Technological review: contrast-enhanced ultrasonography

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Introduction

This paper reviews fundamental physicochemical properties of contrast agents used in ultrasonography (US) and describes their interaction with the ultrasound wave during imaging. It also covers basic principles of contrast-specific imaging techniques and discusses physiological parameters that can be investigated with contrast-enhanced US.

Physicochemical properties of US contrast agents

US contrast agents are microbubbles of gas contained within a shell that imparts flexibility and stability and that provides a definite size. Currently, the most used US contrast agent is SonoVue (Bracco), which consists of sulfur hexafluoride gas within a phospholipid shell. Since the gas is lipophilic, it has low solubility in blood and does not diffuse out of the shell. The diameter of the SonoVue microbubble ranges from 1 to 10 µm, with a median value of 2.3 µm. Thus, these microbubbles are too large to permeate blood vessel walls and enter the interstitial fluid. As a result, SonoVue is considered a blood pool agent and a marker of blood circulation. This property distinguishes SonoVue from contrast agents used in CT and MRI, which can diffuse into the extracellular space.

A second difference between SonoVue and contrast agents used in CT and MRI regards the concentration of active component required to provide a measurable signal. The concentration of sulfur hexafluoride in SonoVue is 8 µl/mL and only a few milliliters are used per examination. For CT and MRI examinations, much higher amounts of contrast agent are necessary (e.g. several grams for iodinated contrast agents). These data testify to the sensitivity of contrast-enhanced US in detecting the presence of contrast agents in the body.

Finally, SonoVue is eliminated by exhalation through the lungs rather than by renal excretion, as is the case for CT and MRI contrast agents. Therefore, its use is not contraindicated in patients with impaired renal function.
Microbubble-ultrasound interactions

A unique feature of US contrast agents, not observed with CT and MRI contrast agents, is that they are modified by the wave that is used to detect them. Ultrasound is a longitudinal acoustic wave of alternating high and low pressure that propagates through tissues. In this changing pressure field, the flexible shell of the microbubble is compressed and then expands. The specific response depends on the acoustic pressure, which on modern US scanners is indicated in terms of mechanical index (MI). At very low pressure, microbubbles simply backscatter the ultrasound wave. At low-intermediate pressures (low MI), microbubbles begin to oscillate and generate harmonic frequencies; these conditions are optimal for imaging as the oscillations provide a strong and consistent signal (Fig. 1). Finally, at high pressure (high MI) the microbubble shell is destroyed and the gas is released, generating an intense but brief signal, called stimulated acoustic emission. In perfused tissue, this is seen as a flash and then a loss of signal, followed by a progressive return as additional intact microbubbles enter the tissue from the circulation. These echogenic properties of microbubble contrast agents are the basis for various imaging techniques.

Fig. 1 a–d. Effects of increasing acoustic pressure on the signal produced by microbubble contrast agents during liver imaging. a At low acoustic pressure (MI=0.12), the liver tissue shows homogeneous enhancement. b At MI=0.6, partial loss of enhancement. c At MI=1.0, microbubble destruction results in complete loss of signal in liver parenchyma (large vessels maintain signal because of rapid replenishment from the circulation). d Low MI image obtained with transducer rotated 90° illustrates plane in which microbubble destruction occurred. Reproduced with permission from [3]
Low MI contrast-specific imaging

While all US scanners are able to detect signals from US contrast agents, the ability to collect contrast-specific information requires a contrast-specific mode of imaging and data analysis that can distinguish among signals from tissue, blood and contrast agent. This is achieved today mainly by multipulse imaging techniques in which the tissue is insonated repeatedly with two alternating ultrasound waves that differ in either amplitude (power modulation technique) or phase (phase modulation technique, Fig. 2). The waves reflected from tissues, which are linear scatterers, cancel out and give no measurable signal. Instead, the waves reflected from microbubbles, which are non-linear scatters due to their oscillations, do not fully cancel out; the residual signal that reaches the probe is entirely attributed to the contrast agent.

The information obtained from contrast-enhanced imaging is supplementary to – and does not replace – that from conventional (B-mode) US imaging. A clinical examination with US should start with conventional US, with high MI imaging of tissue; this is followed by a switch to a low MI, contrast-specific mode whereby the image becomes black. After an injection of contrast medium, the image rapidly becomes bright with the arrival of microbubbles, first in large vessels and then in the microvasculature of the tissue. After a few minutes, the signal dissipates as the microbubbles are washed out. Thus, the contrast-enhanced imaging technique is a continuous real-time examination in which information is dynamically collected.

Fig. 2 a–c. Fundamentals of phase modulation technique for detecting contrast-specific signals. a Tissue is insonated by two ultrasound waves that differ in phase by 180°. b Waves backscattered from tissues directly reflect the insonated phases, and therefore cancel out at the probe. c Due to microbubble oscillations in the ultrasound field, backscattered waves are not direct reflections of the insonated waves. Therefore, cancellation is not complete and the residual signal is attributed entirely to the contrast agent.
Since a great amount of the diagnostic information from contrast-enhanced US comes from the dynamic sequences that evolve over a few minutes, it is essential to record the imaging sequences digitally. Visual inspection and paper printout are insufficient. Adequate analysis requires repeated reviewing of the sequences in a loop, with the possibility of examining each frame. The imaging sequences can be stored temporarily in the scanner’s digital memory, archived on CD-ROM or DVD, or transferred by network to a workstation or a picture archiving and communication system (PACS).

Digital recordings also permit quantification of the microbubble signal, which is linearly related to the in vivo microbubble concentration within the range usually achieved with typical doses [1, 2]. At higher concentrations, linearity is lost because of attenuation effects. The time course of signal intensity can be measured in specific regions of interest in a tissue, permitting comparison between the perfusion of a lesion and that of normal adjacent tissue (Fig. 3). Typically studied parameters are time to peak enhancement and peak intensity. These parameters are easily calculated by several commercially available contrast-specific imaging software programs.

**Physiological parameters investigated with contrast-enhanced US**

Conventional US is an adequate imaging method for obtaining information about the morphology of tissues and of many lesions. Nonetheless, contrast-enhanced US provides additional information regarding morphology and is able to detect lesions not seen on conventional scanning. More importantly, contrast-enhanced US provides information on the blood supply of tissues and lesions. For large vessels, it demonstrates the structure of the lumen and wall in way that might be considered equivalent to MR angiography. Furthermore, contrast-enhanced US allows the real-time visualization of blood flow of both large and small vessels. Although blood flow can also be visualized with colour Doppler US, this technique is limited to larger vessels with elevated velocity and provides little information regarding slow flow in microvasculature. Only contrast-enhanced US can provide information regarding the vascular density and architecture of tissues and solid tumours. Another advantage of contrast-enhanced US is the absence of artifacts due to moving organs (like aorta), often encountered with Doppler US.
Since contrast-enhanced US has high sensitivity for the microvasculature, this imaging method can document slow flow in arterial defects like aneurysms and small amounts of internal bleeding from vascular endoprosthesis (endoleaks) and traumatic injuries. Moreover, it can accurately describe blood perfusion of tissue and tumours. The main parameters of perfusion are (i) extent of vascularization (amount of signal from microbubbles within tissue), (ii) geometry of the vascular tree, which for some tumours is characteristic, and (iii) dynamics and direction of blood flow through major vessels and microvasculature. Together these parameters form the basis for the diagnosis of focal liver lesions (Fig. 4) and other solid tumours.

**References**
