Review Article

My Approach to Contrast Echocardiography

Como eu faço Contraste Ecocardiográfico

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Introduction

Contrast echocardiography (CE) uses ultrasound enhancing agents (UEA) that, when introduced into the bloodstream and subjected to ultrasound (US), contrast the blood due to the great reflective capacity of microbubbles. It completely opacifies the left ventricle (LV), with better definition of endocardial borders, Doppler signal enhancement, and myocardial perfusion (MP).

Commercially available second-generation UEA are composed of high molecular weight gases surrounded by an outer shell of albumin, phospholipid, or polymer. These inert structures aggregate and remain within the intravascular space, presenting kinetics similar to those of red blood cells but at less than half their size (1.0–4.5 μm), which allows them to pass the pulmonary capillary barrier and reach the left chambers. They are predominantly excreted through the lungs, have a high metabolism (half-life, 10–12 min), do not deposit in the tissues, and, unlike iodinated contrast agents, present no known risk factors of nephrotoxicity.[1,2]

Adverse events and safety of UEA

Adverse events related to UEA use are rare, being mostly transient and self-limiting. In a meta-analysis of 110,500 patients, the incidence of severe allergic and anaphylactoid reactions immediately after UEA administration was estimated in 0.009% and 0.004%, respectively.[3] Aggeli et al. evaluated 5,250 patients and found supraventricular arrhythmias (0.1–0.5%), ventricular arrhythmias (0.02–0.20%), headache (5.3%), back pain (0.5%), dizziness (7.4%), and hypersensitivity reactions (0.44%) as the most frequent adverse events related to contrast echocardiography. That study reported no cases of death or acute myocardial infarction (AMI) related to UEA use.[4]

According to the latest American Society of Echocardiography guideline, UEA use is safe in adolescents and children over 5 years of age for Doppler signal enhancement and regional parietal motility (RPM) assessments as well as in children and adults with patent foramen ovale and a small right-to-left shunt. Furthermore, its use is safe in patients with pulmonary hypertension. UEA is contraindicated in patients with a known allergy to its components; moreover, data are lacking on its safety in pregnant women and children under five years of age. As with other advanced echocardiographic modalities, the unit must be properly equipped to manage possible serious complications.[5]

Keywords

Echocardiography; Contrast Echocardiography; Perfusion Imaging.

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Cost-effectiveness of UEA

A prospective cohort of 632 consecutive studies of patients with technically limited windows showed a significantly increased number of LV segments visualized after UEA administration versus no UEA in different settings and scenarios (inpatient, intensive care unit, operating room, and elective patients).

The analysis of RPM abnormality detection also showed an increased number of segments visualized with versus UEA in the same scenarios.

The same study evaluated the impact of the association of UEA with echocardiography on the clinical management of these patients. An influence of the contrast-enhanced technique was demonstrated in 35% of cases considering the drug treatment change and the reduced performance of invasive tests such as transesophageal echocardiography or those involving radiation exposure. These results were associated with a cost reduction of USD 122 per patient.[6]

Image generation techniques

The interaction between US and microbubbles is crucial for blood contrast. The use of low-energy US pulses, i.e., with a mechanical index (MI) < 0.2, makes the microbubbles resonate, producing harmonic frequencies that enable the assessment of LV opacification and the study of MP. The use of an ultrasonic pulse with a high MI (>0.8) makes the gas microbubbles expand, retract, and eventually break, thus losing their reflective capacity.

LV opacification images must be acquired with respect to some technical aspects. In addition to the low MI, the focus should be positioned at the level of the mitral valve to reduce microbubble destruction. The ventricular cavity should be homogeneously filled by UEA, with an acoustic shadow on the left atrium and no swirls in the apical region.

Most current devices have presets for UEA use.

UEA administration techniques

UEA infusion amount and rate affect imaging quality. High doses attenuate (cause a shadow) the image, while low

doses shorten the enhancement duration. A rapid infusion rate can lead to high UEA concentrations at the ventricular apex, causing attenuation artifacts in the LV basal region by generating a shadow on the ventricular cavity, while a slow infusion rate can lead to swirl formation and incomplete opacification (Figure 1 e Video 1).

Initially, peripheral venous access should be punctured in one of the upper limbs (preferably antecubital) with a larger caliber catheter (18–22) to preserve microbubble integrity. Connectors and intermediate tubes should be avoided, as should the use of a 3-way tap with the syringe containing the UEA in the straight position and the saline solution in the transverse line (T) since the microbubbles can be destroyed in the tap "curve." After UEA infusion, the subsequent saline solution flush should be delivered smoothly and slowly.

In Brazil, the available UEA is the SonoVue® (Bracco, Italy), which is used in a bolus infusion of 1.0 mL of pure agent followed by a bolus of 10 mL of 0.9% saline solution for each group of images to be acquired. It is also possible to optimize this bolus by lifting the injected arm 90 degrees (usually the right upper arm). The volume should be adjusted in subsequent injections according to obtained image quality.

Clinical applications

The only formal recommendation approved for UEA use in the assessment of cardiovascular disease is aimed at LV opacification when at least two contiguous myocardial segments are not well visualized during the conventional echocardiographic study. However, current guidelines supported by recent scientific evidence consider other applications such as MP and intracardiac mass assessment, spectral Doppler signal enhancement, and stress echocardiography.[5]

Quantification of volumes, EF, and regional LV parietal motility

Echocardiographic windows with suboptimal images and the presence of myocardial trabeculations hinder the correct identification of the blood interface with the compacted myocardium. After UEA injection, the contrasted blood fills the intra-trabecular spaces up to the compacted myocardium, allowing a more accurate assessment and making ventricular volume measurements more reproducible. These images should be acquired when the LV is completely opacified and the volumes quantified by the two-dimensional biplanar method performed by tracing the interface of the compacted myocardium and the ventricular cavity, excluding the trabeculae (Figure 2).[7] Ventricular volumes obtained by CE are greater than those found in non-contrast two- and three-dimensional echocardiograms with good correlation with the ventricular volumes found in cardiac magnetic resonance imaging.[8]

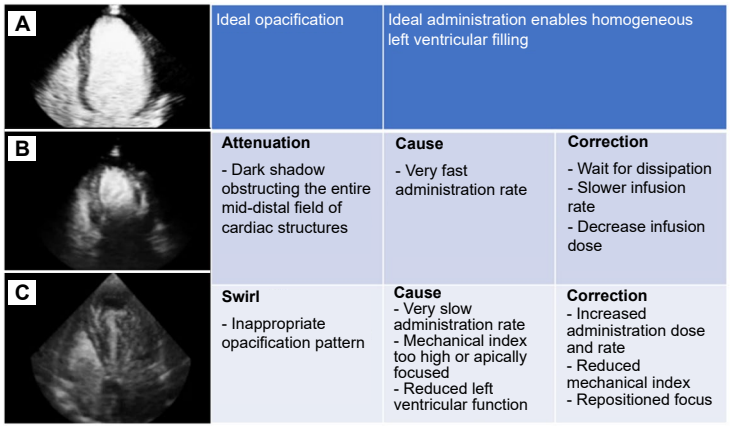
RPM analysis is a subjective assessment that depends on image quality. Thus, UEA should be used to assess ventricular volumes, quantify ejection fraction, and in situations in which volume analysis and RPM require diagnostic accuracy, such as in coronary heart disease, cardiomyopathies, and the follow-up of patients using cardiotoxic drugs.[9]

Echocardiography with myocardial perfusion

Since it presents behavior similar to that of red blood cells, UEA works as a marker of myocardial blood flow. Thus, myocardial perfusion echocardiography (MPE) can be used to assess risk area during AMI, viability after AMI (no-reflow identification), reperfusion therapy efficacy, and in the context of chronic coronary artery disease (Videos 2A, 2B, 2C).

MPE is performed after the infusion of small UEA bolus in low MI images, followed by the application of a high MI ultrasonic pulse – called a flash – to destroy the microbubbles and allow the subsequent analysis of their refilling in the myocardium (Figure 3).[9,10]

MP can be quantitatively evaluated through software post-processing (not yet commercially available for clinical use) or qualitatively evaluated through visual analysis. Qualitative analysis uses a semi-quantitative score with the following graduations: 1 = normal MP (with intense enhancement within 4 s after the flash); 2 = hypoperfusion (normal or



LV: left ventricle; MI: mechanical index.

Figure 1 – *Technical aspects of ventricular opacification. (a) Apical four-chamber plane focused on the right ventricle. Ideal opacification. (B) Apical four-chamber plane. Attenuation. (a) Apical four-chamber plane. Swirling. Video 1.*

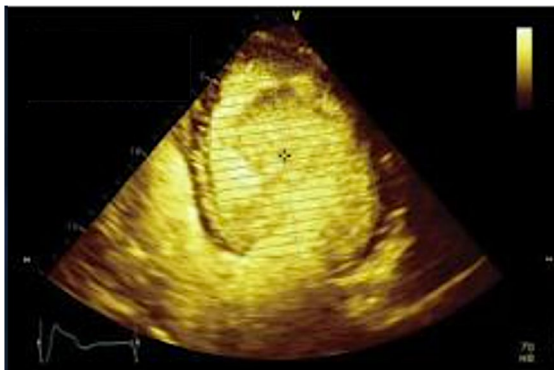


Figure 2 – *Apical four-chamber plane on contrast echocardiography showing sample ejection fraction calculation.*

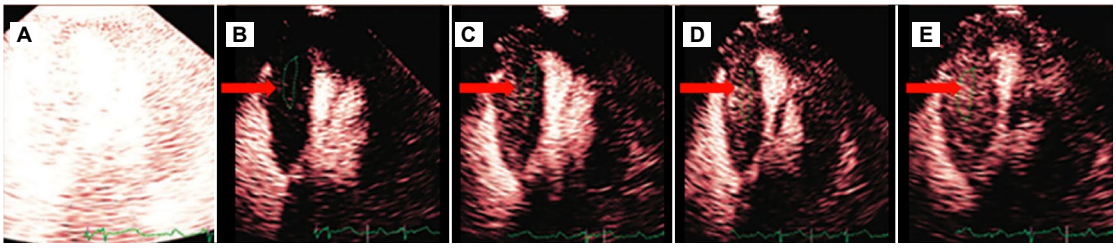


Figure 3 – *Apical four-chamber plane on sample myocardial perfusion echocardiography demonstrating myocardial refilling with an ultrasound enhancing agent after a flash (A) illustrated as a bright frame. After the high mechanical index pulse, microbubbles are destroyed (B), followed by myocardial refilling in subsequent images (C, D, E).*

rarefied enhancement 4–10 s after the flash); and 3 = no MP (little or no enhancement more than 10 s after the flash). Thus, normal myocardial refilling should occur in up to 4 s at rest and in up to 2 s during stress. The presence of normal MP in a given segment is considered a sign of myocardial viability.

Intracardiac abnormalities

Masses can correspond to innocent structures such as a false tendon, accessory papillary muscle, and prominent trabeculation; or pathological structures such as a thrombus or tumor. Thus, UEA can be used to confirm or exclude a suspected finding in this context.

Intracardiac thrombi

Despite advances in other imaging modalities, echocardiography is the most commonly. used initial diagnosis and risk stratification tool for patients predisposed to developing intracardiac thrombi.

LV thrombi are commonly located in the apical region. Their identification by conventional echocardiography can be challenging; however, using CE, the thrombus is visualized as a "filling defect" since the UEA does not penetrate its interior since it is an avascular structure (Figure 4A).[11]

Intracardiac masses

MPE characterizes the vascularization of cardiac masses, helping differentiate between malignant and benign tumors. This evaluation is qualitative and based on the visual analysis of the UEA refill time after a flash.

Benign tumors such as myxomas are poorly vascularized and have a perfusion similar to that of the myocardium (Figure 4B).

Malignant tumors are hypervascularized. Thus, increased tumor mass perfusion suggests malignancy (Figure 4C).[12]

Hypertrophic cardiomyopathy

CE can be performed in suspected cases of hypertrophic cardiomyopathy (HCM), especially the apical variant in which cardiac apex visualization is challenging.

Complete opacification of the LV by the UEA allows the identification of apical segment hypertrophy and the typical spade-like shape of the ventricular cavity in diastole (Figure 5A). Complications associated with HCM such as apical aneurysm and thrombus can also be identified.[13]

Noncompaction myocardium

Complete opacification of the LV cavity facilitates the recognition of deep trabecular recesses characteristic of noncompaction myocardium, increasing differentiation between compacted and non-compacted portions of the myocardium.[14]

Complications after myocardial infarction

In limited echocardiographic windows, CE may be essential

for visualizing LV aneurysm and associated complications such as thrombus (Figure 5C). Pseudoaneurysms, free wall rupture, and interventricular septum communications can also be identified using UEA.[15]

Stress echocardiogram

CE can increase the sensitivity, specificity, and diagnostic accuracy of tests under physical or pharmacological stress due to the adequate visualization of endocardial borders and RPM (Figure 6).[16]

The UEA should be administered with the patient at rest and later at peak stress 5–10 s before the end of the exercise or during the infusion of the pharmacological agent using the same route to compare the two moments. Additionally, an MP analysis helps assess subtle contractility abnormalities due to subendocardial ischemia since perfusion abnormalities occur before parietal motility abnormalities in the progression of the ischemic cascade.[17]

Therefore, the use of UEA during stress echocardiography is recommended whenever at least one myocardial segment is not well visualized.[18]

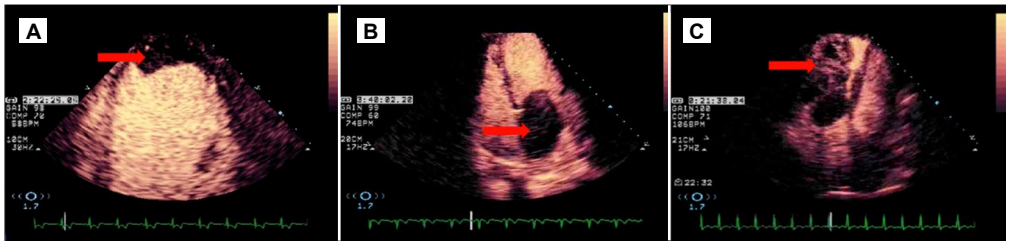


Figure 4 – *(A) Apical four-chamber plane on sample myocardial perfusion echocardiography focused on the right ventricle showing an unenhanced mass consistent with a thrombus. Video 3A. (B) Apical four-chamber plane of a left atrial myxoma mass with almost no enhancement.Video 3B. (C) Apical four-chamber plane of a right ventricle metastasis. The hypervascular mass demonstrates increased perfusion and areas of necrosis. Video 3C.*

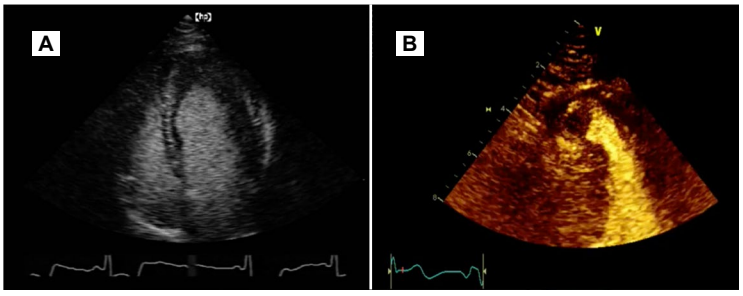


Figure 5 – *(A) Apical four-chamber plane on cardiac echocardiography demonstrating apical myocardial hypertrophy. Video 4A. (B) Apical two-chamber plane on cardiac echocardiography focused on the left ventricle showing an apical aneurysm with a thrombus. Video 4B.*

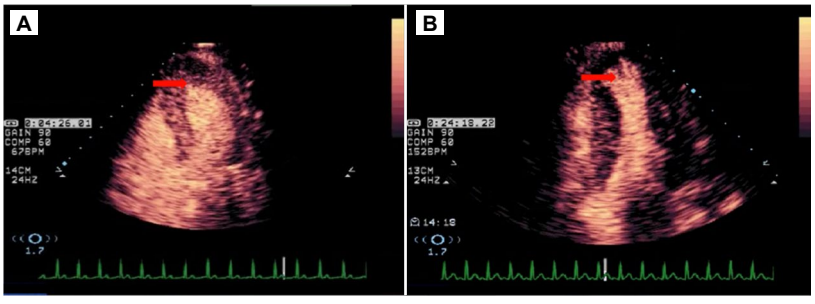


Figure 6 – *Sample contrast echocardiography under pharmacological stress with dobutamine and atropine. (A) Apical four-chamber plane at rest showing normal regional parietal motility and myocardial perfusion (red arrow). Video 5A. (B) Apical four-chamber plane at peak stress showing akinesia and a myocardial perfusion defect in the apical region (red arrow). Video 5B.*

Conclusion

CE is considered an essential component of a modern echocardiography laboratory due to its ability to provide unique information that improves the diagnosis of cardiovascular disease. Implementing UEA requires knowledge on agent-specific imaging protocols, a process that identifies patients likely to benefit from its use, and sound laboratory policies that ensure quality, efficiency, and safety.

Authors' contributions

Conception and writing of the manuscript: Aguiar, MOD; Oliveira, AJ; Stangenhaus, C; Critical revision of the manuscript important intellectual content: Mathias, W.

Conflict of interest

The authors have declared that they have no conflict of interest.

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