

Vascular applications of contrast-enhanced ultrasound imaging

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ABSTRACT

Objective: Contrast-enhanced ultrasound (CEUS) imaging is a powerful noninvasive modality offering numerous potential diagnostic and therapeutic applications in vascular medicine. CEUS imaging uses microbubble contrast agents composed of an encapsulating shell surrounding a gaseous core. These microbubbles act as nearly perfect intravascular reflectors of ultrasound energy and may be used to enhance the overall contrast and quality of ultrasound images. The purpose of this narrative review is to survey the current literature regarding CEUS imaging and discuss its diagnostic and therapeutic roles in current vascular and selected nonvascular applications.

Methods: The PubMed, MEDLINE, and Embase databases were searched until July 2016 using the PubMed and Ovid Web-based search engines. The search terms used included contrast-enhanced, microbubble, ultrasound, carotid, aneurysm, and arterial.

Results: The diagnostic and therapeutic utility of CEUS imaging has grown exponentially, particularly in the realms of extracranial carotid arterial disease, aortic disease, and peripheral arterial disease. Studies have demonstrated that CEUS imaging is diagnostically superior to conventional ultrasound imaging in identifying vessel irregularities and measuring neovascularization to assess plaque vulnerability and end-muscle perfusion. Groups have begun to use microbubbles as agents in therapeutic applications for targeted drug and gene therapy delivery as well as for the enhancement of sonothrombolysis.

Conclusions: The emerging technology of microbubbles and CEUS imaging holds considerable promise for cardiovascular medicine and cancer therapy given its diagnostic and therapeutic utility. Overall, with proper training and credentialing of technicians, the clinical implications are innumerable as microbubble technology is rapidly bursting onto the scene of cardiovascular medicine. (*J Vasc Surg* 2017;■:1-9.)

Contrast-enhanced ultrasound (CEUS) imaging is an emerging, noninvasive imaging modality that offers promise toward diagnostic and therapeutic applications in vascular medicine. CEUS uses microbubbles, which are contrast agents with thin and relatively permeable shells containing high-molecular-weight gases that do not readily diffuse or dissolve within the bloodstream. Microbubbles have a high degree of echogenicity and act as nearly perfect intravascular reflectors of acoustic ultrasound energy without local disruption. Because blood and surrounding tissues are similar in echogenicity, the addition of microbubble contrast agents may be used to enhance the overall contrast and quality of ultrasound images.^{1,2}

In 1968, Gramiak and Shah were credited as the first group to observe contrast effects in M-mode echocardiography.¹ They described the phenomenon by which rapid intracardiac saline injections produced bubbles that enhanced delineation of aortic blood flow. In the late 1970s, Bommer et al were the first to describe the development of miniscule yet stable microbubbles capable of traversing the pulmonary system without destruction.¹ This microbubble technology was subsequently fine tuned for direct in vivo visualization of intact mammalian vessels as small as capillaries. The earliest clinical application of microbubbles was to identify myocardial perfusion patterns with contrast echocardiography.^{1,2} Since the advent of United States Food and Drug Administration-approved commercially available intravenous ultrasound contrast agents, the clinical utility of microbubble technology to assess dynamic spatial and temporal heterogeneity of tissue microvasculature has grown exponentially.

This review presents the current vascular applications of CEUS imaging and discusses its emerging diagnostic and therapeutic roles.

SEARCH STRATEGY

The PubMed, MEDLINE, and Embase databases were searched until July 2016 using the PubMed and Ovid Web-based search engines. The search terms used

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included contrast-enhanced, microbubble, ultrasound, carotid, aneurysm, and arterial.

OVERVIEW OF CEUS

Physics background. Microbubbles of air commonly occur within all living organisms; however, their existence is extremely short-lived due to significant external compressive forces.¹ Microbubble contrast agents, by comparison, are classically composed of an encapsulating shell surrounding a gas core. The shell is typically composed of albumin, galactose, lipids, or polymers and functions to increase the circulation time and durability of the microbubble agent while also reducing the rate of release of the gaseous core.¹ Hydrophilic shell materials are taken up by the immune system more easily, leading to reduced agent circulation time. The elasticity of the shell contributes to the durability of the agent, and shells that are more elastic able to withstand higher levels of acoustic energy before rupture.³

The composition of the gaseous core contributes to the overall stability and echogenicity of the microbubble. Gases with higher molecular weight and lower blood solubility require more time to diffuse through the shell, leading to increased circulation time of the agent. First-generation contrast enhancement used CO₂ bubbles as a contrast medium, but today this has been wholly supplanted by the use of sulfur hexafluoride and perfluorocarbons.^{1,3} A list of commercially available contrast agents is provided in the [Table](#).

Ultrasound transducers emit sound waves leading to rapid variations in acoustic pressure. Microbubbles in the bloodstream undergo resonant volumetric oscillations in response to this variation in pressure, leading to asymmetric changes in microbubble diameter. These bubbles stiffen when compressed during the high-pressure portion of a sound wave, leading to smaller changes in size than is seen during the low compression (low stiffness) phase. The asymmetric changes in microbubble size lead to the reflection of sound waves with strong nonlinear components in multiples of the transmitting frequency, in contrast to the waves with linear components reflected by tissue and tissue motion.²

The strength of the nonlinear components depends on the mechanical index (MI) of the sound field, a standardized estimate of peak acoustic intensity (peak negative pressure divided by the square root of transmission frequency). Early ultrasound machines used acoustic energy with a high MI (>0.2) for imaging. Advantages of a high-MI method include a high signal-to-noise ratio and increased sensitivity for microbubbles, allowing for the assessment of myocardial perfusion.^{1,2} However, it was soon discovered that high-MI perfusion imaging disrupts microbubble shells leading to rapid elimination of the contrast agent, which prevented the simultaneous assessment of wall motion. Conversely, newer machines using low-MI imaging were still able to detect

microbubbles without disrupting them, thereby allowing for both real-time imaging and assessment of perfusion.²

The mechanical index also reflects the likelihood of adverse mechanical (nonthermal) biologic effects on nearby tissues. The interaction of acoustic ultrasound energy with microbubble contrast agents in the vasculature leads to rapid changes in microbubble volume in a process termed cavitation. These changes in microbubble size may be accompanied by increases in pressure and temperature within the contrast agent, leading to mechanical stress on surrounding tissues, fluid microjet formation, or the generation of free radicals. Cavitation involving microbubbles (microcavitation) has been recognized as the most likely mechanism for the nonthermal bioeffects of diagnostic ultrasound imaging, including microvascular rupture, petechiae, and inflammatory cell infiltration. The propensity for microcavitation to occur is related to the transmitting frequency of the ultrasound probe, with cavitation less likely to occur at higher transducer frequencies (low MI). As such, in the United States, the Food and Drug Administration limits ultrasound machine output to an MI of at most 1.9 to avoid inadvertent bioeffects.^{4,5}

Administration of 0.1 to 5.0 mL of an aqueous solution containing ultrasound contrast agents (~10⁹ bubbles/mL) is typically required for enhancement of the blood pool. Microbubble contrast agents may be administered intravenously as a bolus or as an infusion at a rate of ≤1 mL/min, followed by a flush of 5 to 10 mL of 0.9% saline solution. A repeat bolus injection can be added if needed for additional imaging. Once a steady amount of enhancement is obtained, a series of acoustic pulses are applied, which disrupt the bubbles in the ultrasound frame. Subsequently, new bubbles re-enter the frame from adjacent vessels in which the rate of replenishment is directly proportional to the regional blood flow rate.^{2,5} Consequently, areas with a perfusion defect appear less bright than hyperperfused areas in the ultrasound frame for a given time after bubble disruption. Thus, serial measurements of the amount of opacification, or "brightness," as a function of time after microbubble disruption can allow for estimation of the velocity and relative volume of blood flow in the imaging frame.⁵

Mathematical models may be used to estimate blood flow parameters after the administration of microbubble contrast agents. A time-intensity curve (TIC) may be created to reflect the intravascular transit of the contrast agent. TICs reflect the average intensity in a region of interest, measured in absolute intensity units, over time in seconds. Plotting TIC in a given frame allows for quantification of various parameters, including time to peak, peak intensity, area under the curve, wash-in and wash-out time, and mean transit time. Some of these parameters, such as peak intensity and area under the curve, reflect local blood volume in the region of interest, whereas, other parameters (time to peak intensity,

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