Cardiovascular Ultrasound

REVIEW

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Ultrasound enhancing agents in cardiovascular imaging: expanding horizons beyond coronary arteries

Arif Albulushi[1,2*], Feng Xie[1] and Thomas R. Porter[1]

Abstract

From its inception as a two-dimensional snapshot of the beating heart, echocardiography has become an indelible part of cardiovascular diagnostics. The integration of ultrasound enhancing agents (UEAs) marks a pivotal transition, enhancing its diagnostic acumen beyond myocardial perfusion. These agents have refined echocardiography's capacity to visualize complex cardiac anatomy and pathology with unprecedented clarity, especially in non-coronary artery disease contexts. UEAs aid in detailed assessments of myocardial viability, endocardial border delineation in left ventricular opacification, and identification of intracardiac masses. Recent innovations in UEAs, accompanied by advancements in echocardiographic technology, offer clinicians a more nuanced view of cardiac function and blood flow dynamics. This review explores recent developments in these applications and future contemplated studies.

Keywords Ultrasound enhancing agents (UEAs), Sonothrombolysis, Microvascular obstruction (MVO), Peripheral artery disease (PAD), Cardiovascular diagnostics

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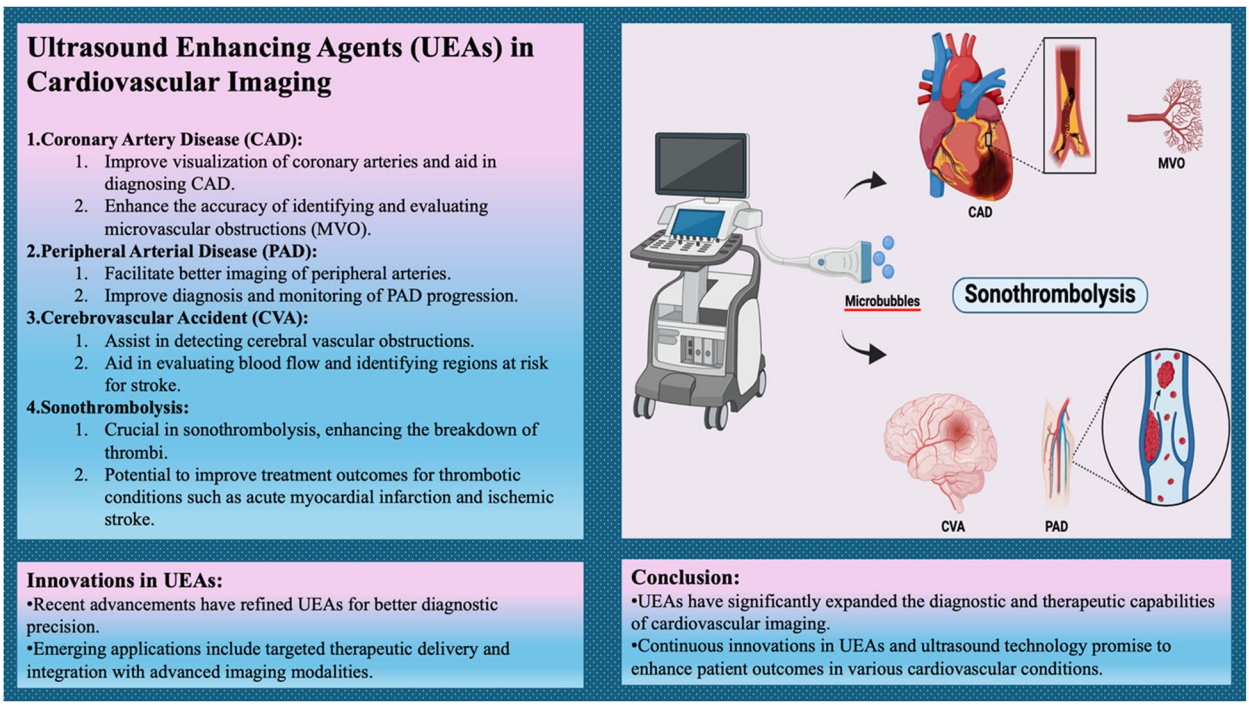
Graphical Abstract



Introduction

Echocardiography has evolved from a simple two-dimensional imaging modality to a sophisticated diagnostic tool integral to cardiovascular medicine [1]. Ultrasound enhancing agents (UEAs) have been pivotal in this evolution, significantly improving the visualization of cardiac anatomy and pathology [2]. Initially used to enhance myocardial perfusion imaging, UEAs now play crucial roles in various non-coronary artery disease contexts, including myocardial viability assessment, endocardial border delineation, and identification of intracardiac masses [3]. Recent advancements in UEAs and echocardiographic technology offer clinicians a more nuanced view of cardiac function and blood flow dynamics [4]. This review provides a comprehensive overview of the current applications of UEAs in cardiovascular imaging, particularly beyond coronary artery disease, and highlights recent advancements and future directions.

Techniques and protocols

UEAs are administered intravenously and consist of microbubbles that enhance ultrasound signals Fig. 1. Standard protocols involve specific imaging settings and safety precautions to maximize diagnostic yield while minimizing risks. Techniques such as low mechanical index imaging and harmonic imaging are commonly employed to optimize the visualization of UEAs.

Critical analysis of clinical data

Recent studies have demonstrated the efficacy of UEAs in various non-coronary artery disease contexts [5]. For example, UEAs have shown promise in improving tissue perfusion in peripheral artery disease (PAD) patients, as demonstrated by Mason et al. Additionally, innovations in endovascular ultrasound techniques have significantly enhanced limb perfusion in acute ischemia settings. Comparative analyses with established imaging modalities underscore the superior diagnostic capabilities of UEAs in specific clinical scenarios.

Addressing the research gap

The exploration of ultrasound enhancing agents (UEAs) beyond coronary artery disease (CAD) is still in its early stages. Despite significant potential, there is a noticeable gap between research advancements and their clinical application [6]. This review aims to bridge this gap by providing a comprehensive analysis of current UEA innovations, practical applications, and future directions in non-CAD conditions. We explore untapped UEA applications that go beyond traditional diagnostics, including

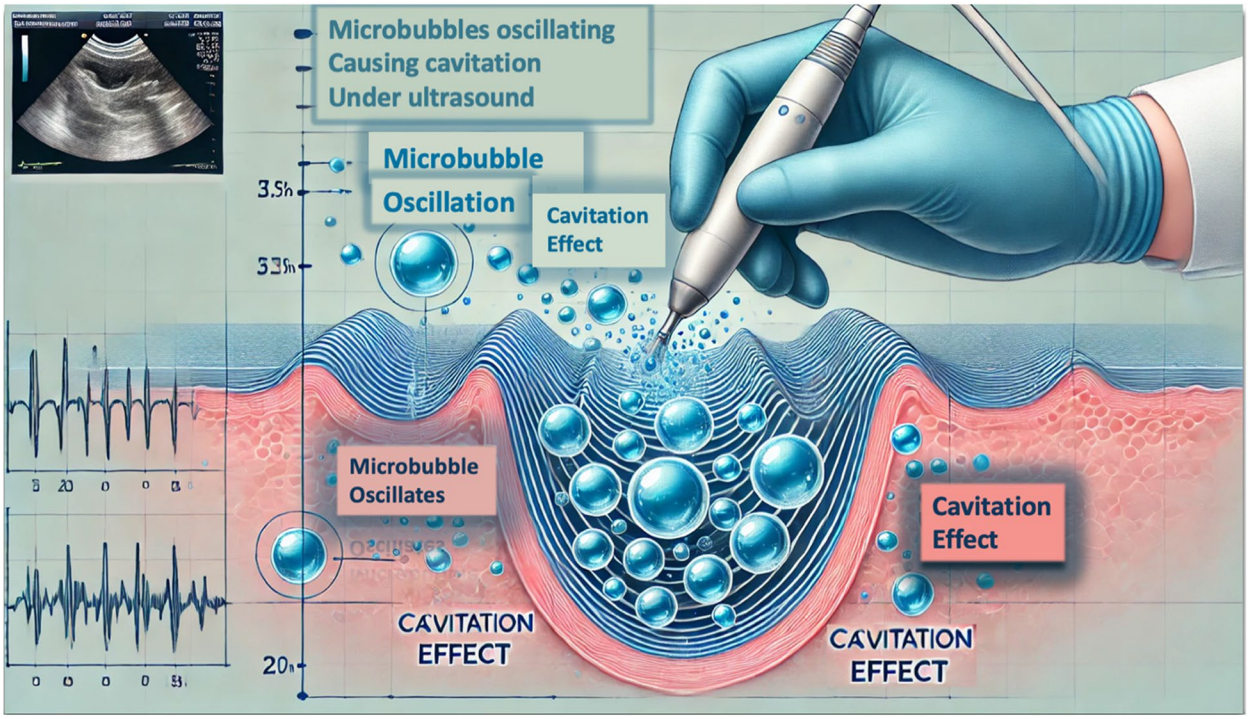


Fig. 1 Microbubble Oscillation and Cavitation Under Ultrasound in the Cardiovascular System

enhancing pharmacological efficacy and targeted therapeutic delivery systems Table 1. These areas, sparsely covered in current literature, represent a frontier in cardiovascular treatment protocols. Additionally, we advocate for integrating UEAs with other imaging modalities to improve diagnostic accuracy and therapeutic outcomes in peripheral vascular disease, carotid artery disease, and other vascular anomalies.

Underutilization of UEAs in clinical settings is often due to limited awareness among healthcare professionals and a lack of comprehensive, evidence-based guidelines. This review synthesizes fragmented evidence into a coherent narrative, promoting UEA integration into routine practice and emphasizing the need for extensive training programs highlighting their multifaceted benefits. We also project future advancements, discussing how next-generation microbubbles and improved ultrasound technology may expand UEAs' therapeutic window. The convergence of molecular imaging with UEAs offers a unique opportunity to understand pathophysiological

Table 1. Central Table summarizing key studies of the use of contrast enhancing agent

Author	Study Year	Methodology	Application	Key Findings	Clinical Implications
Niccoli G et al.	2016	Review Article	Diagnostic techniques in myocardial infarction	Significance of microvascular obstruction highlighted	Improved diagnostic techniques needed in myocardial infarction
Symons R et al.	2018	Longitudinal Study with CMR	Post-infarction management using CMR	CMR provides long-term prognostic value post-STEMI	Advanced imaging utility in post-infarction management
Aggarwal S et al.	2018	Observational Study with Echocardiography	Microvascular assessment in STEMI	Prevalence and predictive value of microvascular flow abnormalities	Importance of microvascular assessment in STEMI
Xie F et al.	2020	Analysis of Event-Free Survival	Survival impact of microvascular perfusion	Event-free survival dependent on microvascular perfusion	Crucial role of microvascular perfusion in patient outcomes
Wu J et al.	2015	Experimental Study	Reducing myocardial infarct size	Modified ultrasound with microbubbles effective in reducing infarct size	Therapeutic potential of ultrasound in myocardial infarction treatment
Slikkerveer J et al.	2012	Pilot Study	Ultrasound-enhanced thrombolysis in STEMI	Feasibility of ultrasound-enhanced thrombolysis demonstrated	Novel approach in early intervention for STEMI
Mathias W Jr. et al.	2016	Clinical Trial	Enhancing microvascular flow in STEMI	Improved microvascular flow with ultrasound impulses	Ultrasound use for enhancing microvascular flow in STEMI
Mason OR et al.	2020	Clinical Study	Tissue perfusion in PAD using microbubble cavitation	Improved perfusion in PAD patients	Potential of UEAs in managing PAD
Muller MA et al.	2021	Clinical Trial	Endovascular ultrasound for limb ischemia	Effectiveness of endovascular ultrasound in treating limb ischemia	Novel approach for acute ischemia management
Lindner JR et al.	2019	Study with CEUS	Monitoring blood flow changes in SCD	CEUS capable of detecting blood flow changes in SCD	Diagnostic potential of CEUS in SCD management

processes at a cellular level, paving the way for personalized medicine in vascular diseases [7]. By highlighting these aspects, this review aims to provide actionable insights and concrete research directives, bridging the gap between theoretical promise and practical application in non-CAD therapeutic strategies.

Clinical applications and progress over the last 20 years

Despite the perception that considerable progress has not been made in the last 20 years, recent developments in UEAs and their clinical applications demonstrate significant advancements. Key studies have shown the efficacy of UEAs in various cardiovascular and non-cardiovascular contexts.

For instance, the application of UEAs in PAD has shown promising results. Mason et al. [8] demonstrated that microbubble cavitation significantly enhances tissue perfusion in PAD patients, leading to improved clinical outcomes. Additionally, advancements in catheter-based endovascular ultrasound techniques have increased limb perfusion in acute ischemia settings [9].

In the realm of myocardial viability, UEAs have refined the visualization of microvascular flow patterns, which is critical for the prognosis of myocardial recovery post-STEMI. Mathias et al. [10] highlighted the potential of diagnostic ultrasound impulses to improve microvascular flow, providing better myocardial recovery and patient outcomes.

Moreover, innovative approaches such as combining UEAs with molecular imaging have shown potential in elucidating pathophysiological processes at a cellular level. This integration opens new avenues for personalized medicine, particularly in vascular diseases.

Novel therapeutic techniques: sonothrombolysis and beyond

Sonothrombolysis represents a significant advance in the management of acute myocardial infarction (AMI), offering a less invasive yet effective means to alleviate thrombotic occlusion [11]. UEAs play a pivotal role in this technique, with their ability to oscillate and resonate under sonication, thus augmenting the thrombolytic effects [12]. This review expands upon the intricate mechanisms at play, detailing how the acoustic pressure waves generated by high mechanical index (MI) ultrasound interact with UEAs to induce microbubble cavitation [13]. This process facilitates the permeation and activation of thrombolytic agents within the thrombus structure, promoting dissolution and enhancing microvascular perfusion [14].

Beyond its application in AMI, sonothrombolysis, facilitated by UEAs, shows potential in other thrombotic conditions such as deep vein thrombosis and ischemic stroke, offering a paradigm shift in thrombolytic strategies [15]. The exploration extends to the latest research on optimizing sonication parameters and UEA formulations to maximize therapeutic efficacy while minimizing potential risks. Furthermore, the integration of UEAs with advanced imaging modalities holds promise for improving the precision of sonothrombolysis, potentially transforming the landscape of thrombus management across a spectrum of cardiovascular diseases.

Risks and benefits of cavitation in contrast-enhanced ultrasound

While the theoretical benefits of cavitation in sonothrombolysis are well-documented, it is essential to address the potential risks associated with this technique. Cavitation can cause microcirculatory disruption and hemorrhage, which necessitates a balanced discussion of both benefits and risks.

Recent studies have explored the optimization of sonication parameters to maximize therapeutic efficacy while minimizing potential risks. For example, Bader et al. [16] investigated the safety profile of sonothrombolysis and found that appropriate control of acoustic pressure waves and microbubble concentrations can significantly reduce adverse effects.

Furthermore, innovative ideas in the development of new ultrasound contrast agents focus on enhancing safety and efficacy. Next-generation microbubbles with improved stability and targeting capabilities are being designed to reduce the likelihood of microcirculatory disruption and hemorrhage while enhancing the therapeutic benefits of cavitation.

The potential of targeted bubbles in clinical applications has also seen significant advancements. Despite the slow progress since Dr. Lindner's report, recent research has demonstrated the feasibility of using targeted bubbles for site-specific drug delivery and imaging, thereby improving clinical outcomes without increasing the risk of adverse effects [17].

Sonothrombolysis

The challenge of persistent microvascular obstruction (MVO) post-revascularization in acute STEMI is a well-documented prognosticator of adverse outcomes [10, 18]. Despite successful angiographic recanalization, MVO is a harbinger of diminished left ventricular function, an increased propensity for heart failure, and a greater likelihood of mortality [19, 20]. Current clinical markers, including angiographic and electrocardiographic indicators, inadequately represent the prevalence of MVO, a limitation that has been elucidated through more sensitive diagnostic modalities such as cardiac magnetic resonance imaging and myocardial contrast echocardiography (MCE) [21, 22].

Pharmacological strategies and interventional tactics aimed at preventing MVO have largely fallen short in reducing the sequelae of reperfusion injury. Notably, conventional therapies like high-intensity statins and beta blockers post-percutaneous coronary intervention (PCI) are not universally effective, with substantial microvascular perfusion abnormalities persisting in a significant cohort of patients [22]. The advent of sonothrombolysis, utilizing ultrasound-induced microbubble cavitation, has shown potential to mitigate these issues. By disintegrating both large vessel thrombi and microthrombi, sonothrombolysis presents a viable solution to restore microvascular flow, as evidenced by pre-clinical large animal models and initial clinical trials [23, 24].

The implications of sonothrombolysis extend beyond the coronary arteries, addressing conditions like atherosclerotic peripheral arterial disease (PAD) where perfusion deficits are paramount. The diagnostic capability of ultrasound, when coupled with microbubble cavitation, has been demonstrated to augment tissue perfusion through mechanisms such as convective shear and purinergic signaling pathways. Studies reveal that these phenomena mediate the release of endogenous vasodilators, enhancing regional blood flow even with limited exposure [8].

Further research in animal models underscores the versatility of sonothrombolysis in PAD. Endovascular ultrasound catheters have been employed to facilitate limb perfusion, presenting promising findings of substantial flow increases in ischemic limbs. These outcomes suggest that such non-cavitating ultrasound modalities, commonplace in human thrombolysis, can ameliorate vascular resistance and augment perfusion in acute ischemic conditions [25].

Moreover, contrast-enhanced ultrasound (CEUS) has been instrumental in discerning microvascular flow alterations in pathologies such as sickle cell disease, capturing physiological changes inherent to vaso-occlusive crises. These findings, although preliminary, provide a foundation for the role of CEUS in capturing dynamic blood flow changes associated with vascular pathophysiology [26].

New and emerging applications of UEAs

Advancements in microbubble physics and imaging techniques are driving new applications in ultrasound contrast imaging, particularly in the realm of sonothrombolysis Graphical Abstract. The development of non-invasive procedures that estimate hepatic fibrosis and portal hypertension with second-generation microbubbles marks a significant leap from traditional, more invasive diagnostic methods. Furthermore, clinicians now have at their disposal new techniques for directly estimating the attenuation coefficient of UCAs, streamlining and improving the efficiency of ultrasound diagnostic procedures in clinical settings [27].

In parallel, activatable contrast agents responsive to biological stimuli are enhancing the capabilities of optoacoustic imaging, with potential adaptations for targeted sonothrombolysis therapies. These agents could revolutionize cancer detection and treatment, allowing for more precise and personalized approaches based on each tumor's molecular phenotype. In addition, novel frequency mixing ultrasound imaging methods using nanobubbles present a new frontier for high-resolution imaging, which could greatly benefit real-time monitoring during sonothrombolytic interventions [28, 29].

The potential of UCAs extends to targeting ErbB2 (+) gastric cancer cells, indicating new therapeutic pathways for sonothrombolysis in cancer treatment. These targeted approaches could lead to significant advancements in patient outcomes, especially when combined with technologies like ultrasound-switchable fluorescence for deep tissue imaging. This multifaceted development signifies UCAs' expanding role beyond cardiovascular applications, stepping into areas such as oncology, hepatology, and molecular imaging with promising clinical implications [30].

Conclusion

The scope of this review extends beyond merely highlighting the potential of sonothrombolysis; it advocates for a paradigm shift in the management of cardiovascular disorders. By harnessing the power of ultrasound-induced microbubble cavitation, we can transcend traditional barriers in the treatment of MVO and PAD, reshaping the therapeutic landscape for patients afflicted with these conditions.

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Conflict of interest
The authors declare that they have no conflicts of interest relevant to the content of this manuscript.

Authors' contributions
A.A. (Arif Albulushi), F.X. (Feng Xie), and T.R.P. (Tom R Porter) all made significant contributions to this study. Specifically: A.A. and F.X. conceptualized the study and designed the research methodology. A.A. collected and curated the data, while F.X. and T.R.P. conducted the formal analysis. T.R.P. and F.X. wrote the main manuscript text and prepared figures 1-3. A.A., F.X., and T.R.P. reviewed and edited the manuscript. All authors have read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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