Use of Contrast Echocardiography in Intensive Care and at the Emergency Room

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Abstract: Bedside echocardiography in emergency room (ER) or in intensive care unit (ICU) is an important tool for managing critically ill patients, to obtain a timely accurate diagnosis and to immediately stratify the risk to the patient’s life. It may also render invasive monitoring unnecessary. In these patients, contrast echocardiography may improve quality of imaging and also may provide additional information, especially regarding myocardial perfusion in those with suspected coronary artery disease. This article focuses on the principle of contrast echocardiography and the clinical information that can be obtained according to the most frequent presentations in ER and ICU.

Keywords: Contrast echocardiography, microbubbles, ultrasound contrast agent, emergency room, intensive care, critically ill.

INTRODUCTION

The evaluation and management of patients who arrive at the emergency department (ER) or intensive care unit (ICU) with acute symptoms and/or worrying clinical condition is a daily challenge. Careful history taking-when it is possible-and clinical examination remain the mandatory first steps. It is of importance to obtain a timely accurate diagnosis and to immediately stratify the risk to the patient’s life. Among the possible investigation tools for a precise diagnosis, imaging modalities are frequently required. Echocardiography is the most versatile method. It is non-invasive, can be performed at the bedside, provides rapid results, and avoids exposure of the patient to radiation. Echocardiography is now available in most ER, allowing immediate, standard transthoracic examination. Bedside echocardiography in the ICU is also an important tool in managing critically ill patients, often rendering invasive monitoring unnecessary [1].

In these patients, contrast echocardiography may improve quality of imaging and also may provide additional information, especially regarding myocardial perfusion in those with suspected coronary artery disease. This article focuses on the principle of contrast echocardiography and the clinical information that can be obtained according to the most frequent presentations in ER and ICU.

ULTRASOUND CONTRAST AGENTS

Contrast on echocardiograms by injecting hand agitated saline solution has been recognized for over 30 years for its ability to opacify vascular structures [2]. The primary mechanism by which injection of such fluids produces ultrasound contrast was determined to be increased backscatter from inclusions of microbubbles (MBB) within the injectant [3]. This way MBB markedly enhanced the blood echo by introducing multiple liquid-gas interfaces. Shortly thereafter, smaller MBB were produced [4] and were rapidly adopted for intracoronary injections in animals and humans [5, 6]. Early attempts to encapsulate the bubbles resulted in agents with improved stability but of a size too large to traverse the pulmonary microvasculature. Therefore, early contrast echocardiography by intravenous injection was used primarily to detect cardiac shunts or examine right heart structures. The first commercial contrast agents of room air, were developed by sonication of 5% human albumin solution, and were small enough to pass through the microcirculation (red blood cell size; i.e. <8 μm). They dissolved rapidly in blood. Consequently their size decreased and they lost their echogenicity. They became commercially available in Europe in 1991 first as Echovist (Berlex, Lachine, Quebec City, Canada). In 1996, Levovist with galactose microcrystals and with a trace of palmitic acid appeared on the market (Bayer Schering, Berlin Germany). In the U.S. in 1994, Albunex was introduced (Mallinckrodt, St. Louis, Missouri). A second generation contrast agents in which the air in the bubble was changed to higher-molecular-weight gases which resulted in more stable bubbles. Being insoluble in blood, the gas, even when it had escaped from the bubble continued to produce effective ultrasound backscatter by acting as a free gas bubble [7, 8]. These new preparations were highly successful in opacifying the left ventricular (LV) cavity and the myocardium from a venous injection. Optison (GE Healthcare, Chalfont StGiles, UK), Definity (BMS, Billerica, Massachusetts) and Sonovue (Bracco, Milan, Italy) are the main representatives of this group. These MBB do not aggregate, are biologically inert and safe [9, 10]. They remain entirely within the vascular space [11], have an intravascular rheology that is very similar to that of erythrocytes [11-13] and are eliminated from the body via the reticulo endothelial system with their gas escaping from the lungs.
INTERACTION OF CONTRAST AGENTS WITH ULTRASOUND

When ultrasound waves encounter a MBB, it alternately compresses and expands the MBB, depending on the applied acoustic pressure. Therefore the MBB becomes symmetrically larger and smaller in response to the oscillations of the pressure caused by the incident wave. The volume expansion of a MBB is maximal at a specific frequency referred to as the natural resonant frequency and is inversely related to its size [14]. At the resonant frequency the MBB scatters and absorbs ultrasound and can present nonlinear vibrations when the insonifying acoustic pressure is high enough. Consequently, the bubble vibration contains second and higher multiples of the transmitted frequency. Therefore, the backscattered signal from the MBB contains not only the fundamental frequency but also harmonic frequencies, most notably at twice the fundamental frequency (second harmonics). This nonlinear reflection is not shown by tissue, allowing the separation of response from the bubble from that of surrounding tissue. Finally, as the peak pressure becomes more intense, many of these MBB are disrupted, exhibiting an irreversible, transient and intense scattering depending on the type of gas released and its dissolution in the liquid. This scattered signal is also highly nonlinear. The parameter which expressed the energy of the ultrasound beam is the mechanical index (MI). It reflects the approximate exposure to ultrasound pressure at the focus of the beam in an average tissue.

CONTRAST IMAGING STRATEGIES

The influence of the response of the MBB to ultrasound waves has led to different strategies to visualize the MBB in echo images. These techniques, exploiting the harmonics, have been implemented in commercial clinical ultrasound systems. Very briefly, the main strategies used are divided in two main families: the high power and the low power imaging techniques. The latter are technologies developed to examine the nonlinear responses of MBB. Even low amplitude MBB backscatter can be isolated from tissue signals for processing. This allows continuous low power imaging to be performed, with limited bubble destruction, enabling simultaneous assessment of wall motion and perfusion in real time. Combining high power burst of ultrasound followed by low power imaging, permits to follow the replenishment of the myocardium capillaries with the MBB over time. This approach provides an estimate of myocardial blood volume and of myocardial blood flow [15]. This can also be obtained by using intermittent high power imaging with a progressive increase in pulse interval.

CLINICAL APPLICATIONS OF CONTRAST ECHOCARDIOGRAPHY IN THE EMERGENCY ROOM AND INTENSIVE CARE UNIT

A. Global and Regional Systolic Function Evaluation at Rest

The evaluation of left ventricular function is often required for patients at the ER and ICU: to make the diagnosis or to rule out acute coronary syndromes and stratify the risk, in patients with suspicion of acute heart failure, to clarify the etiology of a shock or for hemodynamic assessment of patients with sepsis.

In patients presenting with chest pain and a suspicion of acute coronary syndrome, echocardiography plays a key role for the diagnosis, the risk stratification and the management of the disease. Patients with acute chest pain account for a notable proportion (20–30%) of medical admissions to the emergency department [16]. A vast majority of patients have atypical chest pain and/or normal or nondiagnostic ECG; early determination of serum troponin frequently is negative. Marginal elevations of troponin in this clinical setting result in uncertainty. The primary role of rest echocardiography when performed in the emergency room is to assess the presence and extent of regional wall motion abnormalities. The absence of dyssynergy cannot definitely exclude a recent episode of ischemia. Moreover, the presence of a dyssymetrical segment may be difficult to interpret (ongoing ischemia or old myocardial infarction) and can be present in other pathologic conditions than ischemic disease (myocarditis, right ventricular overload, left bundle branch block, pacemaker) but the main limitation is that the recording of reliable images can be technically difficult if a skilled echocardiographer is not available. The infusion of contrast agent opacifying the left ventricle results in improvement of the endocardial border detection and has been shown to improve the sensitivity and specificity of echocardiography at rest and during stress for the diagnosis of acute coronary syndromes [17-23]. In this setting, contrast echocardiography simultaneously allows the observation of myocardial perfusion, providing incremental information. For a given regional function, normal perfusion was indicative of a very low risk whereas abnormal perfusion identified a high risk for acute coronary syndrome [24]. Patients with normal perfusion and function have excellent outcome for early events, whereas those in whom both are abnormal have the worst outcome. Intermediate outcome is noted in those with normal perfusion despite abnormal function [25-30].

Once the diagnosis of acute coronary syndrome is established, contrast echocardiography improves the detection of complications and a better risk stratification of these patients. Considering the critical issue of left ventricular rupture (LVR) with pseudoaneurysm formation after ST-elevation acute myocardial infarction (AMI), there are approximately 500,000 ST-elevation AMIs in the U.S. annually, of which 1% to 6% involve LVR [31]. Free wall rupture may result in pseudoaneurysm, whereby the extravasation of blood into the pericardial space is prevented by adherence of the parietal pericardium to the underlying epicardium. A prompt surgical correction is always indicated for pseudoaneurysm to prevent rupture [32]. The sensitivity of transthoracic echocardiography for the diagnosis of left ventricular (LV) pseudoaneurysm is only 26%, often because of inaccurate imaging windows or failure to obtain a good tomographic view [33]. However, the appearance of an intravenous contrast agent in the pericardial space is not dependent on tomographic slices and is diagnostic of LV pseudoaneurysm [34]. In a study by García-Fernández et al., ultrasound contrast agents were used for the diagnosis of LV pseudoaneurysm in 19 cases. In thirteen of them, contrast was required to make the diagnosis whereas in other 4 patients, the diagnosis was suspected by noncontrast echocardiography but confirmed...
by contrast administration. In the two remaining patients, suspected LV pseudoaneurysm was ruled out by contrast echocardiography, thereby preventing unnecessary emergent operations [35]. On the other hand, ultrasound contrast agents (UCA) frequently result in the diagnosis of LV apical thrombus in AMI, which is a major risk factor for death or stroke [36].

Numerous patients, especially the elderly, are admitted to the emergency room for acute decompensated heart failure. Acute cardiogenic pulmonary oedema may result from acute events or from acute deterioration of a chronic disease. The main mechanisms include reduced outflow, reduced inflow or backward flow. Rapid distinction between heart failure due to systolic versus diastolic dysfunction should be obtained since there are significant differences in treatment. Therefore, the evaluation of systolic performance is critical and a good visualisation of the endocardium improves confidence of the operator in these often difficult to image patients. Patients in the intensive care unit also remain in technically challenging to obtain adequate echocardiographic images. The frequent use of mechanical ventilation, presence of chest bandages, and difficulty in positioning the patient, poor lighting conditions are factors that impair image quality. Contrast echocardiography may play an important role in this setting [37].

On the other hand, the precise evaluation of aortic stenosis severity is mandatory and contrast may help to enhance Doppler signal. Finally, in patients with acute heart failure and no previous history of coronary artery disease, myocardial perfusion echocardiography is able to determine the presence coronary artery disease, and so, is able to identify viable myocardium at the bedside without requiring a more cumbersome assessment through SPECT, PET, or magnetic resonance imaging (MRI) [38].

B. Regional Systolic Function During Stress

Exercise echocardiography and exercise SPECT have been shown to provide comparable short term prognostic information in the triage of chest pain patients, allowing safe early discharge; the negative predictive value was 97% in both methods, but exercise echocardiography is preferable because of a higher positive predictive value [39]. Pharmacological stress echocardiography can be used in patients unsuitable for exercise testing. Graded dobutamine infusion with addition of atropine if necessary, or high dose dipyridamole and atropine, can be used as stressors. Early dobutamine stress after admission to the emergency room has been shown to be feasible and safe. Pre-discharge dobutamine stress echocardiography has important and independent prognostic value in low risk, troponin negative, chest pain patients [40]. As compared to exercise ECG, dobutamine stress echocardiography was found to be more cost effective: the mean length of stay in the hospital was lower; and no event occurred in a 2 month follow-up in patients with a normal dobutamine test, whereas the event rate was 11% in patients with normal exercise ECG [41]. Reduced endocardial border definition is exacerbated during stress because of chest wall motion during hyperventilation and cardiac translational movement during tachycardia. With fundamental imaging, inadequate endocardial definition has been reported in up to 30% of stress echos. In addition, Hoffman et al demonstrated that suboptimal studies have worse reproducibility and a poorer inter-observer variability, with inter-institutional institutional observer agreement as low as 43% for studies with poor image quality [20]. Contrast enhanced echocardiography has proven to increase the accuracy and reproducibility of regional wall motion assessment during stress [17, 18].

Contrast echocardiography for enhancing LV borders in suboptimal studies actually represents the main indication of ultrasound contrast agents and is especially useful in approximately 10% to 20% of routine echocardiographic examinations. During dobutamine echocardiography, the sensitivity of contrast myocardial perfusion echocardiography has also been shown to be higher than that of wall motion at both maximal and intermediate doses of dobutamine for the detection of coronary artery disease and in predicting events [42-46].

C. Tissue Characterization

Contrast echocardiography also has been of value in the structural assessment of the left and right ventricles, the atria, and the great vessels. Ultrasound contrast agents play a key role in the definition of left ventricular apical abnormalities, in complications of myocardial infarction, and in cases of intracardiac masses [47-51]. It may also help to characterize the myocardium in patients with heart failure as illustrated here to allow the distinction between non-compacted and compacted layer in a patient with heart failure and severe left ventricular dysfunction and with non-compaction of the left ventricle (Fig. 1). More recently, in patients with Tako-Tsubo, the potential use of contrast imaging to better define the variance of typical left ventricular ballooning finding in this condition has been emphasized [52] and on the other hand myocardial perfusion imaging has also been shown to be useful [53-55].

![Fig. (1). Parasternal short axis view with and without contrast in a patient presenting with acute heart failure. The contrast injection allows a better separation of the compacted (yellow dots) and non-compacted layer and to apply the criteria of diagnosis in isolated non-compaction of the left ventricle.](image-url)

D. Doppler Signal Enhancement

Doppler echocardiographic assessment of blood flow velocities in the heart and the great vessels is a standard part of the cardiac ultrasound examination. Contrast enhancement
of the Doppler signal has been shown to be of value when the signal is weak or technically suboptimal. Velocity measurement in patients suspected of aortic stenosis may be enhanced with echocardiographic contrast agents as shown in Fig. 2 [56].

![Fig. (2). Aortic stenosis flow Doppler tracing (A) without and (B) with contrast enhancement.]

E. Pericardiocentesis

Echocardiography plays a major role in pericardiocentesis to determine the distribution and the depth of the effusion. During the procedure, continuous echocardiography has been proposed, eventually combined to the injection of agitated physiologic serum to generate contrast and define the tip of the needle (Fig. 3).

![Fig. (3). Pericardial effusion (PE) during pericardiocentesis and injection of microbubbles (Arrow) into the needle used for the puncture. LA indicates left atrium and LV left ventricle.]

SAFETY ISSUE OF CONTRAST ECHOCARDIOGRAPHY IN THE CRITICALLY ILL

Although ultrasound contrast agents have proven utility in the diagnosis and management of critically ill patients [37, 57-59], concern persists regarding the safety of these compounds, particularly in these patients. Recently published single center data demonstrated no increased mortality in hospitalized patients undergoing echocardiography with ultrasound contrast agents in comparison with patients undergoing noncontrast-enhanced examinations [60]. These findings were recently corroborated in large multicenter cohorts [61, 62]. Additionally, multivariate logistic regression modelling demonstrated a significantly lower risk of mortality in the UCA group compared with the no contrast group (24% decreased risk), a finding that may be surprising given recent safety concerns [61]. In a recent prospective study performed early after acute myocardial infarction, administration of echo contrast did not induce any significant change in vital signs, physical examination, and ECG. There were no serious adverse events, and minor events occurred only in five patients [63]. More recently, a study over 22,000 patients who received ultrasound contrast agents, nearly 3000 of whom had critical illness. No association was found between contrast use and the same day mortality [64]. Therefore, in most of these circumstances, the benefit of ultrasound contrast agents far outweighs their risks.

CONCLUSIONS

In the acutely ill patients, transthoracic image quality is often a problem and the use of ultrasound contrast agents to enhance left ventricular opacification improves the accuracy of echocardiography by rendering examination interpretable. Consequently, this may have implications in patient management. Moreover, perfusion study with contrast echocardiography may add information for diagnosis and risk stratification in patients presenting at the emergency room or hospitalized in intensive care unit. Although there were several concerns regarding the safety with the use of ultrasound contrast agents in the acutely ill patient, recent studies have provided reassurance about the use of contrast in this setting.

CONFLICT OF INTEREST

No conflict of interest to declare.

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