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Nano-Structured and Micro-Structured Materials as Contrast Agents in Echocardiography

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ABSTRACT

Ultrasound imaging is a safe and effective technique used to visualize essential organs due to its significant tissue penetration depth. Echocardiography, a specialized application of ultrasound, has seen substantial advancements over the years and is now widely used to diagnose various cardiac disorders, including cardiac transplant rejection and ischemia-reperfusion injuries. Ultrasound contrast agents are primarily categorized into two types: 1) microbubble-based contrast agents and 2) non-microbubble-based contrast agents. Microbubbles, typically 1 to 4 microns in size, are gas-liquid emulsions with a gaseous core encased in a shell. Our study involved an extensive review of literature, including 34 articles from PubMed, 52 articles from Google Scholar, and 17 articles from ScienceDirect, focusing on nano/micro contrast materials and their applications in echocardiography. Articles were selectively omitted based on relevance, specifically excluding those with limited applications or those focusing on diverse contrast agents rather than nano contrast agents. Ultimately, 24 articles were thoroughly analyzed, emphasizing the use of contrast agents in ultrasound and echocardiography.

Keywords: Echocardiography, Ultrasound, Contrast media, Nanoparticles, Imaging.

INTRODUCTION

Ultrasound imaging is a usually used imaging technique due to its substantial tissue penetration depth, safety, and low cost, combined with a real-time imaging ability that makes it useful over other common modalities such as magnetic resonance imaging [MRI], computed tomography [CT], and positron emission tomography [PET] [1-5]. The cost factor for ultrasound is approximately five times lower than MRI and three times lower than CT [6]. Applications range from first- look examinations in abdomen or extremities to cardiac applications and endosonography, e.g., in the female genital tract [7], however, differentiation of tissues of diagnostic importance is often impeded by similar ratings of echogenicity. Furthermore, clinical Doppler can't image vessels smaller than 200 μm in diameter, thus preventing the mapping of the capillary system of an organ or a tumor [8] also ultrasound imaging has limitation in uses of

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gas containing organs like lungs and osseous structure for imaging [9]. Echocardiography is one of the most indispensable uses of ultrasound which plays its crucial role in diagnostic radiology [6], has developed to a great deal over recent years and it has become a prevalent method for diagnosing numerous disorders and diseases like cardiac transplant rejection and ischemia- reperfusion [10]. This modality is a safe and rather inexpensive method compared to other molecular imaging methods. The use of contrast agents in echocardiography has played prominent role in this field's development. In this technology microparticles or nanoparticles are used to bind with epitopes which are functionally specific, following a systematic injection [10]. The first application of contrast ultrasound in the area of cardiology was when mixed saline was infused into part of body whose place was detectable via transducer [11]. Overtime facts which remain unknown using 2-dimensional echocardiography became revealed through the mixture off acoustic instrumentation improvements and contrast agents [12]. Therefore, this technology can help us to diagnose and treat major cardiac disorders, and since the use of this technology and the researches around it has increased recently in health systems it seems necessary for researchers to review the recent studies, investigations and to help this field to improve more. Contrast-enhanced ultrasound (CEUS) is the application of ultrasound contrast medium to traditional medical sonography. Ultrasound contrast agents rely on the different ways in which sound waves are reflected from interfaces between substances. This may be the surface of a small air bubble or a more complex structure. CEUS usage started in the late 1960s after finding that the injection of agitated saline caused an evident signal change during US examination [11,13-15]. Contrast enhancement was caused by the compressible gas core of saline bubbles, enabling the bubble to backscatter the applied US wave. Those first saline bubbles were unstable due to the high surface tension. By injection of autologous blood at adequately rapid rates, the creation of more steady bubbles was described [13-15], none the less those bubbles still lacked sufficient life time and a defined size. Bubbles produce contrast because of their changing response to altercations in acoustic pressure [6]. It took more than 20 years to develop the first stable, commercially available and FDA- approved USCA [13,15], Albunex®, an albumin- coated and air-filled microsphere. From that time, stability and biocompatibility of USCA have been constantly improved and bubbles have been changed to exactly aim certain surface molecules expressed in pathological alterations. While the application of micro-bubbles has shown encouraging results, their possible range of molecular imaging and targeted drug delivery applications in cancer diagnosis and treatment has been limited by a large hydrodynamic diameter [1–8 μm], which naturally limits them to the vasculature [6]. Nanotechnology is a multidisciplinary matter, which covers an massive assortment of devices derived from engineering, biology, physics and chemistry [16] and it is a scientific issue devoted to the molecules and atoms manipulation in order to build miniscule constructions for innovative molecular assemblies at the nanometer scale size [17-20]. The rapid progresses and developments of an extensive spectrum of nano-scale or micro-scale techniques have opened new opportunities of treatment and imaging. The creation of nano-particles and micro-particles enables the fabrication or different types of diagnostic imaging agents by imaging-detectable biomaterials [20]. During the last decade, nanotechnology has achieved enormous improvements [21,22] and several kinds of nano-structured materials have been introduced for biomedical applications [21-23]. In this review, we are going to discuss about contrast nano-structured materials as contrast agents in ultrasound especially echocardiography and contemporary modalities of imaging body through ultrasound by diverse means of contrast agents.

Basic principles of modality physics and contrast imaging

Basic Physics of Ultrasound

The application of ultrasound in medical diagnosis had a persistent enhancement over years. Improvements in technology have been followed by extensive approval and use of ultrasound in medical diagnosis (24). It produces pictures of the inside of the body using sound waves. It uses a small probe called a transducer and gel placed directly on the skin. High-frequency sound waves travel from the probe through the gel into the body. The probe collects the sounds that bounce back. A computer uses those sound waves to create an image. Ultrasound waves are emitted from piezoelectric crystals of the ultrasound transducer. The choice of frequency is dictated by a trade-off between spatial resolution and penetration depth, since higher frequency waves can be focused more tightly but are attenuated more rapidly by tissue. Ultrasound has a wide range of medical applications including cardiac and vascular imaging, imaging of the abdominal organs and in utero imaging of the developing fetus.

Table 1. Approximate frequency ranges corresponding to ultrasound, with rough guide of some applications

Frequency	Term	Example
0.1Hz-20Hz	Infrasound	Monitoring earthquakes
20Hz-20kHz	Acoustic	Low bass notes
20kHz-2MHz	Ultrasound	Animal and chemistry-Medical and destructive
2MHz-200MHz	Ultrasound	Diagnostic and NDE

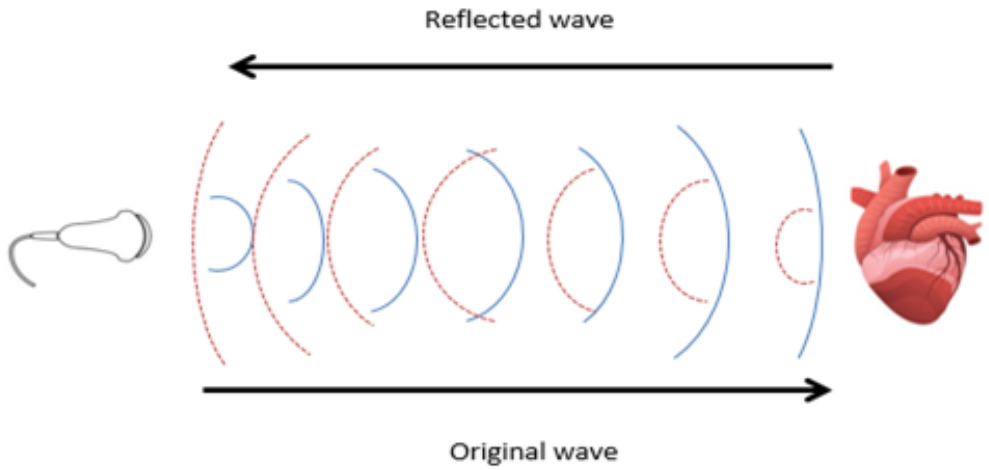

Figure 1. Principle of an active sonar. As shown in this picture sound waves are transferred out of transducer and encountering with object which is finally reflected and image is created.

Basic Physics of Echocardiography

Echocardiography is a low-risk first choice scan, which does not have a large radiation dose associated with it, and can be used on patients with pacemakers, defibrillators, and stents which are MRI-incompatible [25]. Frequencies of about 2 MHz for adult transthoracic studies to about 7 MHz for higher-frequency applications including harmonic imaging and pediatric arid trans-esophageal studies is used in echocardiography [26].

Indications and applications of echocardiography includes assessing early signs of cardiac disease like chest pain, Cardiac embolisms and infarctions, Hearts valve diseases and Cardiac arrhythmias [26].

Modes of image display

The simplest form of echocardiography is M-method which produces an image that is similar to a tracing rather than an actual picture of heart structure. The M-mode technique is an effective way to record the necessary multiple cardiac cycles [27]. In certain situations, M-mode recordings of the valves and interventricular septum can be particularly helpful in making a more accurate and complete echocardiographic cardiac assessment, thus helping to make the examination more cost-effective [27,28]. In addition, the second one is Doppler ultrasound which is a method for detecting the direction and velocity of moving blood within the heart also the method may be used for detection of Cardiac valvular insufficiency and stenosis as well as a large number of other abnormal flows [27]. Doppler mode includes pulsed-wave Doppler, continuous-wave Doppler and color Doppler. Two-dimensional echocardiography creates two-dimensional image which is built up by firing a beam vertically, waiting for the return echoes, all echoes along the beam are received, the picture along the beam is booked, and a new beam is sent out in the neighboring section [29]. Three-dimensional echocardiography involves multiple image from different angels of heart. It will have an important function in congenital heart disease [30]. It`s used as the first step before the heart valve surgery. It`s also used to diagnose heart problems in children.

Physics of contrast imaging

Tissue harmonic imaging (THI) is a relatively new real-time imaging technique that depends on the detection of the harmonic frequencies created by nonlinear beam

propagation through tissue. In this method, higher-frequency harmonic waves produced by nonlinear fundamental US wave propagation are used to generate images that contain fewer artifacts than those seen on conventional fundamental wave US tissue imaging [31,32]. Harmonic frequencies are integer multiples of the fundamental frequency. The frequency at which sound waves leave the transducer is known as the fundamental frequency. The ultrasound waves become distorted on passing through the body as they encounter tissues of differing composition and density. This changes the waveform and generates frequencies different from the incident frequency. These are harmonic frequencies, often shortened to harmonics. Harmonic frequencies include sub-harmonic, ultra-harmonic and multiples of the fundamental frequency. The strongest harmonic signals are multiples of the fundamental frequency [33].

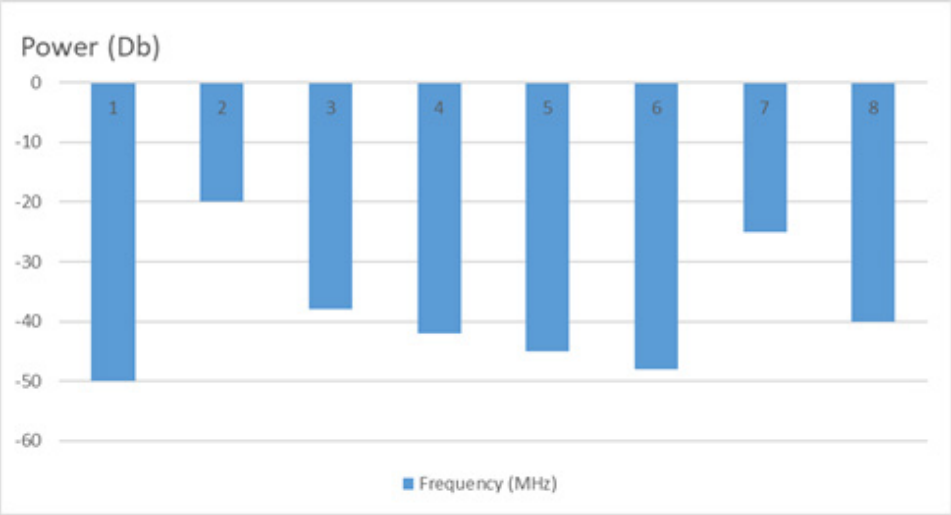

Figure 2. Graph demonstrating the additional – harmonic – frequencies generated when using ultrasound contrast agents [34].

Ultrasound microbubble and nano-structured contrast agents

There is low historical background of nano-structured materials and the importance of these structures have been understood since 1968. Medical ultrasound imaging is based on the pulse echo principle [35]. Increasing the received signal strength is, therefore, the objective of most ultrasonic contrast agents and this is true for vascular as well as organ-specific agents and also there are, however, a number of contrast agents which attempt to alter other acoustic properties of the tissue such as the attenuation and the speed of sound [35].

Ultrasound contrast agents based on size can be divided into two main classes: 1] microbubble based contrast agents and 2] non microbubble based contrast agents [36].

Microbubbles are gas-liquid emulsions consisting of a gaseous core surrounded by a shell and are usually 1 to 4 microns in size [36]. Following insonification with ultrasound, the gaseous core of the microbubbles causes a very high echogenic response that results in a high contrast to tissue background ratio on ultrasound images [36]. Different types of contrast microbubbles have been synthesized by combining different shell compositions such as albumin, galactose, lipids, or polymers, with different gaseous cores such as air, or high molecular weight gases [perfluorocarbon, sulphur hexafluoride or nitrogen] [36,37].

Non Microbubble based contrast agents consist of either submicron or nano sized particles which consist of either liquid or solid colloids that range in size between 10 and 1000 nanometres [36,38]. Non microbubble based contrast agents are advantageous over microbubbles in terms of their ability to enter the extravascular space providing the opportunity to image targets beyond the vascular compartment [36].

Microbubble contrast agents' details and applications

Microbubbles, gas or emulsion containing nanoparticles with intravenous administration are fundamental and intrinsic means in echocardiography contrast imaging also the average microbubble diameter should be less than 5 micro meter in order to pass unimpeded through intravenous administration [39]. Contrast agents intravenous administration can be used with bolus or infusion methods.

First generation agents

Include agitated saline, indocyanine green, sonicated solutions of dextrose, and renograffin, among others [40]. SHU-454, [Echovist, Schering AG, Berlin, Germany] is a first-generation contrast agent stabilized with D-galactose,

commercially available in Germany and awaiting approval in the U.S [41]. The difference between Echovist and Albunex is that Echovist cannot pass the lung capillary bed and therefore cannot opacify the left heart [40-42] but Albunex able to pass through the pulmonary capillaries [40]. SHU-508A [Levovist, Schering AG, Berlin, Germany] an Echovist derivative, is a suspension of galactose and a small amount of fatty acid that releases small air bubbles when mixed with sterile water [40].

Second generation agents

Research on second-generation agents has focused on the size and steadiness of microbubbles, since these properties determine their efficiency [40,43]. Optison [FS069, Molecular Biosystems Inc, San Diego, Calif.] provides continual contrast effect [40]. Unlike Albunex, however, it gives no information about myocardial blood flow when injected into a coronary artery [40,44]. In one study, FS069 created higher levels of harmonic Signals than Albunex [40]. BR-1 [Bracco Research SA, Geneva, Switzerland] is an aqueous suspension of stabilized sulfur hexafluoride microbubbles also Perflenapent emulsion [EchoGen, SONUS Pharmaceuticals and Bothell, Wash.] was the first fluorocarbon microbubble contrast agent to be developed and taken into clinical trials. EchoGen enhance chambers of ventricles and improve wall motion studies [40]. At present three contrast agents are approved for left ventricular [LV] opacification and endocardial definition: SonoVue [Bracco, Italy], Luminity [BMS, USA] and Optison [GE, USA]. The latter is currently not available [45]. All the fundemantal information and data has been summarized in Table 2.

Table 2. First and second generation ultrasound contrast agents by their generation, gas and stabilizing shell

Generation	Name	Gas	Stabilizing Shell
First	Agitated saline	Air	None
	Echovist	Air	None
	Levovist	Air	Palmitic acid
	Albunex	Air	Sonicsted albumin
Second	Optison	Octafluropropane	Sonicsted albumin
	Luminity	Octafluropropane	Lipids
	Sonovue	Sulfur hexafluoride	Phospholipids
	Sonazoid	Perflurobutane	Sonicsted albumin

Levovist

Kupffer cells of the liver adopt contrast agents such as Levovist, Sonovist and Sonozoid by phagocytosis [46], then the body's defensive functions like compliment mediated mechanisms eliminate search bubbles [47]. Among these three Levovist consists of air with a surfactant galactose/palmitic acid surfactant [48].

Sonozoid

Regularity of authority in Japan considers Sonozoid as a late-phase imaging factor [37]."Post-vascular phase" in Sonozoid is a phase where it can endure for several hours in spleen and liver [49,50]. Patients who are sensitive to egg are not recommended to use this agent but it has low number have side effects in normal patients like: albuminuria, diarrhea and neutropenia [51]. It contains perfluorobutene microspheres with hydrogenated egg phosphatidyl serine covering, which an amorphus sucrose surrounds it [52].

Table 3. Comparison of Levovist and Sonazoid microbubble contrast agents [53].

	Levovist	Sonazoid
Microbubble	Air	Perflurobutane
Shell	None	Yes [lipid]
Imaging technique	High mechanical index	Low mechanical index
Signal	Disruption	Harmonic
Tumor vessel	Real time	Real time
Tumor stain	Intermittent	Real time
Kupffer phase	One sweep	Stable for long period 10-60 minutes tolerable for multiple scanning
Operator dependent	Yes	No or Low
Machine dependent	Yes	No or Low

Albunex

Albunex, an air filled album and microsphere solution contains sonicated 5% human serum Albumin [54], which has sufficient contrast enhancement. Injecting this agent into coronary arteries does not considerably change coronary blood stream, the function of left ventricle a systematic hemodynamics [54,55].

Optison

Optison was the earliest commercially offered contrast agent which was conference by FDA [56]. Protein-shelled microbubbles like Optison were utilised for transporting targeting ligands and genetic payloads [57,58]. This agent includes artificial albumin microspheres containing octafluoropropane [59], because octafluoropropane is not much soluble and diffusible in blood it can be steady in the blood flow following the injection [60]. As a disadvantage of this agent we can mention that Li et al. who studied PVCs in rats, found that Optison can increase PVCs especially when the rats' exposure to Optison was initiated with end systole [61-63].

Sonovue

Sonovue microbubbles outer structure is made of lipid that encloses sulfur hexafluride gas [60]. It is used in sonography when injecting contrast for evaluation of histerosalpingo-contrast- sonography, also in ascites to assess hepatic hydrothorax, bile ducts by means of percutaneous trans hepatic cholangiography and drainage [64,65], sialography, cholangiography [66], Zenker's diverticulum, pseudo cysts [67], nephrostomy tubes and enema [68-71].

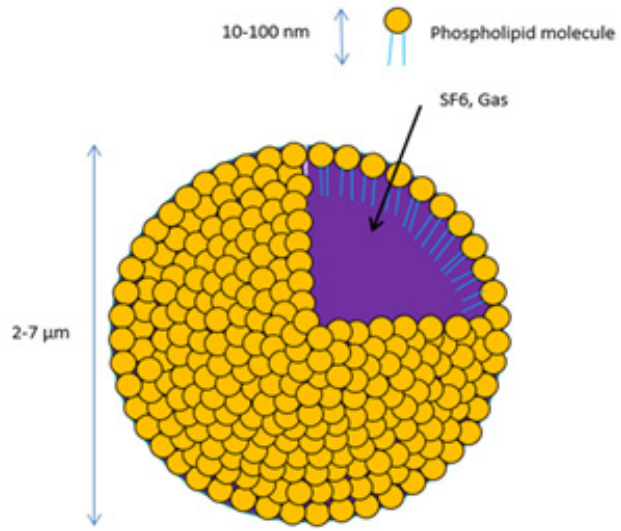

Figure 3. Composition of an ultrasound contrast agent microbubble [SonoVue ®]. The microbubbles are formed by a shell membrane filled with gas. In the case of SonoVue ®, the shell consists of phospholipids comprising a hydrophilic head [red] and two.

Echovist

Echovist is a suspension of galactose microparticle/air microbubble [72]. The intravascular life-time of Echovist is not sufficient for passing through the pulmonary circulation and for evaluating cardiac blood stream, so later more persistent contrast agents became available like Albunex and Levovist [73].

Table 4. Microbubble contrast agents' details by the category of manufacture name, shell, gas and mean size [74-76].

Name	Shell	Gas	Mean Size
Albunex	Albumin	Air	4.3
Optison	Albumin	Octafluoropropane	2-4.5
Definity	Lipid/surfactant	Octafluoropropane	1.1-3.3
Imagent	Lipid/surfactant	N2/perfluorohexane	6
Sonovue	Lipid	Sulphur hexafluoride	02-03
Levovist	Lipid/galactose	Air	02-04
Al-700	Ploymer	Decafluorobutane (DFB)	8

Advantages of microbubbles contrast media

On top of the strengths mentioned in the medical sonography entry, contrast-enhanced ultrasound adds these additional advantages:

The body is 73% water, and therefore, acoustically homogeneous. Blood and surrounding tissues have similar echogenicities, so it is also difficult to clearly discern the degree of blood flow, perfusion, or the interface between the tissue and blood using traditional ultrasound [77]. Ultrasound imaging allows real-time evaluation of blood flow [77]. Destruction of microbubbles by ultrasound [78] in the image plane allows absolute quantification of tissue perfusion [79]. Also ultrasonic molecular imaging is safer than molecular imaging modalities such as radionuclide imaging because it does not involve radiation [77]. In addition, alternative molecular imaging modalities, such as MRI, PET, and SPECT are very costly. Ultrasound, on the other hand, is very cost-efficient and widely available [80]. Since microbubbles can generate such strong signals, a lower intravenous dosage is needed, micrograms of microbubbles are needed compared to milligrams for other molecular imaging modalities such as MRI contrast agents [80] Targeting strategies for microbubbles are versatile and modular. Moreover, targeting a new area only entails conjugating a new ligand. Active targeting can be increased [enhanced microbubbles adhesion] by Acoustic radiation force [81,82] using a clinical ultrasound imaging system in 2D-mode and 3D-mode [83-85].

Disadvantages of microbubbles contrast media

In addition to the weaknesses mentioned in the medical sonography entry, contrast-enhanced ultrasound suffers from the following disadvantages:

Microbubbles don't last very long in circulation. Also They have low circulation residence times because they either get taken up by immune system cells or get taken up by the liver or spleen even when they are coated with PEG [80]. In addition, Ultrasound produces more heat as the frequency increases, so the ultrasonic frequency must be carefully monitored. Microbubbles burst at low ultrasound frequencies and at high mechanical indices [MI], which is the measure of the negative acoustic pressure of the ultrasound imaging system. Increasing MI increases image quality, but there are tradeoffs with microbubble destruction. Microbubble destruction could cause local microvasculature ruptures and hemolysis [80]. Low-targeted microbubble adhesion efficiency, which means a small fraction of injected microbubbles bind to the area of interest [86]. This is one of the main reasons that targeted contrast-enhanced ultrasound remains in the preclinical development stages.

Nano-structured contrast agents' details and applications

Here is the list of nano-structured ultrasound contrast agents and their applications with complete details. These kind of contrast agents are mostly used in molecular imaging of ultrasound which also can be used in echocardiography. Molecular imaging is the visualization, characterization, and measurement of biological processes at the molecular and cellular levels in humans and other living systems [87]. To elaborate; Molecular imaging typically includes 2- or 3-dimensional imaging as well as quantification over time [87,88].

Echogenic liposomes

Liposomes are vesicles composed of phospholipid bilayers surrounding an aqueous space also they have been shown to be safe for injection and suitable for antibody conjugation [89]. Liposomes also have the advantage that they can easily be formulated below 1 μm in diameter which is desirable for safe pulmonary capillary passage [89].

Per-fluorocarbon emulsion [PFC] nanodroplets

Perfluorocarbons [PFCs] are synthetic organic compounds in which all or most of the hydrogen atoms have been replaced with fluorine atoms [90]. These molecules have the unique

property of being both lipophobic and hydrophobic. The use of perfluorocarbons has been explored for various medical applications, including percutaneous transluminal cardiac angioplasty [PTCA] [91-93] partial liquid lung ventilation and gastrointestinal X-ray contrast agent [89,92,94,95].

Nanobubbles

Due to the rapid development in the field of nanotechnology, a number of NB contrast agents have been produced using liposomes, inorganic materials, metals and polymers [96,97]. During the synthesis of NBs, the organic solvent is removed by evaporation or extraction, and the internal water-phase is eliminated during lyophilization or spray drying [96]. NBs may possess a porous internal structure with multiple voids that are amenable to analysis with scanning or transmission electron microscopy [97].

Solid nanoparticles

Solid nanoparticles such as amorphous solid particles including silica or iron oxide particles contain gas pocket sin their pore sand fissure sand have been shown to generate Detectable backscatter for ultrasound imaging. Liuetal [36,98] imaged the liver of mice after intravenous administration of 100nm silica nanoparticles and showed that theme an acoustic intensity increased by 30% compared to back-ground. Iron oxide based nanoparticles [SPIO] were used to delineate malignant gliomas orthotopically implanted into the brain of rats in another study [36,99].

Table 5. Nano-structured contrast agents' details and applications.

Name	Components	Common Uses
Echogenic liposomes	Phospholipid bilayers	Injection and suitable for antibody conjugation
Per-fluorocarbon emulsion [PFC] nanodroplets	Fluorine atoms	Percutaneous transluminal cardiac angioplasty [PTCA] partial liquid lung ventilation and gastrointestinal X-ray contrast agent
Nanobubbles	liposomes, inorganic materials, metals and polymers	-
Solid nanoparticles	Silica or iron oxide particles	delineate malignant gliomas orthotopically implanted into the brain

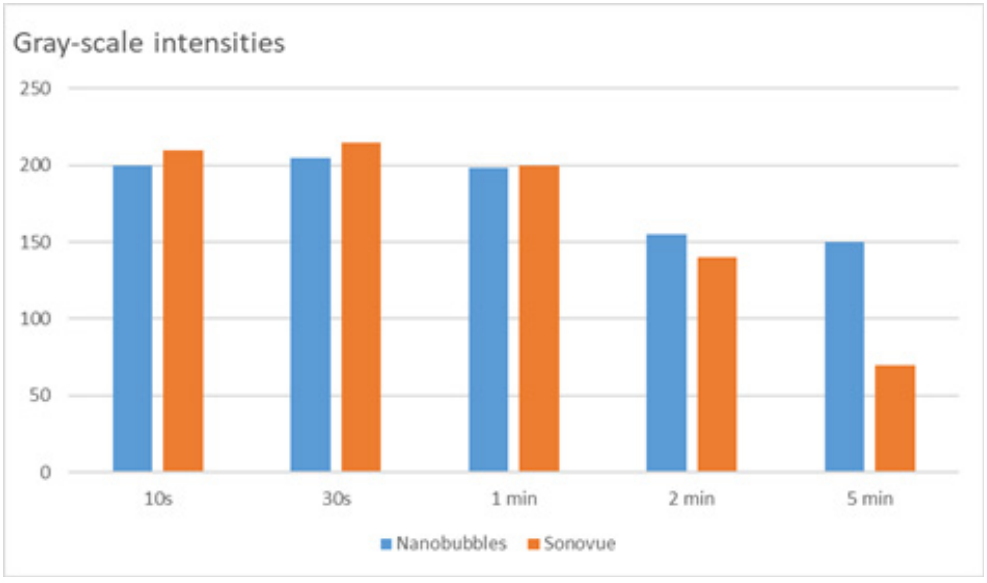

Figure 4. A comparison of microbubbles and nano CM through tumor gray-scale enhancement after caudal vein injection with nanobubbles [red] and SonoVue [blue]. **P < 0.01 gray-scale intensity comparison between nanobubbles and SonoVue at the same time point [100].

CONCLUSION

Magnificent discoveries and inventions in the early days of ultrasound have revolutionized diagnosis and treatment for numerous diseases. To appreciate the advancements in this field, it is important to explore its historical development. Contrast media for ultrasound imaging include various formulations of microbubbles or microspheres, primarily used in echocardiography and Doppler imaging. Ultrasound contrast agents can be categorized in two ways: by their generation and by their size. Non-microbubble-based contrast agents consist of submicron or nanosized particles, which include either liquid or solid colloids ranging from 10 to 1000 nanometers. Based on their composition and size, different types of submicron or nanosized particles have been synthesized for ultrasound imaging, including echogenic liposomes, perfluorocarbon (PFC) emulsion nanodroplets, nanobubbles, and solid nanoparticles.

LIMITATIONS

Echocardiography contrast agents, while beneficial for enhancing diagnostic capabilities, present several limitations and potential issues in practical applications. The cost of contrast agents can significantly increase the expense of echocardiographic exams, potentially limiting their use in resource-limited settings (26). Access to these agents may be restricted in certain regions or healthcare facilities, and some patients may experience allergic reactions or adverse effects, necessitating careful screening and monitoring. Technical challenges in the administration and short half-life of microbubble contrast agents require timely imaging to capture optimal results (44). Additionally, while microbubbles enhance visualization of cardiac chambers and the endocardium, their ability to penetrate deeper tissues is limited, and their presence can introduce image artifacts. Regulatory approval and adherence to clinical guidelines vary by region, impacting adoption and use in clinical practice. Storage and handling requirements add logistical complexities, and variability in protocols can lead to inconsistent results, necessitating standardization. Certain patient populations, such as those with severe pulmonary hypertension, may be at higher risk of complications, and effective use requires specialized training and expertise that may not be uniformly available (28). Potential interactions with other medications and inconsistent reimbursement policies further complicate practical applications. Addressing these challenges through improved training, standardization of protocols, regulatory harmonization, and cost-effective solutions will be crucial for maximizing the benefits of contrast-enhanced echocardiography in clinical practice (6).

CONFLICTS OF INTEREST

Ramin Ghasemi Shayan, Amin Fathi, Al Ghaffari, Forough Rezvani and Mona Fazel Ghaziyani's declare that they have no conflict of interest.

LEGENDS

CEUS: Contrast Enhanced Ultrasound; FDA: Food and Drug Administration; US: Ultrasound; UCA: Ultrasound Contrast Agent; DFB: Decafluorobutane; PFC: Per-Fluorocarbon Emulsion; PTCA: Percutaneous Transluminal Cardiac Angioplasty; USCA: University of South Carolina Aiken.

AUTHOR CONTRIBUTIONS

The main idea of the article was from Mr Ramin Ghasemi Shayan and literature search and data analyses were performed by Ramin Ghasemi Shayan.

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