound images (called B-mode images). Strains are then calculated by spatial derivation following one or possibly two directions for the most evolved approaches. This was the first elastography technique, developed by the Ophir Group [2] at the beginning of the 1990s. Today, the technique is being tested in breast lesion characterization with interesting results [3].

Several commercial implementations of this process were developed at the same time by different constructors as for example:

- Hitachi with its ''Real-time Tissue Elastography''. Based on a quasi-static elastography method, it allows to qualitatively show the stiffness of tissue in a color image super imposed on the standard ultrasound B-mode image;
- Siemens with its ''eSie Touch Elastography Imaging'' method.

The main limitations of this technique are still the control of the stress applied, which remains operator dependent, and the absence of a specific quantification. In addition, the use of a stress applied by the operator limits the technique to superficial organs, mainly the breast or the thyroid. This technique is simple to implement and is widely spread in the world of radiology, and has been mainly validated for breast lesions classification [4] (Fig. 3).

Vibro-acoustography

Vibro-acoustography is a dynamic elastography method based on the ultrasound radiation pressure and developed by the American Group of James Greenleaf [5]. The radiation pressure is a volumic force created by transfer of momentum within the medium [6]. This momentum is related to the absorption of the ultrasound wave. Vibro-accoustography uses two confocal ultrasound beams with slightly different frequencies $\omega 0$ and $\omega 0 + \omega$. It results in beats at the frequency ω, which give rise to a modulated force at frequency, ω only at the focal spot. Therefore, everything looks like if

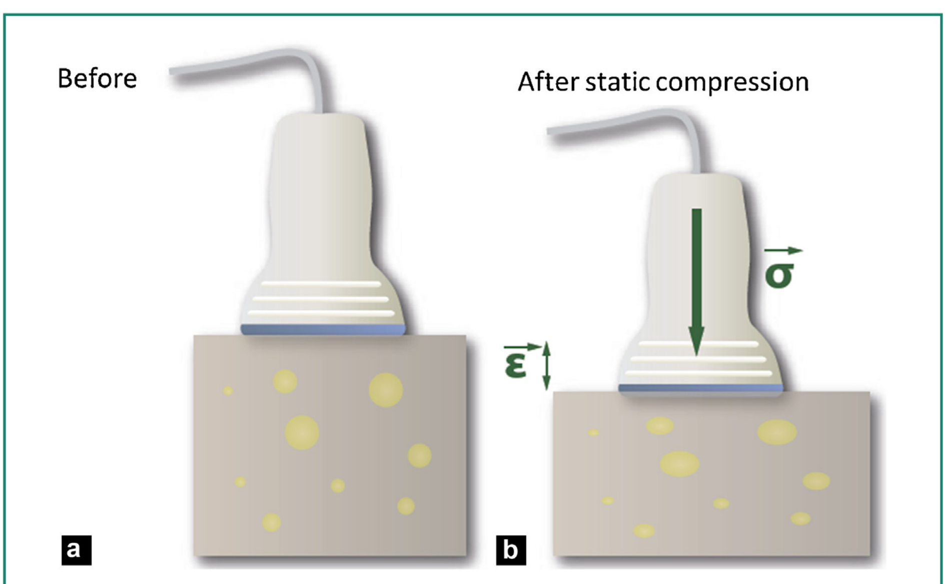

Figure 2. Static elastography reconstructs an elastogram or ''strain image'' by calculating the deformations related to a static compression imposed by the operator via the ultrasound array. The boundary conditions and the variability of the applied stress, which are very important parameters, are however not taken into account.

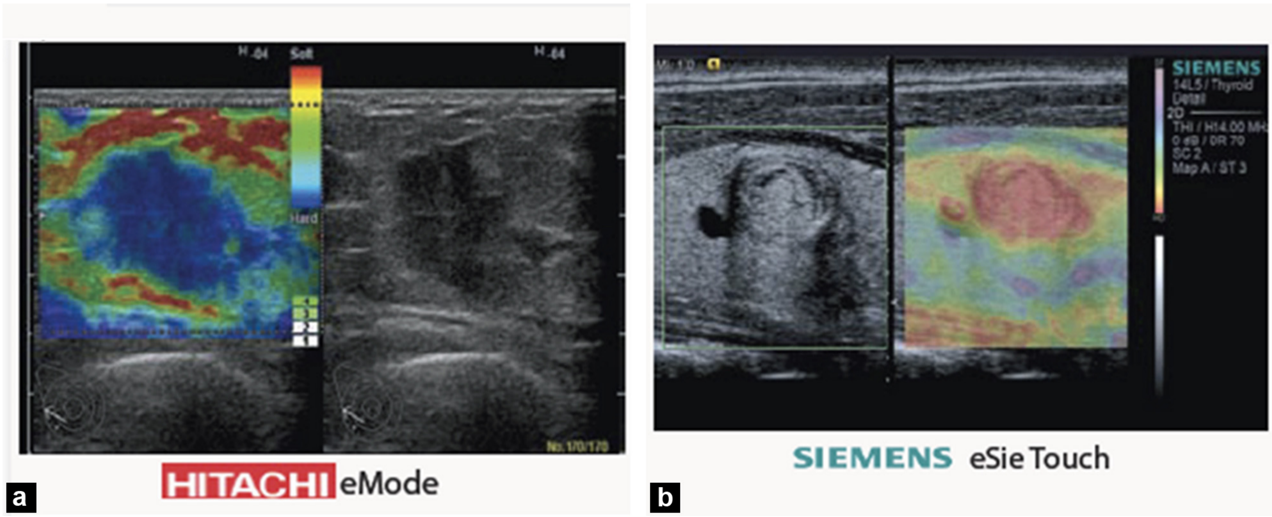

Figure 3. Hitachi with the ''eMode'' commercialized in Hi Vision 900 ultrasound machines and Siemens with its ''eSie Touch Elastography Imaging'' mode in Acuson Antares ultrasound machines are the first commercial versions of static elastography: a: strain image of a carcinoma; b: strain image of the thyroid.
References: www.hitachimed.com, www.siemens.com.

the target vibrates at the frequency ω. It is then sufficient to listen to the sound produced by this excitation to deduce the mechanical properties of the target, particularly its stiffness. For this, one can place a hydrophone that records the response of the target at the frequency ω. In order to create an image, the entire area is swept by moving the focal spot and listening to the response for each point of the image (Fig. 4).

However the sweeping of the entire image causes an important deposit of energy within the medium and a long acquisition time, which makes its implementation in real-time and in vivo difficult. In particular, the measured parameter depends on the stiffness of the zone, but also on the amplitude of the generated force and the geometry of the vibrating object. Therefore images correspond to a mixture of several physical parameters, including elasticity. Greenleaf's team is now trying to combine this method with mammography systems for the diagnosis of breast cancer and with conventional ultrasound machines [7,8].

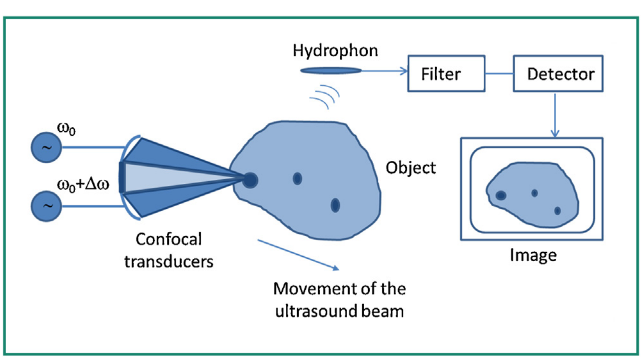

Figure 4. Vibro-acoustography is based on the use of two ultrasound beams at close frequencies and focused on one point of the image, a hydrophone then records the sound wave resulting from the vibration of the tissue induced by the ultrasound radiation force. The image is created by sweeping the zone [6].

Transient elastography methods

Acoustic Radiation Force Impulse Imaging (ARFI) or ''Acoustic Radiation Force Imaging'', is a method developed by the American team of Kathy Nightingale [9].

This technique uses the acoustic radiation force but, unlike vibro-acoustography, ARFI only uses one focalized ultrasound beam. The radiation force slightly displaces the tissue at the focal spot according to Hooke's law. Then the transducer switches into imaging mode and detect displacements of the focal spot by tracking of the ultrasound signal (called ''speckle''). The ultrasound speckle-tracking [10], already used in static elastography, allows to correlate the ultrasound signal window by window in order to detect the displacement of a tissue with sensitivity of less than a micrometer. By window, we mean a piece of an ultrasound signal.

It is therefore possible to follow the displacement and the relaxation of tissue depending on the radiation force. The temporal properties of these relaxation curves allow the deduction of elasticity and viscosity at the focal spot only [11] (Fig. 5).

The ARFI technique also allows reconstructing a complete image by sweeping the zone, like vibro-acoustography. However, this has the disadvantage to increase the acquisition time in order to recover an entire image of the medium, and the deposited energy in the medium, which can cause consequent heating [12,13]. This technique has been tested in vivo in the breast and ex vivo in the prostate. Here again, the measured parameters (displacements, relaxation times, etc.) depend on the Young's modulus of the investigated region, but also on many other parameters, such as the geometries of the beam and of the medium. The technique therefore cannot be used to quantitatively estimate tissue Young's modulus, though the measured parameters strongly depend on it. However, it has been implemented in many commercial ultrasound systems.

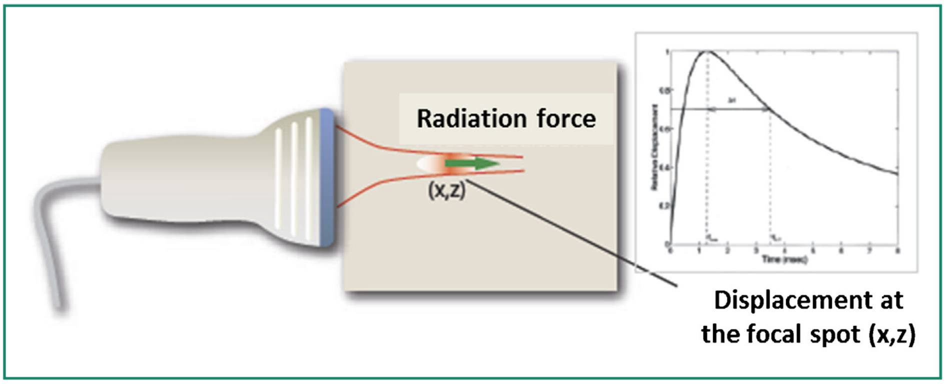

Figure 5. The radiation pressure or ultrasound radiation force, makes it possible to displace the tissue at the centre. The study of the displacement profile, in particular its maximum and its relaxation time, make it possible to obtain information about the stiffness of the medium. This profile of displacement is estimated by axial intercorrelation of the ultrasound speckle on the corresponding line at the focal spot.

Today, Nightingale's team is interested in the propagation of shear waves generated by the radiation force and has recently proposed a new ARFI model called ''ARFI-SWS''. Based on this concept, it allows to quantitatively measure the Young's modulus in a small region of interest [14]. This variation is currently being evaluated for the liver staging [15] and is available on commercial ultrasound systems, such as the Siemens Acuson S2000.

1D transient elastography: the 1D shear elasticity probe

The 1D transient elastography probe was first developed at the Institut Langevin in 1995 by Catheline et al. [16]. It consists of generating a transient impulse (little shock) on the medium and recording the shear wave that propagates within the medium by using an ultrasound transducer (Fig. 6).

First, the front face of the transducer acting as a piston gives a slight mechanical impulse on the surface of medium, which generates a spherical compression wave as well as a spherical shear wave [17]. The displacement generated, which is a function of depth and of time, is thus estimated by correlations of retro-diffused echoes (via ultrasound speckle) recorded at a framerate higher than one thousand time per second with a mono-dimensional ultrasound transducer (5 MHz) (Fig. 7). This device was the first to use the principle of ultrafast imaging in one dimension to visualize in a transient manner the propagation of shear waves.

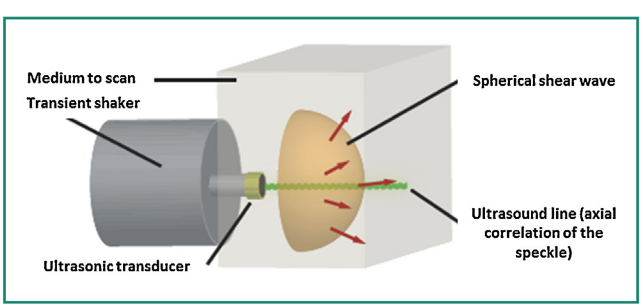

Figure 6. The vibrator gives a low frequency pulse (adjustable from 10 Hz to 500 Hz) in the medium, creating, among others, a shear wave. The ultrasound transducer, which is placed on the vibrator, thus allows following, by axial intercorrelation of the ultrasound speckle and more than one thousand times per second, the propagation of the shear wave depending on the depth over time. We can then deduce the speed of the shear wave and thus the Young's modulus of the medium.

Finally, by measuring the phase for each depth, we extract the phase speed of the shear wave at the central frequency, leading to an estimation of Young's modulus by considering the medium to be homogeneous and non-viscous. This approach, which was initially designed for quality control in the food industry, was then applied to the medical field [18] and developed for the measurement of other mechanical parameters, such as anisotropy, viscosity or elastic non-linearity [19—21].

Since 2001, the company Echosens has been commercializing this technique, 1D transient elastography, under the name FibroScan®. This device allows quantifying hepatic (or splenic) fibrosis by giving an overall score of elasticity at 50 Hz in a given window of depth (from 20 to 60 mm). The 1D transient elastography, a non-invasive method, has become a reference technique in the evaluation of chronic liver diseases and allows a reduction of more than 50% of liver biopsies [22,23].

2D transient elastography

In 1997, at the ''Institut Langevin'', the 1D transient elastography technique was extended to 2D, allowing the creation of elasticity maps of biological tissues. A programmable ultrasound electronic device (Fig. 8), used for time reversal experiments (process of refocalizing acoustic waves) was modified to be able to perform ultrafast imaging based on ultrasound plane wave emission [24]. It allowed storing raw data acquired with a frame rate of more than 5000 images per second. A vibrator was fixed to the ultrasound imaging array, which is then used as an impactor to generate a quasi-plane shear wave (Fig. 9). Once the movie of the propagating shear wave is reconstructed, the wave equation is inverted to recover a map of Young's modulus. The first in vivo tests were carried out in 2003 (Fig. 10) with volunteers at Institut Curie, the results were

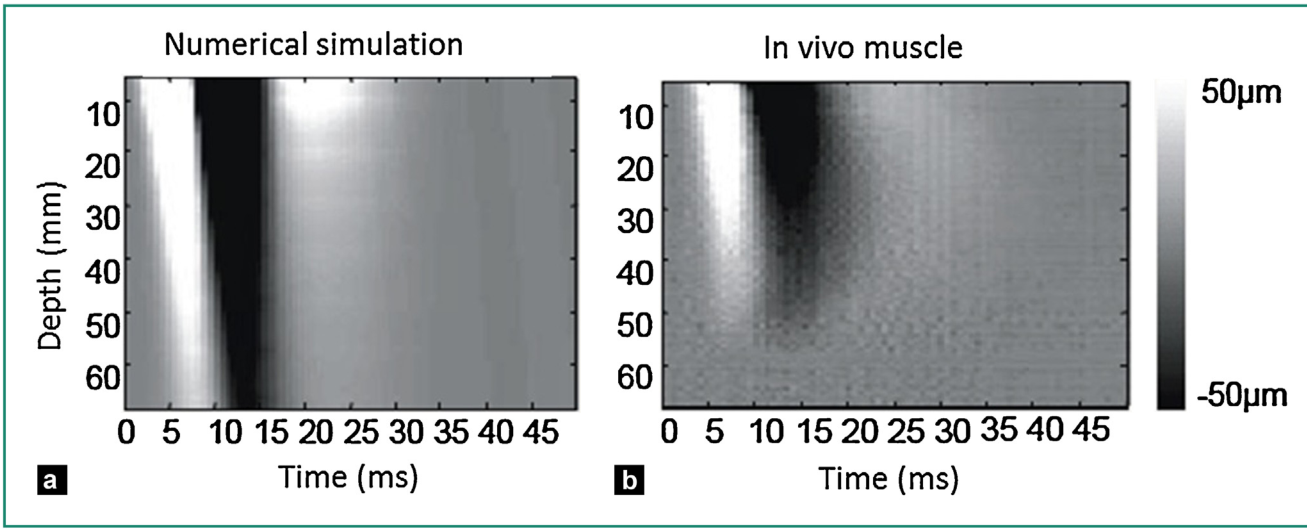

Figure 7. Comparison between the (a) numerical simulation of the time/depth profile and the (b) Time/depth profile in a muscle in vivo. The extraction of the slope allows to work back to the speed of the shear wave and thus the Young's modulus of the medium [18].

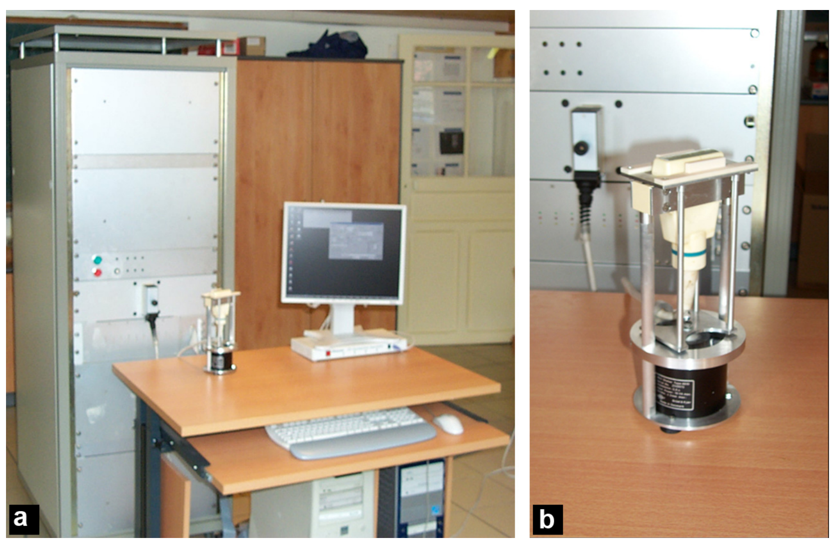

Figure 8. a: ultrafast imaging electronic device developed for the imaging concept of time reversal; b: ultrasound array (4 MHz) fixed on a vibrator allowing to generate via bars a transient shear wave in the studied medium.

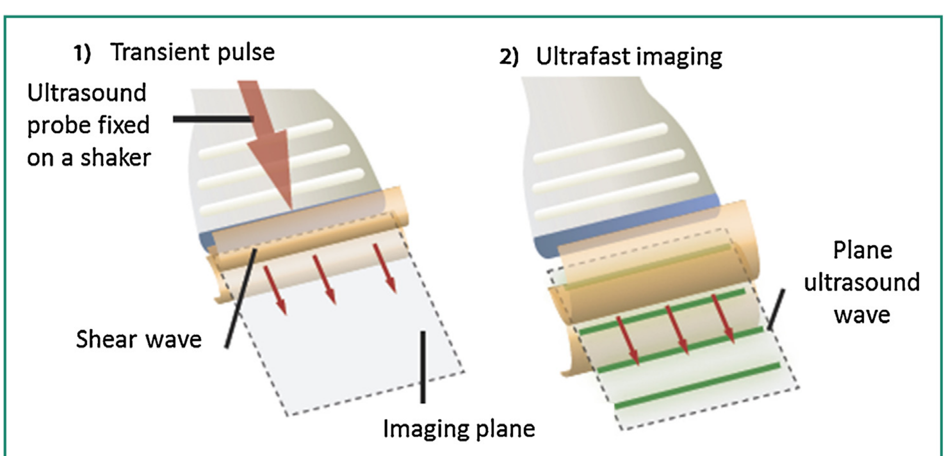

Figure 9. 1: the ultrasound array, mounted on a vibrator, gives a low frequency shock in the medium (around 50 Hz). The shear waves generated on the borders of the array interfere within the imaging plane as a quasi-plane wave propagating on the depth; 2: the ultrasound then switch into an ultrafast imaging mode to follow the shear wave that is propagating through the medium.

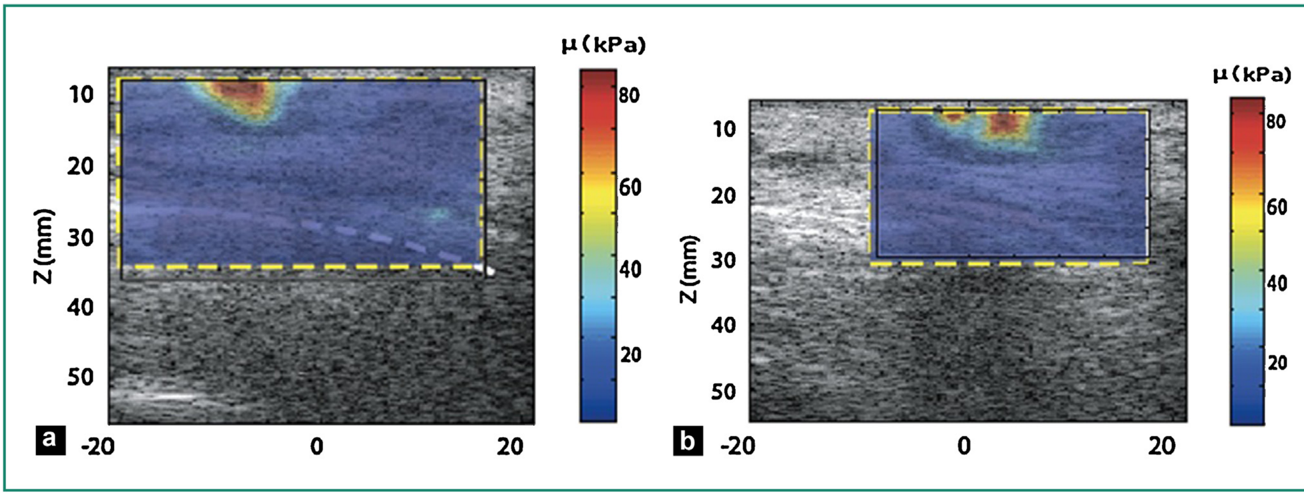

Figure 10. a: breast elastography. An adenocarcinoma appears stiffer in the elasticity image and darker in the ultrasound image; b: second elasticity image of the same lesion [25].

encouraging, but the device was bulky, heavy and difficult to use in practice [25].

The study of shear wave by using ultrafast imaging

The Supersonic Shear Imaging technique is the outcome of researches at the Institute Langevin in transient elastography. The idea of combining radiation pressure or acoustic radiation force and the study of shear waves generated comes from Armen Sarvazyan, which can be considered as a precursor of elastography techniques based on ultrasonic radiation pressure via its technique: Shear Wave Elasticity Imaging [26]. In 2004, two fundamental ideas are developed to overcome the limitations of 2D elastography technique: first acoustic radiation force and second ultrasound ultrafast imaging [27]. These two concepts described below are at the heart of the Supersonic Shear Imaging technique [28] (Fig. 11):

- a Mach cone: ultrasound beams are successively focused at different depths. The different spherical waves generated for each focal beam interfere like a Mach cone [29] in which the source propagates more quickly than the generated shear wave and creates a quasi-plane wave front in the imaging plane (cylindrical in three dimensions). The use of constructive interfaces makes it possible to increase the amplitude of the wave and thus the signal to noise ratio of the displacement field. The generated quasi-plane shear wave in the imaging plane allows also simplifying the propagation hypotheses, which is of great interesting to solve inverse problems. Finally, only one Mach cone allows illuminating almost all of the medium with one plane shear wave; shear wave being generated, the propagation equation of the waves is inverted to rebuild a map of Young's modulus;

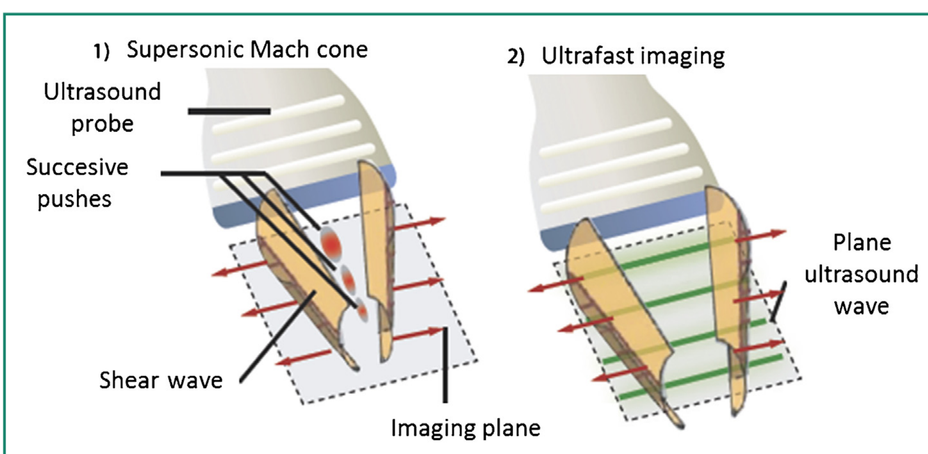

Figure 11. 1: the ultrasounds are successively focused at different depths to create pushes by radiation pressure. The constructive interferences of the shear waves form a supersonic Mach cone (in which the speed of the source is greater than the speed of the generated wave) and a quasi-plane shear wave is created; 2: the ultrasound machine then switch into an ultrafast imaging mode to follow the shear wave that is propagating through the medium.

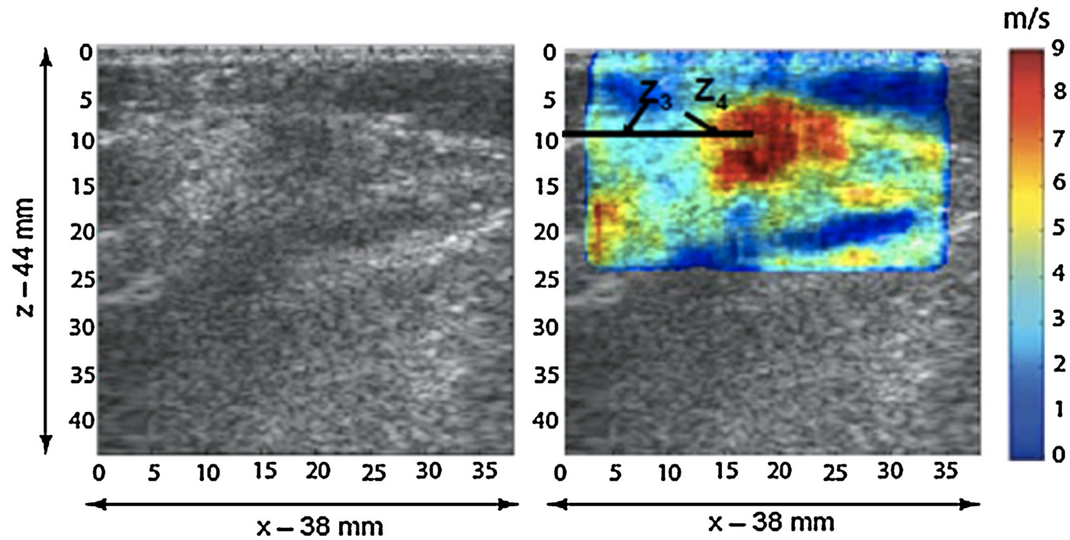

Figure 12. Ductal infiltrating carcinoma. The B-mode image brings out a hypo-echogenic mass with blurry borders with a shadow posterior to the lesion. The lesion is classified as ACR5. The elasticity imaging clearly brings out a very stiff mass at more than 150 kPa (7.1 m/s) [30].

- ultrafast imaging: complete acquisition all at once. Ultrafast imaging allows scanning the entire imaging plane with very good temporal resolution in one single acquisition, typically with a frame rate of 5000 images per second, and up to 30,000 images per second in the case of tissues such as the peripheral arteries or the eye. Therefore there is no need to repeat the acquisition several times by stroboscopy to acquire the entire displacement field. This allows, not only imaging in real-time, which makes the examination easier, but also averaging the very rapidly acquired images to improve image quality.

Therefore, the Supersonic Shear Imaging technique uses the technology of the 2D transient elastography, but substitutes vibrator by the acoustic radiation pressure. The whole excitation-imaging method is then integrated onto one single component: the ultrasound imaging transducer array. Amplified by the Mach cone, the generated shear wave has amplitude of tens of microns. This latter is detectable with a good signal to noise ratio by ultrasound speckle-tracking algorithm and ultrafast imaging. Thanks to ultrafast imaging, the acquisition of the shear wave propagation can be carried out all at once in less than 30 milliseconds. The technique is therefore slightly sensitive to patient movements (as an example breathing) and can be displayed in real-time, like a conventional ultrasound image. The Young's modulus maps are then reconstructed by estimating the speed of the shear wave between two points of the image, using a time of flight algorithm. The first in vivo experiences with this technique were conducted at the Institut Curie where, in approximately 50 patients, the use of the technique to differentiate benign tissue from malignant tissue was demonstrated [30] (Fig. 12).

This technique was implemented on an ultrasound diagnostic imaging device called, the Aixplorer® (Supersonic Imagine, Aix-en-Provence, France) and its diagnosis performance as well as its reproducibility were demonstrated in several organs, and more particularly in the breast [31]. In particular, a multicentric study in 939 patients with breast cancer showed an important increase in specificity for breast lesion characterization (+17.4%) with the addition of the elasticity parameters to the classical BIRADs criteria [32].

Conclusion

Elastography is an important research field It has also been evaluated in the clinical field for more than 10 years. It has provided a new feature to assess tissue stiffness and has shown that tissue elasticity is of great value for diagnosis. Indeed the variation of the Young's modulus in biological tissues offers a contrast that is potentially more interesting than conventional ultrasound. If the elastography techniques developed in research laboratories start making their commercial appearance, they are not all quantitative or operator independent, the word ''elastography'' can hide very different physical phenomena. It is therefore important to know how to decrypt the underlying physics of each elastography method in order to understand their advantages and physical limitations. Shear wave based techniques have strong advantages over quasi-static techniques, as they are more reproducible, quantitative, rely on automatic shear wave generation and provide good elasticity contrast. The availability of true quantitative numerical data allows adjustment of the dynamic range to optimize the visualization of structures. These advantages should certainly lead to new applications of shear wave elasticity imaging, not only for diagnosis but also for follow-up. The real-time capability of some of these SW techniques also allows the development of 3D elastography imaging that should facilitate the clinical use for detection, therapy planning and monitoring in the routine clinical practice. Finally, the integration of elastography techniques in conventional ultrasound systems open the door for routine application during ultrasound examination and will allow information fusion with other imaging techniques to strengthen their diagnostic performance.

Disclosure of interest

Mathias Fink and Mickaël Tanter are founders of the company Supersonic Imagine.

Jean-Luc Gennisson is a scientific consultant for the company Supersonic Imagine.

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