Despite technological advances in echocardiography, such as harmonic imaging, a significant number of rest or stress echocardiography studies are labeled as nondiagnostic. Even in the presence of adequate image quality, some cardiac structural abnormalities pose a diagnostic challenge. Ultrasound contrast agents (UCAs) have been shown to improve the diagnostic accuracy of echocardiography. Furthermore, assessment of myocardial perfusion by means of contrast echocardiography has been extensively studied with proven independent diagnostic and prognostic benefits. This paper (a) briefly highlights some technical aspects of UCAs and the relevant imaging techniques and (b) summarizes the use of contrast echocardiography in daily clinical practice.

Ultrasound contrast agents

Use of UCAs in echocardiography is not new. In 1968, Gramiak and Shah noted a cloud of echo at the tip of cardiac catheters while doing M-mode studies on the aortic root in the cardiac catheterization laboratory [1]. Injection of agitated saline for identifying right-to-left intracardiac shunts or pulmonary arteriovenous malformation continues to remain a valuable clinical tool in daily practice. Air microbubbles that act as the contrast agent are approximately the same size as red blood cells with strong backscatter; however, they dissolve in blood quickly and therefore do not normally reach the left heart. Despite knowing for many years that mixing a small amount of blood with agitated saline increases microbubble stability (as blood surfactant forms a protective shell around the microbubble), it was only in early 1990s that commercial UCAs became available [2]. Thus, in order to overcome the instability of contrast microbubbles in blood, they should be either protected with a shell or should contain a gas that is insoluble in the blood so that they can reach the left ventricular cavity and the myocardium. The first generation of UCAs had air or nitrogen microbubbles protected by a thick shell (such as albumin). The second generation of UCAs instead has high-molecular-weight gases that are insoluble in blood. UCAs should also ideally have distinct acoustic properties to provide efficient backscatter, have a similar size to red cells in the blood, and circulate and must survive the pulmonary passage without aggregation. The most important factor in the echogenicity of the UCAs is their size, and therefore the biggest possible size of a UCA that is able to cross the lungs will produce the highest ultrasound backscatter. Table 1 summarizes some of the commercially available UCAs. Unlike red cells that only become echogenic in aggregation and slow blood flow state, UCAs produce ultrasound backscatter even in normal blood flow that is typically up to 100 million times stronger than red cells.

The acoustic behavior of UCAs in response to the different range in ultrasound mechanical index (MI) is an important part of contrast echocardiography. MI is directly proportional to an ultrasound beam’s peak negative pressure and inversely proportional to the frequency of the beam and is considered as the ultrasound acoustic power. In an MI > 0.1, contrast microbubbles contract and expand unequally, which means they will produce ultrasound backscatter with a lower amplitude than the transmitted fundamental frequency, the so-called nonlinear response. In lower MI myocardial tissue backscatter, however, typically shows a linear response, i.e., producing backscatter signals at the same amplitude. Modern scanners will be able to cancel out the tissue backscatter and image only reflected signals from the UCA. An MI of more than 0.9 will cause destruction of the UCA resulting in brief but strong nonlinear backscatter signals that also can be used in contrast echocardiography. In summary, the two techniques are called low-MI and high-MI imaging, respectively. The real-time low-MI (<0.3) techniques are those that are more routinely used in clinical practice [3].

Clinical utility of contrast echocardiography

Contrast echocardiography is used for a variety of diagnostic and prognostic reasons. Table 2 summarizes the clinical indications of contrast echocardiography recommended by major society guidelines.

Left ventricular opacification

Left ventricular function

Assessment of global and regional left ventricular function has both diagnostic and prognostic value in a range of cardiac conditions such as coronary artery disease, heart failure, and cardio-oncology. It is well reported that up to 15% of echocardiography studies are uninterpretable owing to poor image quality. This is even more prominent in critically ill patients and has been reported to be as high as 30% [4]. Both American and European guidelines advocate the use of
UCAs to improve endocardial border delineation when two or more segments of the left ventricle cannot be well defined [5, 6]. The salvage of such nondiagnostic studies using left ventricular opacification (LVO) has been reported to be as high as approximately 50% with higher rates of salvage in the intensive care unit [7–9]. It is only with the advent of contrast echocardiography that the percentage of nondiagnostic echocardiography studies has dropped to less than 5% [4]. Moreover, quantification of ejection fraction is imperative in daily practice both in clinical decision-making, e.g., eligibility for device therapy with an ejection fraction <35%, and in serial studies such as monitoring of the left ventricular function in valvular heart disease. Measurement of ejection fraction by unenhanced two-dimensional (2D) echocardiography has inherent limitations resulting in underestimation by up to 6% and a significant variability of up to 14% [10, 11]. Several studies have shown that LVO improves the accuracy of ejection fraction measurements and reproducibility [6] and is recommended in relevant clinical indications. UCAs have also been used with three-dimensional (3D) echocardiography. Recent studies have shown that 3D contrast echocardiography provides the closest results to cardiac magnetic resonance in measuring left ventricular volumes. It further reduces variability and improves accuracy of left ventricle volume measurements when compared with 2D contrast echocardiography [12, 13].

Image Optimization. Conventional 2D echocardiography uses high MI that results in destruction of contrast microbubbles. When performing an LVO study, this will result in contrast swirling, especially in the apical area that is closer to the ultrasound beam source. Furthermore, at high MI, tissue will also produce harmonic backscatters (nonlinear response) that make delineation of the endocardial border more difficult. For these reasons, LVO studies should be performed with low MI (<0.3), which is usually available on modern echocardiography machines, to reduce microbubble destruction and tissue signals. The focal zone should be at the level of the mitral valve annulus and a minimum frame rate of 25 MHz is required. Adjusting time gain compensation helps to achieve a homogeneous opacification of the left ventricle from the apex to the base. Bolus injections are usually used for LVO studies and should be of such volume that adequate opacification of the left ventricle is reached. In high volumes of contrast, however, microbubbles can act as a barrier to the ultrasound beam and cause attenuation resulting in the far field view being attenuated. This can be resolved by using the “flash” or “burst” function that sends high-MI ultrasound beams over 4–5 frames and destroys the contrast allowing for a better differentiation of the endocardial border (Fig. 1).

Cardiac structural abnormalities

Intracardiac masses

Transesophageal echocardiography has a sensitivity as high as 93% for diagnosing cardiac masses [14]. Left ventricular thrombus is the most commonly diagnosed mass that can pose a diagnostic challenge, especially in cases of poor image quality or near-field artifact. Use of real-time low-MI LVO will help delineate a mural or laminar thrombus (Figs. 2 and 3). Using the flash option that destroys the microbubbles allows for visual assessment of replenishment of the adjacent myocardium to determine any perfusion defects, implying a substrate for thrombus formation. Although in the majority of cases other diagnostic clues will help in differentiating thrombus from a tumor, destruction/reperfusion techniques can be used to characterize the mass vascularity. A thrombus will be avascular, whereas a malignant mass or vascularized tumor will show high vascularity, and a stromal mass will present as partially vascular.

Diagnosis of suspected apical hypertrophic cardiomyopathy on transthoracic
echocardiography can be confirmed by an LVO study demonstrating the spade-
shape apex with the thick apical cap and apical systolic cavity obliteration. 
Contrast LVO can also help differentiate prominent trabecula from noncom-
paction morphology.

LVO can also be used in the detect-
tion of acute myocardial infarction com-
plications such as pseudo-aneurysm. It 
has also been used with transesophageal 
echocardiography to facilitate the diag-
osis of left atrial appendage closure par-
cially before direct-current cardiover-
sion [15].

Stress echocardiography

The aforementioned limitations of transtho-
racic echocardiography in visualization of 
the endocardial border can pose an 
even more significant challenge in stress 
echocardiography, when definition of 
the endocardial border for detection of 
regional wall motion abnormalities is 
crucial. Even in cases with adequate 
image quality, the respiratory effort in 
the case of an exercise test or tachycardia 
resulting from use of inotropic agents 
and the narrow window in acquiring 
images could all lead to difficulty in 
interpreting the studies. Suboptimal 
studies have been reported as high as 
30% in routine stress echocardiography 
with an inter-institutional agreement as 
low as 43% in those with poor image 
quality. LVO has been shown to reduce 
the nondiagnostic stress echo studies to 
less than 10%, to improve test accuracy 
and reader confidence, and to reduce 
variability in several studies [16–21].

Again, real-time low-MI imaging is 
the preferred method. While bolus in-
jections are easier to adopt for exercise 
stress echocardiography and should be 
administered about 30 s before acquir-
ing images, an infusion can be used in 
pharmacologic stress echocardiography. 
Given that the infusion of the contrast 
takes longer to reach the adequate con-
centration, it is best started at least 45 s 
before image acquisition is performed. 
As discussed, a higher concentration 
of microbubbles can act as a barrier to 
the ultrasound beam causing attenua-
tion. Thus stress echo imaging should 
be started with apical views since atten-
uation from the higher concentration 
of the microbubbles in the right ventri-

cle can affect the image quality of the 
parasternal left ventricular views.

LVO for improvement of endocar-
dial border definition both at rest and 
stress along with its role in defining car-
diac structural abnormalities are the li-
censed applications for the use of UCAs 
and should be an integral part of any 
echocardiography laboratory. Contrast 
echocardiography can also be used for en-
hancement of Doppler signals. This can 
be achieved even after fragmentation of 
contrast microbubbles, in the absence of 
visible opacification of the cardiac cav-
ities, owing to remaining microbubble 
shells in the circulation. More advanced 
use of UCAs includes myocardial con-
trast echocardiography (MCE), which is 
technically challenging and requires sig-
nificant experience. The adoption of this 
technique, despite several favorable clin-
ical studies, has been slow and is limited 
to expert centers.
Myocardial contrast echocardiography

Coronary blood flow is equally distributed between the arteries and arterioles, capillary network, and venules. Myocardial blood volume represents a third of total coronary flow, of which more than 90% resides in the capillary network [22]. MCE relies on the intensity of the backscattered ultrasound from the filled capillaries with UCA and suppression of those reflected from the myocardial tissue. UCAs are pure intravascular traces and if they are the only source of the backscattered signals then the intensity of such signals will be proportionate to the myocardial blood volume. Providing the rate of myocardial blood filling by the contrast microbubbles is measurable, then the myocardial blood flow, which is a product of myocardial blood volume multiplied by velocity, can be calculated.

There are essentially two main MCE imaging techniques. Destructive (high MI) imaging techniques use an MI > 1 that will cause microbubble destruction, resulting in a nonlinear response and generation of strong harmonic signals in multiples of the transmitted fundamental frequency. However, after the destruction phase, the myocardium will require some time to be refilled with contrast. Therefore, it is not possible to perform real-time MCE and imaging should be done by triggering ultrasound every few frames (1, 2, 3, and up to 10). This means that assessment of wall motion abnormality with triggered imaging is not possible, which is considered an important disadvantage. Moreover, it is difficult to maintain the same imaging window between triggered frames. For these reasons, high-MI MCE is not the preferred modality in daily practice.

The two main destructive techniques are harmonic power Doppler and pulse inversion Doppler. In harmonic power Doppler, two consecutive pulses are transmitted in the same scan line. The reflected backscatter from the first pulse will be from both tissue and myocardial capillaries, while the signals from the second pulse will be solely from myocardial tissue (because of microbubble destruction by the first pulse). If the myocardial capillaries are not filled with contrast because of a perfusion defect, then there will not be a shift in frequency, whereas a normally perfused myocardium will result in backscatter signals from both tissue and microbubbles from the first pulse and only the tissue from the second pulse. In pulse inversion Doppler, two pulses are sent down shortly after each other that are 180° out of phase. Since the response of the myocardial tissue to the transmitted signal will be linear, they will cancel each other out. However, microbubbles will respond in...
Fig. 3 – a–c Confirmation of apical thrombus in the left ventricle apex in a left ventricular opacification study showing a filling defect (yellow arrow).

Fig. 4 –a Real-time low-MI myocardial contrast echocardiography. a, b Immediately after flash function; c as contrast appears in the myocardium, yellow arrows show a large area of perfusion defect in the lateral wall in the apical four-chamber view; d red arrows show the perfusion defect in the inferolateral wall in the apical three-chamber view. Coronary angiography findings were consistent with a critical stenosis in the left circumflex artery.

Fig. 5 – Another case of real-time low-MI myocardial contrast echocardiography that demonstrates a myocardial perfusion defect in an apical two-chamber view. Blue arrow epicardial wall, yellow arrow subendocardial perfusion defect, red arrow transmural perfusion defect. Coronary angiogram showed significant right and left coronary artery disease.

Nondestructive or real-time low-MI imaging techniques allow for simultaneous assessment of the left ventricular regional wall motion with perfusion imaging. This means a minimum frame rate of 25 MHz is required and thus a lower MI (usually less than 0.2) is used to avoid microbubble destruction, but this is at the cost of a weaker backscatter from the microbubbles. The nondestructive techniques are essentially the same as destructive ones but use a lower amplitude of transmitted waves. In power modulation technique (Phillips, USA), multiple pulses are transmitted in each scan line with each alternate phase only in 50% amplitude pulses. The ultrasound scanner doubles the received signals from the 50% amplitude pulses and then subtracts that from the received signal from the 100% amplitude pulses. Therefore, backscattered signals from the myocardial tissue, which produces a linear response, will be cancelled out. Power modulation is considered a highly sensitive technique but has lower resolution and image quality [3].

Pulse inversion Doppler, as was explained in high-MI imaging, can also be used in the real-time low-MI MCE. In this technique, essentially, nonlinear scatters from the microbubbles will be detected while linear response from myocardial tissue will be canceled resulting in high-resolution images. However, because it can only receive even harmonics, there will be attenuation artifact, particularly in the basal myocardial segments. The contrast pulse sequencing (Siemens,
USA) is another multiphase technique that uses both alternate amplitude and polarity resulting in high image quality and sensitivity but is still subject to attenuation ([3]; Figs. 4 and 5).

An important advantage of MCE compared with other noninvasive imaging modalities is the ability to calculate myocardial blood flow. This is measured by multiplying myocardial blood volume and myocardial contrast velocity and was first introduced by Wei and Kaul in 1998, using high-MI intermittent triggered imaging. When the ultrasound pulsing interval is incrementally varied, mean microbubble velocity and peak signal density (representing myocardial blood volume) and thus myocardial blood flow can be measured [23]. Use of the flash option, in real-time low-MI imaging, destroys the UCA in myocardium (while microbubbles remain intact in the left ventricle owing to a higher concentration) and allows for measurement of contrast replenishment velocity and thus quantification of myocardial blood flow (Fig. 6). A prerequisite for MCE is that the relationship between the contrast concentration and the scatter intensity is linear. With a contrast bolus injection, at a certain level, when the maximum UCA concentration is achieved, the linear relationship is lost. At this point, even a hypoperfused region may appear falsely normal. It is only during the contrast decay that the myocardial contrast intensity and hence the myocardial blood volume can be assessed. Thus, with the bolus injection, maintaining a window where the UCA can be detected and yet not saturated is crucial. Whereas with the contrast infusion, an optimal level of microbubble concentration within the myocardium can be easily achieved. Moreover, since the mean transit time of the microbubbles during contrast injection cannot be calculated, it is impossible to measure myocardial blood flow. For these reasons a contrast infusion is preferred for performing MCE.

**Stress MCE**

Exercise, vasodilators, or inotropes can be used for stress MCE. The incorporation of MCE into an exercise stress test is challenging but has been shown to be feasible with improvement of both left ventricular wall assessment and perfusion [23, 24]. It is known that a perfusion defect precedes a wall motion abnormality in the ischemic cascade. MCE has the ability to detect such perfusion defects during dobutamine stress echocardiography. Dolan et al. demonstrated that the presence of a perfusion defect during dobutamine stress echocardiography, even in the absence of any wall motion abnormality, is an independent prognostic factor for death and nonfatal myocardial infarction [25]. Stress MCE has been studied against the gold standard of coronary angiography in 20 trials with different protocols involving 1683 patients, demonstrating sensitivity and specificity of 83% and 80%, respectively [26]. A meta-analysis investigating the accuracy of stress MCE, single-photon emission computed tomography (SPECT), and dobutamine stress echocardiography against coronary angiography as gold standard also showed a higher sensitivity in favor of stress MCE [27]. Despite several favorable studies, in a more recent European multicenter study using coronary angiography as a gold standard, although stress MCE yielded better sensitivity (75%) in detecting coronary stenosis of >70% against SPECT, it was significantly inferior in specificity (52%).

**MCE for myocardial viability**

MCE can be used for the assessment of myocardial tissue viability since an intact tissue will be replenished with contrast because the capillaries and microvasculature will still be intact, whereas an ischemic or fully infarcted territory will show patchy or absent contrast density. In fact, the contrast density has an inverse relationship with myocardial colla-
MCE has been used for evaluation of the myocardial viability in both acute and chronic settings. Ito in 1992 demonstrated that despite a patent artery related to an infarcted zone, up to 25% of patients did not show myocardial opacification in an infarcted area and thus no myocardial viability, a phenomenon that is called “no flow” and was first described by Kolner in 1974. Other studies have shown the independent prognostic impact of assessment of the infarct-related myocardial region (treated with either thrombolysis or percutaneous intervention) on left ventricular remodeling and death [23]. Perfusion imaging with MCE has also been studied in nonacute coronary artery disease. Quantification of myocardial blood flow with MCE has been shown to improve accuracy in detecting viable myocardium when compared with both dobutamine stress echocardiography and SPECT in those with left ventricular dysfunction and coronary artery disease [28]. The overall sensitivity and specificity of perfusion imaging with MCE have been reported as 85% and 70%, respectively [6].

MCE in suspected acute coronary syndrome

A study by Gaibazzi et al. showed that a positive stress MCE predicted a 1-year incidence of acute coronary syndrome in those who presented to the emergency department with chest pain and unremarkable ECG changes and negative troponin findings. This suggests a possible role for bedside stress MCE in risk stratification of these patients [29].

Safety

Despite the initial concern about the safety of UCAs, there is a universal consensus that contrast echocardiography is safe. Although extremely rare, anaphylactic reaction remains a true side effect that has been reported in approximately 1 in 10,000 patients. Use of UCAs in pulmonary hypertension, right-to-left shunt through a patent foramen ovale, and in critically ill patients that were of initial concern have been proved in several studies to be safe [3].

Conclusion

Contrast echocardiography should be an integral part of a modern echocardiography laboratory and is considered as a quality control marker. LVO has an established role in a wide range of clinical scenarios in rest echocardiography and improves the accuracy of stress echocardiography. Perfusion imaging with MCE, although supported by a large body of evidence, has not passed the regulatory processes in the EU and USA and thus remains an off-label indication and currently limited to expert centers. Beyond daily clinical use, UCAs are currently being tested in trials for molecular imaging and targeted drug delivery and thrombolysis.

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Compliance with ethical guidelines

Conflict of interest. M. Eskandari and M. Monaghan declare that they have no competing interests.

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