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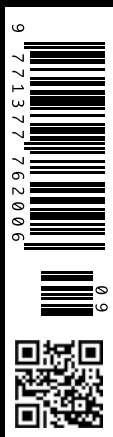
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# Ultrasonography in clinical practice

## New roles for an old actor?

Presents a brief overview of the physics related to different sonographic techniques, indications, new improvements and possible applications in future.



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**N**o one in the early days of the ultrasonography (US) era would believe the current clinical role of this imaging modality. As a courageous and innovative application of sonar and radar technology in biological tissues, the first US images obtained from the human body were far from perfect. Contrary to current features, early US devices consisted of huge systems in which patients were to be submerged in water, by which only rough outlines of internal body structures could hardly be obtained. However, in a relatively short time, and with the help of great achievements in acoustic, electronic and computer technology, US systems have become not only smaller, but also more sensitive and precise. In this article, a brief overview of the physics related to different sonographic techniques, indications, new improvements and possible applications in future will be presented.

### Seeing by Acoustics

In daily life, we are all surrounded by an acoustic world, of which we can only hear a tiny fraction. Using the sonic components beyond our limits of perception, many creatures like dolphins or bats, can “see” to avoid obstacles and reach food. This phenomenon was first realized by Lazzaro Spallanzani from Pavia, Italy in the 18th century, triggering the achievements ending up with modern US systems. Later developments like the determination of sound speed through water by Jean-Daniel Colladon, and observation of piezoelectric effect in some materials by Pierre and Jacques Curie led to the technologic developments paving the road to medical US.

Basically, medical US systems consist of components of acoustics and processing. Sound waves are first emitted in the system, and then introduced into the human body to encounter different media. The amplitudes of reflected echoes received by the same system depend on the composition, position, size and acoustic transmitting properties of various body structures along the course of the sonic wave. Some media (eg, gas, air, bone, stone) reflect the sound wave

totally, while others like low-density liquid do just the opposite. However, most body tissues produce echoes in intermediate amplitudes and attenuate the sound wave as it travels deeper.

The acquired echoes from the body carry detailed information about the physical properties of individual structures, including solidity and homogeneity. Quick and meticulous processing of these data, followed by production of representative visual information in a wide spectrum of shades of grey, constitute the basis of anatomic greyscale US imaging. Using this technique, one can easily and confidently differentiate organs from adjacent ones, delineate their components like blood vessels and biliary channels, as well as various structural changes due to solid and/or cystic tumours and parenchymal diseases including inflammation or infiltration. The modality makes it possible to evaluate the organ position, size and integrity quickly and reliably, providing valuable information about congenital or acquired abnormalities.

Contrary to stationary targets, moving media in the body produce echoes with frequencies differing from that of the initially emitted sound wave. This phenomenon (ie, the Doppler effect) and the magnitude of resulting frequency difference constitute the basis for Doppler US techniques, in which motion in the body, blood flow in most cases, can be assessed. As a noninvasive technique, Doppler US has enabled medical professionals to evaluate the patency of vessels, diagnose obstruction and analyse temporal haemodynamic changes resulting from pathologic processes.

The ability for fast structural and haemodynamic evaluation of human body parts has enabled medical professionals to use US for a wide spectrum of clinical indications. This cheap, widely available and noninvasive modality has helped diagnosis of various pathologies like cancer, stenosis in vessels or haemodynamic malfunctions. Due to its inherently radiation-free nature, US has proved to be a perfect means of follow-up, not only in diseases requiring close surveillance, but also in physiological processes like fetal

growth in pregnancy, enabling noninvasive evaluation of fetus and related maternal structures, from the very first weeks of life until birth.

Thanks to the huge advances in electronic miniaturisation technology, high-resolution US devices have become available on every possible medical site, including ambulances, emergency rooms, intensive care units or operating rooms, where noninvasive and quick imaging of the human body is mandatory. The dimensions of high-resolution US units have been currently reduced to the scale of laptop computers, and even that of smartphones. Consequently, US devices are now exploited as the main actors in point-of-care imaging, hence called “visual stethoscope” by some authors (Gillmann and Kirkpatrick 2012).

Another important and distinctive feature of medical US technology is the very high temporal resolution it inherently possesses. Due to the very short signal processing time, the operator can monitor every visceral motion nearly instantaneously as it occurs. This real-time imaging capability has made it possible to visualise and evaluate the movements of various body parts (eg, heart valves, directional and temporal changes of blood flow), but more importantly to keep an eye on the position of a needle or any other instrument we insert in the body for any medical purpose. Although one can use fluoroscopic x-ray techniques for the same purpose, US provides a radiation-free alternative. Guiding diagnostic and therapeutic procedures, US technology has become one of the main contributors to the tremendous procedural improvement of medical interventions like biopsy, drainage or ablation, which are now possible to be applied as a bedside and daytime procedure without requiring any hospitalisation or general anesthesia.

### Acoustic Touching

As a relatively newer application, US technology has begun to be used in assessing the elasticity of various body parts. The inspiration for this technology was the palpation technique of physical examination, which has been used by doctors for thousands of years. Simply touching and feeling body parts has revealed valuable information about disease processes since ancient times, when diagnostic equipment consisted of only the five human senses. Implementing different US techniques, it is now possible to quantify the changes of stiffness in organs secondary to various pathologic processes, a capability to be used in diagnosis or monitoring of various body disorders. One technique relies on real-time analysis of displacement in image elements (“speckle tracking”) in return for any external compression, while the other is based on measurement of sound speed, which is a derivative

of stiffness of the medium. Thus it is now possible to use dedicated US devices not only to imagine, but also to assess the stiffness of body structures. One of the most significant consequences of this improvement has been the dramatic reduction of frequency rates in periodic biopsy controls to evaluate the degree of hepatic parenchymal fibrosis in patients suffering chronic liver disease (Gennisson et al. 2013).

### Contrast Agents in Ultrasonography

For years, US was partially limited due to the lack of a specific contrast agent capability. However, advances in pharmaceutical research on ultrasound contrast agents (UCA) have revolutionised and expanded the clinical indications of US in recent years. The introduction of echogenic microbubble-based or nano-scaled UCA into vessels has made it possible to visualise very slow flow, thus providing information on tissue perfusion, which makes not only perfusion defects, but also small pathologic masses more apparent. Using contrast-enhanced ultrasound (CEUS) and the high temporal resolution capability of US, it is now possible to evaluate time-dependent vascularisation, perfusion and excretion patterns of individual neoplastic lesions, thus to reveal their pathologic nature in terms of malignancy or benignity. Specific uptake of some UCA by hepatic (Kupffer) cells provides a unique opportunity to reveal inconspicuous lesions as echo-poor areas on background parenchymal enhancement.

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These advances have made US one of the first-step modalities to detect and characterise mass lesions in visceral organs, especially those in the liver. CEUS has proven to be comparably successful in differentiating malignant tumours from benign ones in sonographically demonstrable lesions, omitting the need for more expensive, time-consuming modalities like magnetic resonance imaging (MRI) or computerised tomography (CT) (Ryu et al. 2014). Among many other applications of CEUS, those in paediatric practice, where ionising radiation is a serious concern, trump others. Using contrast-enhanced voiding urosonography, it is now possible to diagnose and monitor cases of children with vesicoureteral reflux, a potential cause of serious renal infection that may result in chronic

renal failure (Papadopoulou et al. 2014). As in this example, the clinical use of CEUS not only provides a cheaper, more practical and radiation-free alternative in medical practice, but also a far more safer application of a contrast agent. In terms of contrast media reactions, it has been demonstrated that UCA have extremely low rates of adverse reactions, when compared to those used in conventional radiology, CT or MRI examinations.

Another unique and innovative implementation of UCA is targeted CEUS imaging (molecular ultrasound). In this currently developing strategy, the UCA are covered with binding ligands, which cause them to accumulate at targets related to various disease processes like cancer or atherosclerosis. This approach provides new opportunities not only for early diagnosis, but also for applying targeted treatment and monitoring early response to it (Sutton et al. 2013). Due to the obligatory intravascular character of microbubble-based UCA, they are used in the detection of intravascular processes like angiogenesis, inflammation and thrombus formation. Likewise, some nano-based UCA targeted with antibodies or peptides and loaded with thrombolytic agents have proven to be effective in the treatment of thromboembolic processes like deep venous thrombosis, pulmonary embolism, myocardial infarction and acute ischaemic stroke. Intensive research on other nano-scaled UCA is being carried out to exploit the aforementioned diagnostic and/or therapeutic capabilities also in the extravascular space. These tiny particles, which are capable of extravasation, have been demonstrated to accumulate in sites of pathology, if targeted beforehand. Nanobubbles reaching the lesion may coalesce to form larger microbubbles to be visualised with US. If loaded with drugs, these nano-scaled UCA can even be used to deliver them right into the lesion after being activated by high-energy acoustic impulse. In comparison to nonselective systemic introduction of therapeutic agents, this targeted strategy gives the chance to reduce the total drug dose given to an individual patient, and to isolate healthy tissues (Güvener et al. 2017).

Last but not least, research and clinical trials are ongoing on sonoporation, in which pores in the cell membranes and inter-endothelial junctions are created using the mechanical effects of local destruction or excitement of micro-bubbles by US pulses. This technique allows transient and local enhancement of vessel permeability in various organs, including the brain, where temporary permeation of blood-brain barrier can be achieved. As a novel technique in progress, sonoporation has the potential to improve local delivery of drugs in many diseases like neoplastic, cardiovascular and neurodegenerative processes (Güvener et al. 2017).

## Conclusion

Since the early days of US in medicine, the imaging data obtained with this radiation-free modality has permanently revolutionised clinical practice in nearly all disciplines. Throughout its history, the modality has become more portable and precise in each year. With the inclusion of new techniques, including Doppler US, sonoelastography and CEUS applications, its contribution to medical practice has become even greater and more indispensable. Becoming smaller and more sensitive, US devices are expected to be in the hands of nearly all appropriately trained clinicians in the near future. The ongoing research on novel diagnostic and therapeutic applications like targeted CEUS imaging and sonoporation foreruns the possibly expanding role of this unique modality in clinical medicine. ■

## KEY POINTS

- ✓ Through continuous development ultrasonography has become the essential hand tool for every clinician
- ✓ With elastographic capability, it is now possible not only to visualise the lesions with ultrasonography, but also to "touch and feel" them
- ✓ As an old actor in medical imaging, ultrasonography renews itself to take a pivotal role in targeted molecular diagnosis and therapy



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