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Role of Contrast in Ultrasonography: significance, types, benefits, and limitations. A comprehensive review

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Abstract

Contrast-enhanced ultrasonography (CEUS) has revolutionized diagnostic imaging by significantly improving the accuracy and capabilities of ultrasound technology. By utilizing contrast agents, CEUS offers enhanced visualization of blood flow, superior detection of vascular diseases, and delineation of pathological from healthy tissues. Real-time imaging capabilities afforded by CEUS have been shown to be instrumental in guiding interventions and assessing treatment efficacy, thereby contributing to personalized patient care and improved clinical outcomes. This document provides a comprehensive review of the current benefits, limitations, and future directions of contrast-enhanced ultrasonography. It

acknowledges the potential for allergic reactions, the necessity for specialized training, high costs, and the occurrence of image artifacts as drawbacks, while also anticipating advancements in targeted agents and imaging techniques. Moreover, the document emphasizes the need for ongoing research to evaluate the long-term safety and efficacy of contrast agents and their impact across various medical disciplines. Despite the challenges, the integration of CEUS into clinical practice holds enormous potential to further refine diagnostic processes and enhance patient management.

Keywords: ultrasound; contrast-enhanced ultrasonography; ultrasound contrast agents; UCAs; CEUS; diagnostic imaging.

Understanding contrast in ultrasonography: an overview

Ultrasonography, also known as ultrasound, is a widely used medical imaging technique that relies on the use of high-frequency sound waves to create detailed images of the body's internal structures. It offers a non-invasive and radiation-free alternative to other imaging modalities such as CT and MRI [1]. It is often employed to examine organs such as the liver, gallbladder, kidneys, and reproductive organs. This non-invasive and safe procedure has proven valuable in diagnosing various medical conditions and guiding medical interventions.

Contrast in ultrasonography has revolutionized medical imaging, allowing improved visualization of blood flow, tissue perfusion, and the characterization of focal lesions. By introducing contrast agents into the body, ultrasonographers can highlight specific areas of interest and obtain more detailed and accurate images.

In the following sections, we will delve into the different types of contrast agents used in ultrasonography, the benefits of contrast-enhanced ultrasonography, and the potential

drawbacks or limitations associated with its use. By understanding the significance of contrast in ultrasonography and gaining insight into its various applications, we can appreciate the valuable role it plays in diagnostic imaging and patient care.

The role of ultrasonography in modern medicine

Ultrasound images are made by reflecting waves off body structures. The amplitude and travel time of the sound signal provide the necessary data to generate an image [2]. Ultrasound probes contain a piezoelectric crystal with the unique ability to change shape in response to an electric charge. When it is exposed to electrical energy, it generates a sound wave similar to how a drumhead or cymbal produces sound when deformed. On the other hand, when influenced by an incoming sound wave, the crystal produces a slight electric charge itself. This generated electrical signal from the returning sound wave is then amplified and manipulated by a computer in order to create almost instantaneous images on an ultrasound monitor [3].

Ultrasound is highly valuable clinically because of its noninvasive nature, excellent visualization characteristics, and relatively easy management process [4]. Its ability to provide real-time visualization of anatomical structures such as organs and tissues, along with physiological processes, makes it invaluable in a wide range of medical specialties, including obstetrics for pregnancy monitoring, cardiology for assessing heart function, gastroenterology for evaluating digestive system disorders, and more.

What is contrast in radiology?

Contrast agents are substances that enhance the visibility of specific structures or processes during imaging procedures. These agents work by altering the contrast between different tissues or blood vessels, making them stand out more in the image [5].

There are various types of contrast agents used in radiology, including iodine-based contrast agents (commonly used in CT scans and angiography), gadolinium-based contrast agents (used in MRI), and microbubble-based contrast agents (used in ultrasonography). In the context of ultrasonography, contrast refers to the use of contrast agents that are injected into the patient's bloodstream or administered directly into the target organ or tissue [5].

The introduction of ultrasound contrast agents in the early 1970s [6] represented a significant advancement in the field of diagnostic imaging. Since that time, there has been ongoing enhancement and adaptation of UCAs to improve their stability and compatibility with living tissues. These modifications aim to target specific surface molecules associated with pathological changes [7]. It took over two decades to create the initial stable UCA approved by the FDA for commercial use, which is Albunex® [8], consisting of albumin-coated microspheres filled with air.

Different types of contrast agents used in ultrasonography

Ultrasonography utilizes various contrast agents, with microbubbles [9] and liposomes [10] being particularly significant. Each type of contrast agent has its own distinct mechanism of action, influencing how it interacts with the body's tissues and organs.

Ultrasound contrast agents (UCAs) usually consist of small gas microbubbles stabilized by a surfactant. Some of the surfactants in current use are serum albumin, polymer, and phospholipid. When phospholipid is used as the surfactant for gas stabilization, one of two types of structures is typical: gas bubbles with a lipid monolayer at the surface (commonly named microbubbles), or gas-containing liposomes (echogenic liposomes) [10].

Microbubbles are among the most commonly [11] used contrast agents in ultrasonography, which represent a class of agents predominantly utilized as intravascular contrast media. Microbubbles exhibit limited diffusion out of the circulation and function as blood-pool markers. They resonate in response to the ultrasound waves, leading to the generation of contrast signals that can be detected and used to create detailed images of blood perfusion. Innovative multipulse insonating sequences have been developed specifically for their detection with Doppler systems, enabling selective display of their presence in large vessels or microvasculature - offering a new opportunity to examine these areas using ultrasound. Their effectiveness is attributed to the compressibility of gases compared to almost incompressible tissue [12]. The size of clinical microbubbles is crucially determined by the diameter of the pulmonary capillaries, which are the narrowest in the body. It is essential for them to be able to cross the lung bed and produce systemic enhancement after intravenous injection. This necessitates that they must be smaller than 7 mm in diameter. The type of gas they contain (usually air or a perfluoro gas) and their stabilizing shell (denatured albumin,

surfactants, or phospholipids) both play critical roles in determining their effectiveness as contrast agents [12].

On the other hand, **liposomes** are self-forming lipid bilayer arrays that separate an internal aqueous compartment from the bulk aqueous phase. Unlike lipid monolayer structures, liposomes have extended, two-dimensional, and clearly separated hydrophilic and hydrophobic regions. The hydrophilic parts of bilayer lipids face towards the external and internal aqueous phases, while the hydrophobic parts of both lipid layers face each other to form the membrane's internal core [10]. Liposomes function by binding specifically to certain tissues or molecular markers, allowing targeted imaging of specific organs or pathological processes within the body. This provides valuable diagnostic information for healthcare professionals.

Understanding the varied mechanisms of action of these contrast agents is crucial for optimizing their use in ultrasonography. By appreciating the distinct ways in which different types of contrast agents interact with the body and influence imaging, healthcare providers can make informed choices regarding the most suitable agents for specific diagnostic purposes.

Benefits of contrast usage in ultrasound procedures

UCAs are generally considered to be very safe, with a minimal occurrence of side effects. They do not have any harmful impact on the kidneys and do not pose any interactions with the thyroid. As such, there is no need for renal function laboratory tests prior to their administration [13].

The significance of contrast in ultrasound imaging lies in its ability to enhance the visualization of blood flow and improve the detection and characterization of various pathologies. This leads to more accurate assessments, better monitoring of treatments, and improved guidance during interventions. Contrast agents in ultrasound imaging help to overcome the limitations of conventional grayscale imaging by providing better differentiation between tissues and highlighting areas of interest. This is particularly useful in the diagnosis and monitoring of conditions such as deep vein thrombosis, peripheral artery disease, and liver cirrhosis [5].

Furthermore, contrast-enhanced ultrasonography provides valuable information for guiding interventions such as biopsy procedures [14], facilitating more accurate tissue sampling and reducing the risk of complications.

Additionally, the enhanced visualization of tissue perfusion enables better characterization of focal lesions, aiding in the differentiation between benign and malignant masses, which improves early detection of cancers and treatment outcomes [15]. This is particularly beneficial in the assessment of liver and renal tumors, where accurate diagnosis is crucial for treatment planning and patient management.

Moreover, the application of contrast in ultrasonography extends beyond diagnostic imaging, with emerging uses in assessing the response to therapy and guiding targeted drug delivery [16]. By providing real-time feedback on tissue perfusion and treatment response, contrast-enhanced ultrasonography contributes to personalized medicine and improved patient outcomes.

In conclusion, contrast in ultrasonography holds great significance in improving the accuracy and diagnostic capabilities of the imaging technique [17].

Clinical use of contrast in ultrasound imaging

One of the studies [18] has demonstrated the effectiveness of a new ultrasound imaging technique called Cumulative Phase Delay Imaging for visualizing and measuring the movement of ultrasound contrast agents. Unlike conventional ultrasound tomography, which relies on changes in sound speed and attenuation, CPDI is based on a marker that specifically targets UCAs. This allows for dynamic contrast-specific ultrasound tomography. In breast imaging, DCS-UST provides a more convenient, efficient, and less operator-dependent approach compared to standard echo-contrast methods while maintaining accurate imaging of contrast movements [18].

Another CEUS technique has been created for evaluating the microcirculation in skeletal muscles, showing potential for studying individuals with peripheral arterial occlusive disease or diabetic microangiopathy. There is a possibility that using targeted microbubbles could improve and broaden the diagnostic abilities of current vascular ultrasound imaging by

identifying particular molecular activities involved in the development of vascular diseases [19].

Intravascular microbubbles allow ultrasound to monitor changes in blood flow to tumors and inflammatory areas. Its safe use without ionizing radiation and nephrotoxicity makes it a preferred option in different clinical settings, especially for pediatric patients [20]. It is well-suited for both the initial assessment and follow-up of trauma and is recommended for cases of pediatric blunt abdominal trauma [21].

UCAs have also been extensively used in adult cardiology patients to enhance the endocardial border's delineation, and they have been shown to be safe and well-received in this patient group. Additionally, there is an increasing volume of research examining the benefits of contrast-enhanced sonography for differentiating between benign and malignant liver lesions in adults, as well as characterizing non-hepatic malignancies in adults [22].

Liver masses are frequently detected incidentally through cross-sectional imaging or during surveillance scans in high-risk or symptomatic patients. The characterization of focal liver lesions typically relies on their enhancement patterns seen in contrast-enhanced imaging, with Computed Tomography or Magnetic Resonance being the primary modalities used for this purpose. More recently, the use of microbubble contrast agents has broadened the role of sonography in diagnosing focal liver lesions based on their vascularity and specific enhancement features, offering real-time imaging advantages, and using strictly intravascular contrast agents [23].

Retrospective or single-center prospective research with relatively limited samples has shown that contrast-enhanced ultrasound can improve the accuracy of percutaneous biopsy. Recent studies have shown that contrast-enhanced ultrasound-guided biopsy of focal liver lesions is a highly effective and safe procedure. It offers improved diagnostic accuracy compared to regular ultrasound-guided biopsy, especially for diagnosing hepatocellular carcinoma and for lesions smaller than 2.0 cm in size [14].

Incidental kidney abnormalities are commonly discovered during regular ultrasound screenings. Although simple cysts can be fully described using ultrasound, other irregularities require further examination, typically through multiphase imaging techniques like contrast-enhanced CT and MRI. Contrast-enhanced ultrasound has emerged as a valuable additional

method for visualizing kidney irregularities. It provides clear benefits compared to conventional approaches because it does not have nephrotoxic effects, avoids the use of ionizing radiation, and can quickly evaluate the enhancement pattern of kidney lesions in real time. Its established applications include distinguishing between solid tumors, pseudolesions, and complex cysts; characterizing complex cysts with varying malignant potential; and evaluating tumor ablation [24].

CEUS can also be utilized to identify ureteric reflux in the urinary bladder [25] and evaluate tubal patency in the uterus [26].

Drawbacks and limitations of contrast-enhanced ultrasonography

In addition to the benefits of contrast-enhanced ultrasound, it is important to acknowledge its limitations as well [27].

Some patients may experience allergic reactions or side effects, ranging from minor symptoms like nausea or headaches to more serious conditions such as anaphylaxis. Postmarketing surveillance indicates that the leading cause of severe adverse events is an anaphylactoid reaction, with an estimated rate of approximately one in 7000 (0.014%) for both the perflutren microspheres approved for cardiac indications in the United States and the sulfur hexafluoride microspheres approved in Europe [28]. Additionally, there are certain contraindications to the use of contrast agents in specific patient populations, such as those with allergies to the contrast agent components. Therefore, careful patient selection and monitoring for any adverse reactions are crucial when using contrast agents in ultrasonography [29].

There is a theoretical possibility that the combination of diagnostic ultrasound and UCAs may result in biological impacts. Laboratory studies have shown cellular reactions like sonoporation, hemolysis, and cell mortality. Despite being observed *in vitro*, these effects could be relevant to real-world settings as they stem from interactions between individual gas bubbles and cells. Research on small animals suggests that microvascular rupture could occur when microbubbles are exposed to ultrasound. This raises safety concerns in certain situations where vascular damage would have significant clinical implications, such as during ocular and brain ultrasounds [13].

Another significant obstacle is the limited availability and high cost of contrast agents, potentially restricting their use in some healthcare settings. This scarcity and expense can pose substantial barriers to access for many patients who could benefit from this technology.

The use of contrast agents in ultrasonography also requires specialized training and expertise to ensure proper administration and interpretation of the enhanced images. The interpretation of contrast-enhanced ultrasound images can be subjective and dependent on the skill and experience of the operator [27].

Additionally, the UCAs can result in transient image artifacts, such as blooming or acoustic shadowing, which may affect image interpretation, and lead to false or misleading findings [30-31]. Moreover, UCAs have a short duration of enhancement, which limits their utility in certain imaging scenarios where longer duration of enhancement is desired.

It is also important to note that not all anatomical structures or pathologies may benefit from the use of contrast agents in ultrasonography. For example, certain structures or conditions may not have sufficient blood flow or specific molecular markers for effective contrast enhancement.

Future directions in contrast-enhanced ultrasonography technology

Using contrast agents in ultrasound imaging has shown significant potential in enhancing the technique's accuracy and diagnostic capabilities. Future advancements in contrast-enhanced ultrasonography technology are expected to include more specific and targeted contrast agents that can selectively bind to certain molecular markers, enabling even more precise detection and characterization of pathologies.

Additionally, there may be improvements in imaging techniques and equipment to optimize the visualization and signal-to-noise ratio of contrast-enhanced ultrasound images. These developments could lead to wider integration of contrast-enhanced ultrasound in various clinical settings, enhancing its utility as a non-invasive diagnostic tool.

Researchers are also exploring various strategies to prolong the circulation time of the agent during image acquisition. This may potentially enable extended imaging sessions without the need for multiple injections, thus improving overall efficiency and patient experience.

Another area of future research in contrast-enhanced ultrasonography involves exploring the integration of ultrasound with other imaging modalities, such as Computed Tomography or Magnetic Resonance Imaging. This collaboration promises to provide complementary information and improve diagnostic accuracy.

Furthermore, advancements in image processing algorithms may play a significant role in enhancing the capabilities of contrast-enhanced ultrasonography by aiding automated image analysis and interpretation.

Discussion

Contrast agents have been extensively studied and proven to be effective in improving the visualization and characterization of various pathologies in ultrasound imaging. The ability of contrast agents to enhance the visualization of blood flow, improve the detection and characterization of various pathologies, and provide real-time imaging during interventions highlights their essential role in advancing patient care. As technology continues to progress, further research and development in contrast-enhanced ultrasonography are expected, aiming to enhance its diagnostic accuracy and utility in various clinical settings.

While contrast-enhanced ultrasound has shown great promise in improving diagnostic accuracy, there are certain limitations and drawbacks to consider. These include patient tolerance and potential adverse reactions to contrast agents, limited availability and high cost of contrast-enhanced ultrasound equipment and supplies, and the need for additional training and expertise in performing and interpreting contrast-enhanced ultrasound studies. Further research is still needed to evaluate long-term safety of contrast, efficacy in different clinical scenarios, and potential impacts on patient outcomes. This research could involve large-scale clinical trials, comparative studies with other imaging modalities, and long-term monitoring of patients who undergo contrast-enhanced ultrasound.

Promoting CEUS remains crucial for radiologists and patients to take advantage of this effective imaging choice, despite the obstacles. It is cost-effective, can be conducted at the patient's bedside, involves no ionizing radiation or nephrotoxicity, and importantly, offers precise diagnostic information comparable to CT and MRI. The evidence supports its advantages over the obstacles encountered [32]. Overall, contrast-enhanced ultrasound has significant potential to improve the accuracy, diagnostic capabilities of ultrasound imaging

and clinical decision-making in various medical specialties [5,15]. It is important for healthcare professionals to stay updated on the latest advancements and evidence in contrast-enhanced ultrasound to ensure optimal patient care and accurate interpretation of imaging.

Disclosure

Author's contribution

Conceptualization: Krzysztof Rosiak and Kamil Waloch; Methodology: Joanna Wojtania; Software: Kacper Reguła; Check: Kacper Pleska and Michał Łepik; Formal analysis: Andrzej Czajka and Bartłomiej Szymański; Investigation: Michał Łepik and Szymon Piaszczyński; Resources: Andrzej Czajka; Data curation: Zofia Uszok; Writing - rough preparation: Kacper Pleska and Zofia Uszok; Writing - review and editing: Kacper Reguła and Kamil Waloch; Supervision: Szymon Piaszczyński; Project administration: Krzysztof Rosiak and Bartłomiej Szymański; Receiving funding - no specific funding.

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The authors deny any conflict of interest.

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