

Contrast Echocardiography in Real Life: Practicality, Safety, and Cost-Effectiveness

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After approximately 2 decades of use in practice, based also on several clinical studies, it can be stated that ultrasound enhancing agents (UEA) are extremely safe, following recommendations for their preparation and administration.¹⁻⁵ Severe adverse events are very rare, with an approximate prevalence of around 1 in every 10,000 administrations, anaphylactoid reactions being the most frequent.^{1,6-8} Specifically with the contrast SonoVue® (sulfur hexafluoride) used in Brazil, Furtado, Rassi, et al., in their safety study, reported a very low incidence of only 0.6% of allergic reaction in their population of 1,099 patients who received this agent.⁹ In general, allergic reactions occur immediately or within 30 minutes after administration; they are of mild intensity and transitory. The most common presentation is the appearance of erythematous skin lesions and urticaria. In this scenario, however, special attention should be paid to respiratory signs and symptoms, such as dyspnea, laryngeal stridor, and bronchospasm, as well as signs and symptoms of progression to eventual circulatory collapse, such as dizziness, paleness, and hypotension, as these are warning signs for the onset of anaphylactic shock. Patients must be carefully evaluated and observed, and measures aimed at anaphylaxis should be promptly instituted with antihistamines, corticosteroids, and epinephrine, following the care protocol of the institution, whose personnel must be very well trained.³

In October 2007, the United States Food and Drug Administration (FDA) issued a general contraindication (“black box”) for the use of Definity® and Optison® agents in acutely ill patients after analysis of 11 deaths potentially related to the use of these UEA. This restriction was later withdrawn after subsequent clinical studies provided extensive evidence of safety. Advanced pulmonary disease and pulmonary hypertension initially represented contraindications, but clinical trials confirmed their safety.¹⁰⁻¹² Additionally, in relation to the suspicion or presence of significant intracardiac shunt, also a previous contraindication, it was suspended by the FDA in 2016.^{2,12} Currently, only history of allergic reaction to any component

of UEA constitutes an absolute contraindication to their use.

Further supporting their safety, there is also the fact in which clinical scenarios UEA are used, often in technically more difficult exams of severely ill patients. Even so, multiple studies have not demonstrated an increase in morbidity and mortality outcomes. Additionally, in these adverse scenarios, it is also valid to argue that UEA can provide important definitions, such as assessment of left ventricular (LV) systolic function in critically ill patients with marked limitation of the echocardiographic window or search for intracavitary thrombus, making intervention possible, with improved evolution and prognosis.

In medical practice, we must always base our conduct on what is known as “evidence-based medicine,” on well-conducted and reliable studies. The medical literature is extremely important and must be followed. Nonetheless, I recognize that we must also consider the knowledge generated by the application of the various techniques in “real life,” a genuine translation of theory into practice with the challenges we face on a daily basis. A good example would be the use of UEA in stress echocardiography (SE), which is one of the main applications of contrast. Classically, its use is formally indicated when there is no clear visualization of at least 2 contiguous LV myocardial segments, but, in “real life” practice, it is justified in all exams in which the echocardiographer does not feel confident and judges the acoustic window suboptimal for interpretation, which is fundamental in this type of examination.^{2,13} UEA, in addition to increasing the sensitivity of the method, are also associated with an increase in the reproducibility of the wall motility score.¹⁴⁻¹⁶ In this field, I highlight an interesting study conducted by Larsson et al. The authors reported that, in 83 unenhanced exams, with acoustic windows considered adequate (with no formal indication for the use of UEA) and concluded as negative for the presence of myocardial ischemia, 46 patients (55%) showed evidence of myocardial ischemia (positive) when analyzed after the use of UEA and were reclassified.¹⁷ Finally, I quote another situation that is not uncommon for those who routinely perform SE. Eventually, an exam with an adequate resting echocardiographic window may become suboptimal in the peak stage as cardiac imaging becomes more difficult to acquire. This certainly causes difficulties and can lead to inaccurate interpretation, especially in a context where there are symptoms suggestive of ischemia and electrocardiographic changes. Undoubtedly, UEA can be of great help at this crucial moment.

The association with real-time myocardial perfusion (RTMP) adds even more in terms of sensitivity and positive predictive value for the presence of obstructive

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coronary artery disease and as a prognostic predictor, as demonstrated by Tsutsui et al.^{18,19} However, this technique, in addition to still being considered “off-label” by various medical societies, requires an additional expertise of the echocardiographer, who must have experience in this analysis in multiple exams. This is a fact that makes RTMP less widely used; moreover, it is better applied in stress tests with a vasodilator, such as dipyridamole, which is known to be less frequently used than dobutamine. The observation of a “darkened” zone (perfusion deficit), without myocardial refilling with contrast after a pulse with a high mechanical index (“flash”), assists with eventual doubts regarding worsening of segmental contractile function (Figure 1). On the other hand, a bright myocardial segment denotes adequate flow in the microcirculation, and this may help to define normal local contraction.

In relation to cost-effectiveness, UEA also have a favorable profile. A cost-effectiveness analysis of a diagnostic test considers the cost of the method itself compared to what results from it, in other words, how much the test, based on a diagnostic definition that it provides, reduces or eliminates the need for additional tests for the same purpose, promoting or modifying a conduct. In this sense, UEA have been shown to be cost-effective in different scenarios of cardiology. This is mainly evident in critical medicine and in SE.^{1,2,20}

Technically difficult echocardiograms, with limited and suboptimal ultrasound windows in the emergency room and intensive care units are very common in daily care routine. This fact may be related to patient positioning, limited access to the thorax, inappropriate local lighting, among others. In these cases, for example, there may be a significant impairment or even impossibility of assessing

the LV systolic function, leading to inconclusive tests, and sometimes requiring the use of another imaging method in the diagnostic process, which might eventually be more expensive, for example, cardiac magnetic resonance (CMR). Within this adverse scenario, an accurate definition of LV volumes and calculation of the ejection fraction become possible with the aid of UEA, without requiring other methods. The use of contrast makes the echocardiographic examination more accurate and reproducible, similar to CMR, considered the gold standard. This will guide medical management, confirming its favorable cost-effectiveness profile.^{14,17} This is very evident, for example, in patients with morbid obesity. In these patients, due to the limited acoustic window, an eventual search for intracavitary thrombi may be inaccurate, especially in the apical region of the LV, which is more difficult to visualize. The use of UEA makes this exam possible, eliminating the need to complement it with CMR and guiding the conduct regarding anticoagulation for the patient, with an evident impact on cost.²¹ Finally, contrast echocardiography is virtually the only diagnostic method to confirm myocardial rupture in a critically ill patient at the bedside.

In chest pain units, even though it is not included in several protocols at different services, the integration of SE with the aid of UEA to assess LV segmental contractility, with or without assessment by RTMP, can be an interesting alternative compared to other more expensive tests, such as tomography angiography of the coronary arteries and myocardial scintigraphy.²² Echocardiography with UEA may represent a cheaper, more accurate alternative, without radiation. When there is a positive result for myocardial ischemia, it is also more definitive regarding the need to refer the patient for coronary angiography,

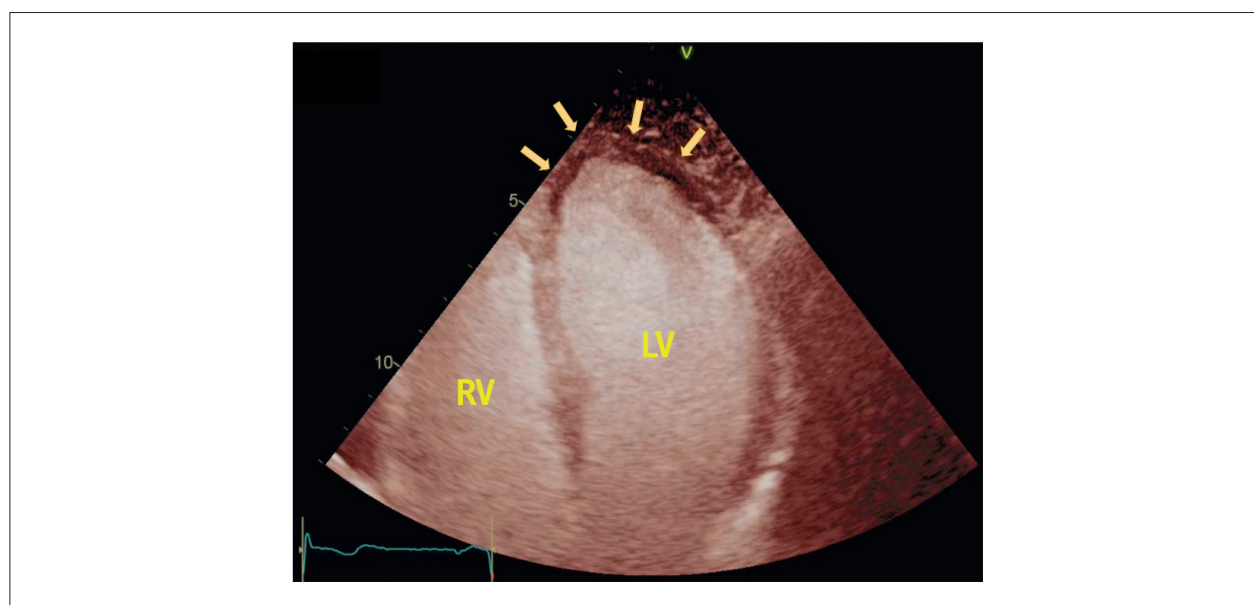


Figure 1 – A 60-year-old woman undergoing contrast-enhanced echocardiography with pharmacological stress with dobutamine. She had chest discomfort and presented a ST-segment depression in precordial leads on the electrocardiographic tracing. An area of hypoperfusion was identified in the apical region of the LV associated with local hypokinesia (arrows). Positive test for the presence of myocardial ischemia. LV: left ventricle; RV: right ventricle.

reinforcing its favorable cost-effectiveness profile.^{23,24} Similarly, when it does not reveal myocardial ischemia, it is possible to discharge the patient safely. Exams without evidence of ischemia are associated with a very low risk, with an annual cardiovascular event rate of less than 1%.^{18,25,26}

In the general field of SE, whether using physical or pharmacological stress, UEA have also been shown to be cost-effective. As shown by Mathias et al., SE with suboptimal windows in resting images can be “saved” using UEA, thus optimizing cost, given that it eliminates the need to add another method in the diagnostic process (Figure 2).²⁷

In conclusion, over the years contrast echocardiography has shown its value in theory and in “real life” practice. Theory provides the basis for practice. Practice feeds theory and provides the foundation for experience. In the words of the historian Thomas Fuller (1608 to 1661): “Knowledge is a treasure, but practice is the key to it.”

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This article does not contain any studies with human participants or animals performed by any of the authors.

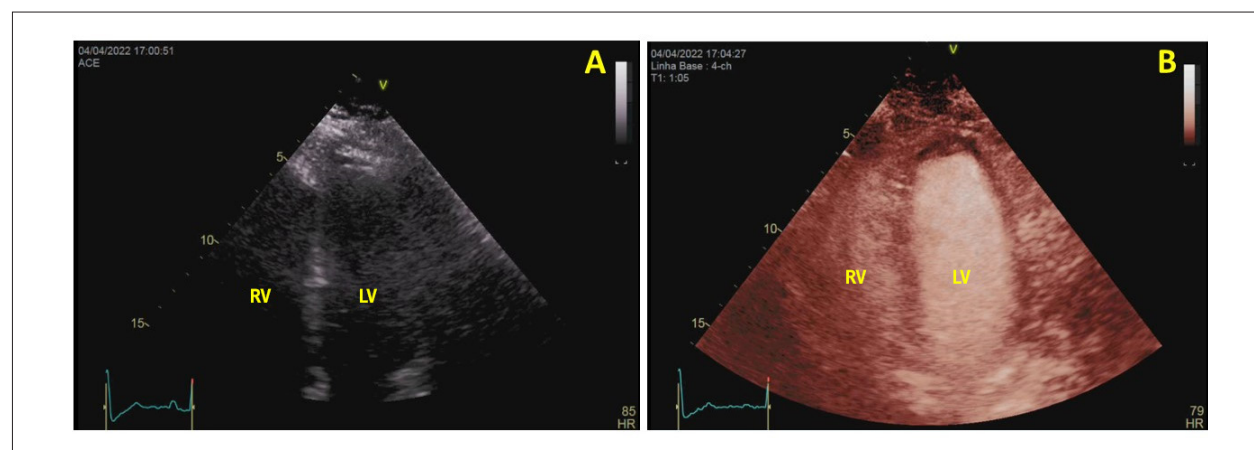


Figure 2 – A 60-year-old man with obesity and chronic obstructive pulmonary disease. An elective dobutamine stress echocardiogram was ordered. A) Suboptimal resting acoustic window for the exam. B) Echocardiographic contrast (sulfur hexafluoride; SonoVue®) was used, making the exam possible.

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