Intrinsic Imaging
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Guidance for Sponsors
Volume 5, Issue 6 · 2026 Edition

Contrast Echocardiographic Imaging in Clinical Trials

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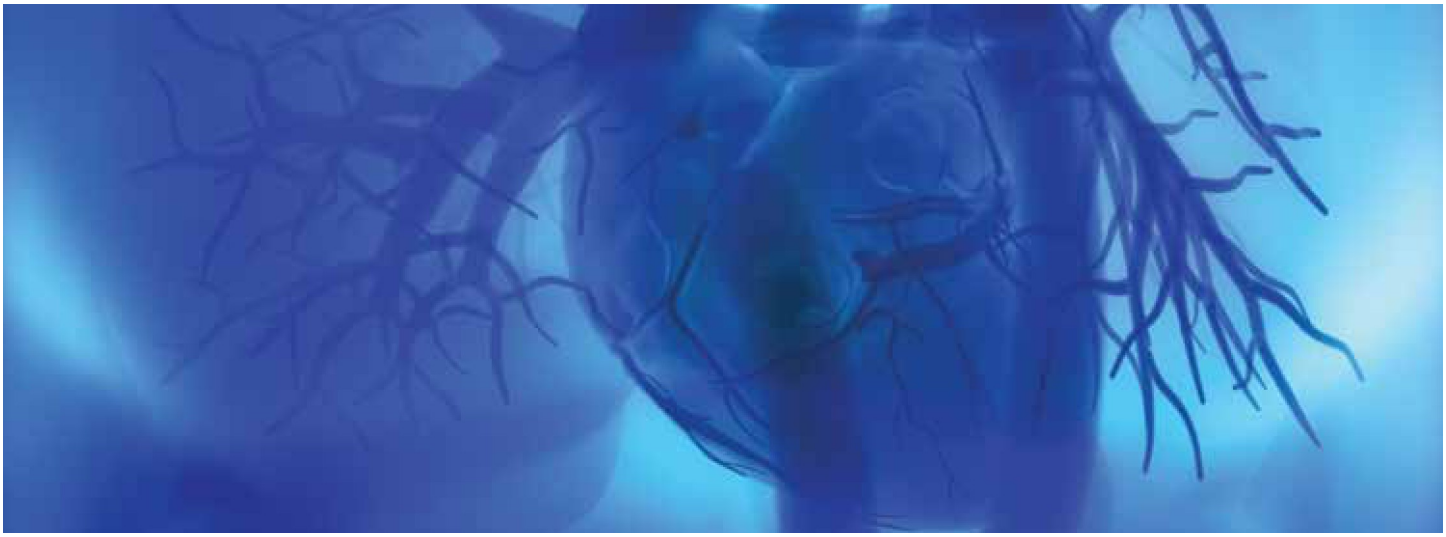

Ultrasound enhancing agents turn a difficult echocardiogram into a diagnostic one. By opacifying the left ventricle and sharpening the endocardial border, they improve the accuracy and reproducibility of ejection fraction and wall motion analysis, measures that sit at the heart of many cardiovascular and cardio-oncology trials. Over the past two decades, regulators have progressively relaxed the restrictions placed on these agents as their safety record has grown. This issue reviews the technology, its regulatory history and the role of myocardial perfusion, and sets out what sponsors should specify when contrast echocardiography supports a trial endpoint.

The Clinical Need

Cardiovascular disease remains the leading cause of death worldwide, claiming an estimated 19.8 million lives in 2022, about 32% of all deaths.[1] Clinical trials of new diagnostic and therapeutic tools are correspondingly numerous, and echocardiography, portable, safe and inexpensive, is the workhorse of cardiac assessment within them.

Image quality has always been the limitation. Despite remarkable advances in transducers and processing, body habitus, lung disease and chest wall anatomy still leave a meaningful share of studies technically difficult. Augmenting the reflected signal with contrast complements improvements in hardware and raises the signal-to-noise ratio substantially.

From Agitated Saline to Microbubbles

Contrast echocardiography began with saline agitated with room air. Those bubbles were trapped and harmlessly destroyed in the pulmonary capillaries, so they reached the left heart only through a right-to-left shunt, which remains their diagnostic use today. Modern agents encapsulate an inert, high-molecular-weight gas within a shell of albumin, lipid or polymer. The resulting microbubbles, smaller than red blood cells, traverse the pulmonary circulation, opacify the left heart and resonate in the ultrasound field, strongly enhancing the returning signal. The American Society of Echocardiography now refers to these products as ultrasound enhancing agents (UEAs).[2]

Approved Uses and Evidence

Three UEAs are approved by FDA, and their approved cardiovascular use is left ventricular opacification.[3] In patients with suboptimal images, contrast improves endocardial border delineation and brings ejection fraction measured by echocardiography closer to the reference standard of cardiac magnetic resonance. In stress echocardiography, it improves the detection of wall motion abnormalities and obstructive coronary disease, even when operators judge unenhanced images adequate, and it allows patients with difficult body habitus to be studied.[2]

A Maturing Safety Record

In 2007, after four deaths and about 190 severe cardiopulmonary reactions temporally associated with administration, FDA added a boxed warning to UEA labeling. As evidence accumulated, the agency reversed course in stages: contraindications were downgraded to warnings in 2008, mandatory 30-minute post-injection monitoring for higher-risk patients was removed in 2011, and between late 2016 and early 2017 the contraindication in patients with known or suspected intracardiac shunts was removed for all three agents.[4,5] Serious reactions remain rare, and the current ASE guideline supports UEA use whenever it improves diagnostic confidence.[2]

Myocardial Perfusion

Wall motion abnormalities are late manifestations of ischemia; perfusion defects appear earlier. Myocardial contrast echocardiography exploits the fact that microbubbles behave as intravascular tracers: after high-mechanical-index pulses destroy the bubbles in the myocardium, the rate and plateau of replenishment reflect myocardial blood flow and blood volume. Perfusion echocardiography is well established in research and supported by guideline recommendations, but it remains outside the approved labeling of the available agents.[2,3] In trials, it is therefore best positioned as an exploratory or mechanistic endpoint, with acquisition and analysis rigorously standardized.

Applications in Clinical Trials

Contrast-enhanced echocardiography offers reproducible measurement of left ventricular volumes and ejection fraction, a key safety endpoint in cardio-oncology, where cancer therapy-related cardiac dysfunction is defined in part by declines in ejection fraction and global longitudinal strain.[6] It also supports trials in heart failure, ischemic heart disease and structural intervention, and the detection of left ventricular thrombus.

Guidance for Sponsors

Using contrast echocardiography in a trial

- **Define when contrast is used.** State in the protocol whether contrast is mandatory, or triggered by a prespecified image quality threshold.[2]
- **Standardize the method.** Specify agent, dose, infusion or bolus delivery, mechanical index and imaging presets.[2]
- **Be consistent across visits.** Do not compare contrast-enhanced with unenhanced measurements in the same subject.
- **Treat perfusion as exploratory.** Prespecify perfusion analysis as exploratory unless agreed with regulators.[3]
- **Read centrally.** Use blinded core laboratory analysis under a documented imaging charter.[7]

Summary

Ultrasound enhancing agents bring echocardiography closer to the accuracy of cardiac MRI while preserving its accessibility and low cost. With a safety record that has led regulators to remove most early restrictions, and with perfusion imaging continuing to mature, contrast echocardiography is a powerful instrument for clinical trials, provided that its use is defined, standardized and analyzed with care.

About the Author

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References

1. World Health Organization. Cardiovascular diseases (CVDs) fact sheet. who.int

2. Porter TR, Mulvagh SL, Abdelmoneim SS, et al. Clinical applications of ultrasonic enhancing agents in echocardiography: 2018 American Society of Echocardiography guidelines update. *J Am Soc Echocardiogr.* 2018;31(3):241–274. asecho.org

3. Centers for Medicare & Medicaid Services. Local coverage determination L38786: Echocardiography for myocardial perfusion. cms.gov

4. Chai SC, Tan PJ, Tong KL. A review of the safety and clinical utility of contrast echocardiography. *Singapore Med J.* 2020;61(4):181–183. pmc.ncbi.nlm.nih.gov

5. Lantheus Medical Imaging. Lantheus announces FDA approval of Definity label update. February 2, 2017. investor.lantheus.com

6. Lyon AR, López-Fernández T, Couch LS, et al. 2022 ESC guidelines on cardio-oncology. *Eur Heart J.* 2022;43(41):4229–4361. academic.oup.com

7. U.S. FDA. Clinical trial imaging endpoint process standards: guidance for industry. April 2018. fda.gov

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