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Clinical practice of contrast echocardiography: recommendation by the European Association of Cardiovascular Imaging (EACVI) 2017

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Contrast echocardiography is widely used in cardiology. It is applied to improve image quality, reader confidence and reproducibility both for assessing left ventricular (LV) structure and function at rest and for assessing global and regional function in stress echocardiography. The use of contrast in echocardiography has now extended beyond cardiac structure and function assessment to evaluation of perfusion both of the myocardium and of the intracardiac structures. Safety of contrast agents have now been addressed in large patient population and these studies clearly established its excellent safety profile. This document, based on clinical trials, randomized and multicentre studies and published clinical experience, has established clear recommendations for the use of contrast in various clinical conditions with evidence-based protocols.

Keywords echocardiography • contrast echocardiography • stress echocardiography • myocardial contrast echocardiography • contrast agents • safety of contrast agents • left ventricular function • left ventricular structure

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Abbreviations

ACS	acute coronary syndrome
AMI	acute myocardial infarction
CAD	coronary artery disease
CA	contrast agent
CFR	coronary flow reserve
CMR	cardiac magnetic resonance
DSE	dobutamine stress echocardiography
EBD	endocardial border delineation
exECG	exercise stress ECG
LA	left atrium
LAD	left anterior descending coronary artery
MBF	myocardial blood flow
MCE	myocardial contrast echocardiography
MI	mechanical index
RWMA	regional wall motion abnormalities
SE	stress echocardiography
SPECT	single-photon emission computed tomography

Introduction

Contrast echocardiography is now an established technique in clinical cardiology. Contrast echocardiography is performed for the assessment of regional and global left ventricular (LV) function both at rest and under stress for the optimal evaluation of LV structure and for the assessment of myocardial perfusion. However, despite its availability, the clinical use of contrast in rest echocardiography remains low. In stress echocardiography (SE), the uptake is higher than in rest echocardiography, but it is not optimally utilized in parts of Europe and in the USA. The use of myocardial perfusion remains very low. Although safety issues of contrast have been addressed, lingering concerns remained. However, over the last 5 years, new data have emerged in contrast echocardiography and contrast protocols have become more established. Furthermore, usefulness of contrast echocardiography has been demonstrated in clinical conditions not recommended before. In addition, more data on safety in large study population have now emerged. Thus, strong data supporting use in previously indicated clinical conditions and newer indications has prompted this recommendation paper. We have classified the level of recommendation as Class 1 (evidence and/or general agreement that a given procedure is beneficial and effective), Class II (conflicting evidence and or divergence of opinion about the usefulness/efficacy of procedure, Class IIa (weight of evidence is in favour of its usefulness/efficacy), Class IIb (weight of evidence is less well established regarding efficacy) and Class III (evidence or general agreement that the given treatment or procedure is not useful/effective. We have classified the strength of recommendation as Level A (based on multiple randomized studies or meta-analysis), Level B (single randomized study or multicentre trials or large trials) and Level C (expert opinion, small registry studies and small clinical trials).

Contrast agents

Present-generation contrast agents are microbubbles approximately the size of a red blood cell (<7 μm in diameter) consisting of a shell and encapsulated gas. The echogenicity and ultrasound properties of the contrast agents are determined by the size, shell and encapsulated gas of the microbubbles within the various contrast agents. Microbubble ultrasound scattering is proportional to the sixth power of the radius, so the largest bubble capable of passing through the pulmonary microcirculation will have the best backscatter properties.[1–4] However, the signals obtained from ultrasound contrast agents are not only due to scattering.

The harmonic properties of microbubbles are a function of their non-linear oscillation, which means that they reflect sound not only at the fundamental frequency of the ultrasound source but also at higher harmonics.[5] The microbubbles must be stable enough to resist destruction at normal ultrasound power outputs and so maintain a sufficient concentration in the heart to give a satisfactory image. This is largely a factor of solubility of the gas in blood, with high-molecular-weight bubbles being less soluble and less diffusible and therefore more stable.[5] Lipid or albumin shells have been used to reduce outward gas diffusion. Characteristics of the three commercially available contrast agents are listed in *Table 1*.

Recommendations

All commercially available contrast agents are suitable for assessment of LV function, structural LV abnormalities and myocardial perfusion (Class I, Level B).

Contrast imaging modalities

Contrast imaging utilizes the non-linear scattering properties of ultrasound contrast agents to facilitate their detection within the heart.[6–8] The microbubbles oscillate within the ultrasound beam and the

Table 1 Current commercially available ultrasound contrast agents

Agent	Manufacturer	Shell	Gas
Optison®	GE Healthcare	Albumin	Perfluoropropane
Definity®/ Luminity®	Lantheus Medical Imaging	Lipid	Perfluoropropane
SonoVue®/ Lumason®	Bracco Diagnostics	Amphiphilic phospholipids	Sulfur hexafluoride

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degree of oscillation, in part depends upon the intensity of the incident ultrasound. The measure for intensity of the transmitted ultrasound is the mechanical index (MI), which is the peak negative pressure of the ultrasound wave divided by the square root of centre frequency and is >0.8 for most non-contrast imaging. At higher ultrasound intensities (MI > 0.5) microbubble destruction can occur, and when the gas is released from the bubbles, a strong acoustic signal is produced, which can be detected by the ultrasound system. However, contrast microbubble destruction makes high MI imaging modalities unsuitable for real-time contrast imaging.[9,10]

To use real-time imaging of contrast within the LV cavity and/or myocardium, it is necessary to reduce significantly the transmitted ultrasound power (intermediate or low MI imaging), and this has required more sophisticated, contrast-specific imaging modalities.[11] These modalities have unique features and have been named according to the developing ultrasound system manufacturer: power pulse inversion, power modulation and cadence (or coherent) contrast imaging (*Figure 1*). All these types of modalities rely on the fact that tissue is essentially a linear and relatively predictable ultrasound scatterer, especially at low ultrasound energy levels, whereas contrast microbubbles are not and are therefore described as being 'non-linear'. When using this kind of imaging modality, the image will normally be totally dark prior to contrast administration, confirming effective suppression of tissue data. This type of imaging is very effective for LV endocardial border enhancement, as it demonstrates a sharp demarcation between the contrast-enhanced cavity and the myocardium. With minor modification and increased contrast concentration, it can also effectively detect and display contrast within the myocardium, facilitating the evaluation of myocardial perfusion as described later.[11] It is common to combine this form of low MI contrast imaging with a burst of a few frames of high MI imaging (Flash) to destroy contrast within the myocardium. This allows the qualitative and quantitative assessment of contrast replenishment into the myocardium and is also discussed later.

Harmonic imaging has become the standard imaging technique for native (tissue) echocardiography, although it was originally developed to enhance the detection of contrast agents (*Table 2*). To use it optimally for contrast studies, the transmit power must be reduced from an MI of 1.0 to 0.2–0.5. However, even this power level is still relatively high and can cause destruction of the contrast in the near field of the transducer as well as create confounding tissue signals in the myocardium, which impairs the delineation of the endocardium and therefore MI may be reduced to <0.2.

Intermediate and low MI imaging

For clinical studies, the newer contrast-specific imaging modalities (Pulse inversion, Power Modulation and Cadence Pulse Sequencing) provide the best LV opacification (LVO) (homogeneous contrast and excellent endocardial border definition).[12] Contrast-specific imaging modalities apply a lower transmit power (MI < 0.5) compared with the power transmitted in non-contrast echocardiography (MI > 0.8). In commercially available echocardiography scanners, there is often an option between intermediate MI (<0.5) and low MI (<0.2) settings. The latter have been used for myocardial perfusion imaging. However, the low MI contrast-specific settings are also recommended for assessment of LV function.

Because of the low transmit power, less contrast is destroyed and, therefore, less contrast is required compared with the high MI methods for optimal imaging. In addition, myocardial opacification, which allows assessment of perfusion, can be assessed simultaneously. Thus, perfusion can be assessed without prolongation of the LV contrast opacification (LVO) contrast study and without increasing the amount of contrast agent infused. Scanning with the new low-power contrast-specific imaging modalities for the detection of myocardial perfusion is an 'off-label' application, as none of the currently available contrast agents have been approved for this indication. It should be noted, however, that because the real-time low MI modes transmit multiple pulses down each image scan line, relatively low frame rates may result in older systems, which are not optimal for wall motion assessment. This may be usually overcome by narrowing the sector width until the frame rate is at least 25 Hz that is preferable for optimal wall motion assessment during SE.

Low MI contrast-specific techniques display the contrast within the cavities of the heart, and because contrast microbubbles are red blood cell tracers, they accurately display the myocardial blood within the intra-myocardial vessels. The blood volume within the myocardial vessels comprises only 12% of the myocardium. Therefore, the myocardial opacification is always much less intense than the cavity opacification, providing an excellent differentiation between the two for endocardial delineation. The myocardial contrast is also very useful for assessing thickening of the myocardium—reduction of wall thickening is the hallmark for myocardial ischaemia—and myocardial perfusion. However, for the assessment of LV structure, particularly non-compaction or very small thrombi very low MI may miss these abnormalities. This is because of the limited spatial resolution these structures will not reflect harmonic signals at this low MI and delineation with contrast will be difficult. On the other hand, with intermediate MI imaging, harmonic signals from these structures will help to delineate these pathologies better. Low MI imaging modalities are also available for transoesophageal echocardiography (TOE) on some scanners, where they could be used for assessment of LAA thrombi (see Left atrial appendage visualization with contrast agent use during TOE section).

Recommendations

Contrast-specific imaging modalities should be used (Class I, Level B). The low MI methods are particularly useful, as they provide simultaneous assessment of wall motion and myocardial perfusion and require less contrast agent compared with methods using higher MI (Class I, Level B). For the optimal assessment of LV structure, switching to intermediate MI imaging is preferable (Class IIa, Level B).

Contrast administration

Infusion method

Infusion of contrast agent has been used in multiple studies using SE—in particular when myocardial perfusion was assessed in addition to LV wall motion (see Myocardial contrast echocardiography section). Continuous infusion of ultrasound contrast agents usually requires an infusion pump, although it is also possible to do this using a modified gravity fed intravenously (IV) for Luminity®/Optison®. However, intermittent agitation of the contrast is required to maintain the homogeneity of distribution of the microbubbles, because they rise quickly within

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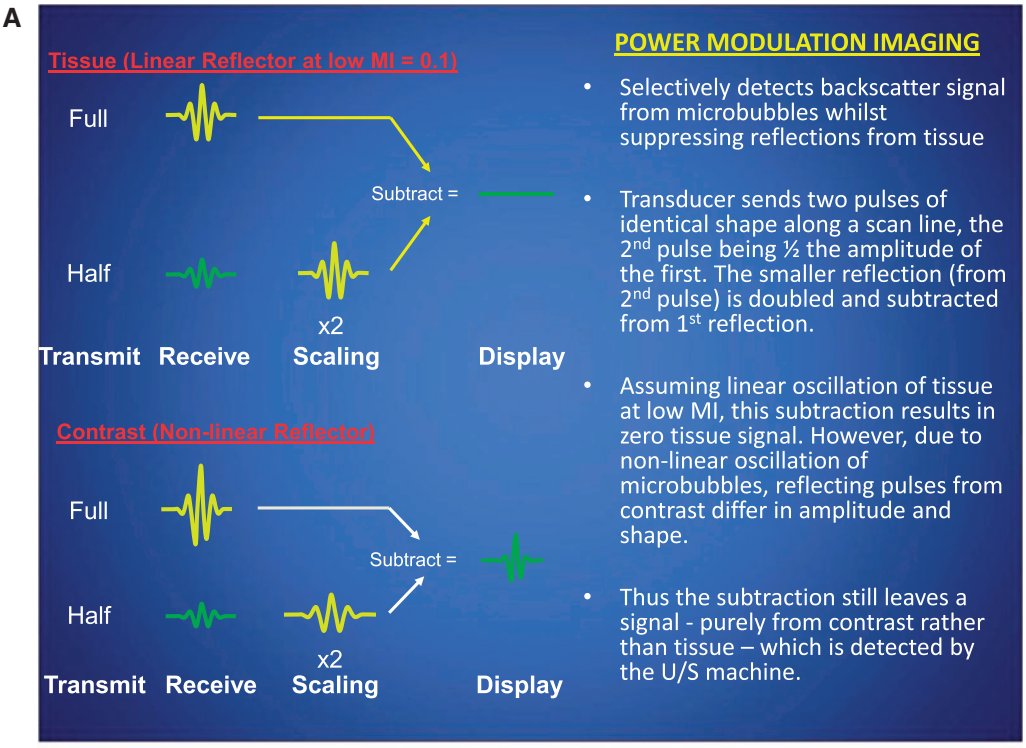

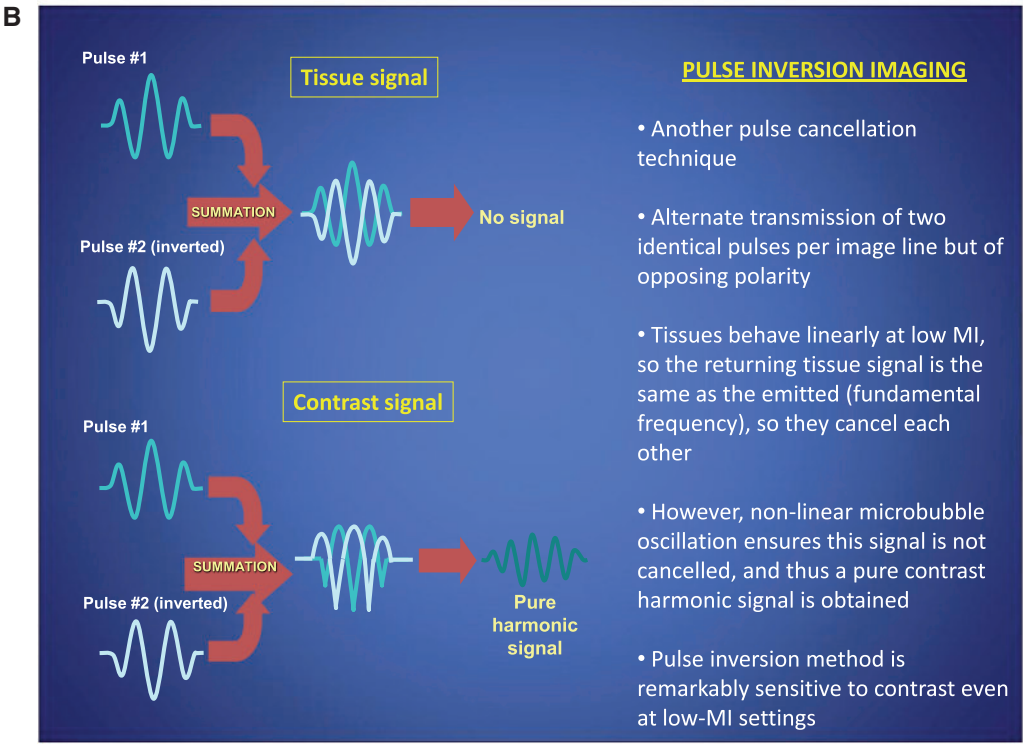

Figure 1 Contrast-specific imaging using power modulation (*A*) and pulse inversion (*B*): multiple pulses are transmitted down each scan line. Alternate pulses are 180° out of phase with other or vary in magnitude of amplitude by a fixed ratio or are a combination of both strategies. When alternate backscattered signals are received, which are perfectly out of phase or proportionally altered in amplitude, they are processed by the imaging software as being derived from tissue and therefore are filtered out and suppressed. All remaining 'non-linear' signals are considered to be derived from contrast microbubbles and are displayed. (Senior et al EACVI Echo Tool Box)

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Table 2 Contrast imaging modalities

Power (MI)	Type of Imaging	Technology	Advantages	Disadvantages
High (0.8–1.0)	Intermittent	• Power Doppler (ultraharmonics)	• Very sensitive for detection of contrast	• Cannot assess wall motion simultaneously • Contrast is destroyed
Intermediate[a] (0.2–0.5)	Continuous (real time)	• Harmonic imaging • Power modulation • Power pulse inversion • Cadence pulse sequencing • Coherent contrast imaging	• Wall motion can be assessed in real time • Destruction-replenishment modes available	• Simultaneous assessment of perfusion is limited • Artefacts from bubble destruction in the near field • Less sensitive for contrast detection compared with very low MI contrast imaging modalities
Low[a] (<0.2)	Continuous (real time)	• Power modulation • Power pulse inversion • Cadence pulse sequencing • Coherent contrast imaging	• Perfusion can be assessed simultaneously • Destruction-replenishment modes available	• Limited spatial and temporal resolution and dynamic range

[a]In the ASE Sonographer Guidelines, intermediate MI corresponds to low MI and low MI to very low MI imaging.

the solution. Agitation can be performed manually by slowly rocking the syringe or the bag to and fro. A special infusion pump has been developed for SonoVue®, which provides constant agitation. The pump can be prepared in a few minutes prior to the study while the patient is being prepared or during the baseline echo examination. By an alternating rotating action, the contrast agent is agitated preventing bubbles separating and floating to the surface. The pump is then kept in a standby mode. The pump is started by the echocardiographer using a remote control and no additional staff is needed. Although the pump provides the possibility of an initial small bolus, a constant infusion of Sonovue® 0.8 mL/min from the start is usually satisfactory and need not be changed in the majority of patients. In contrast to a bolus injection, a continuous infusion over a short time provides stable conditions to acquire loops from different scan planes and provides a steady-state level to quantitatively assess myocardial perfusion. During SE, the infusion can be stopped at any time and resumed when needed. Between infusion periods, the contrast agent is automatically agitated. During dobutamine stress echocardiography (DSE), the contrast infusion should be connected through a three-way tap or a small bore Y connector at the IV cannula, permitting simultaneous dobutamine infusion.

Bolus injection

It is also possible to use slow bolus injections of all agents (Sonovue® 0.5 mL, Luminity® 0.2 mL and Optison® 0.2 mL), followed by slow 5 mL saline flush over 20 s. However, bolus administration is not as controlled or reproducible as infusion to provide a steady and uniform opacification of the LV cavity and or the myocardium. Bolus injection has been used in most of the published studies for the assessment of LV structure and function.

Recommendations

Bolus injections of the contrast agent are adequate for the assessment of LV function and diagnosis of structural LV abnormalities such as apical hypertrophy, aneurysms, cardiomyopathies and thrombi (Class I, Level A). Infusion of contrast is optimum for the assessment of myocardial perfusion and for perfusion assessment of cardiac masses (Class I, Level A).

For infusion of the ultrasound contrast agents, a special pump that agitates the contrast agent is preferable (Class IIa, Level B).

Simultaneous infusion of ultrasound contrast agents with dobutamine or adenosine can be performed through the same IV cannula (Class I, Level B).

Efficacy of contrast agents in echocardiography

Enhancement of LV endocardial border

There is a large body of evidence for the use of contrast agents in enhancing endocardial LV borders. The application of ultrasound contrast agents leads to an improved delineation of endocardial LV borders (*Figure 2*). All the three currently approved ultrasound contrast agents have been evaluated in larger multicentre trials required by European Medicines Agency (EMA) and Food and Drug Administration (FDA) for approval.[13–15]

In addition to the multicentre studies for approval, further single-centre studies were performed and demonstrated the ability of contrast echocardiography in improving endocardial definition (*Table 3*).[16–31] Three studies have demonstrated the utility of contrast enhancement in patients on intensive care units.[27–29] The earlier clinical trials for approval have been performed using fundamental imaging. The introduction of harmonic imaging for routine echocardiographic imaging has resulted in a significant improvement of image quality.[32,33] However, there is still a significant proportion of studies obtained with harmonic imaging in which images are suboptimal, and these studies benefit from the application of ultrasound contrast agents.[34] But the

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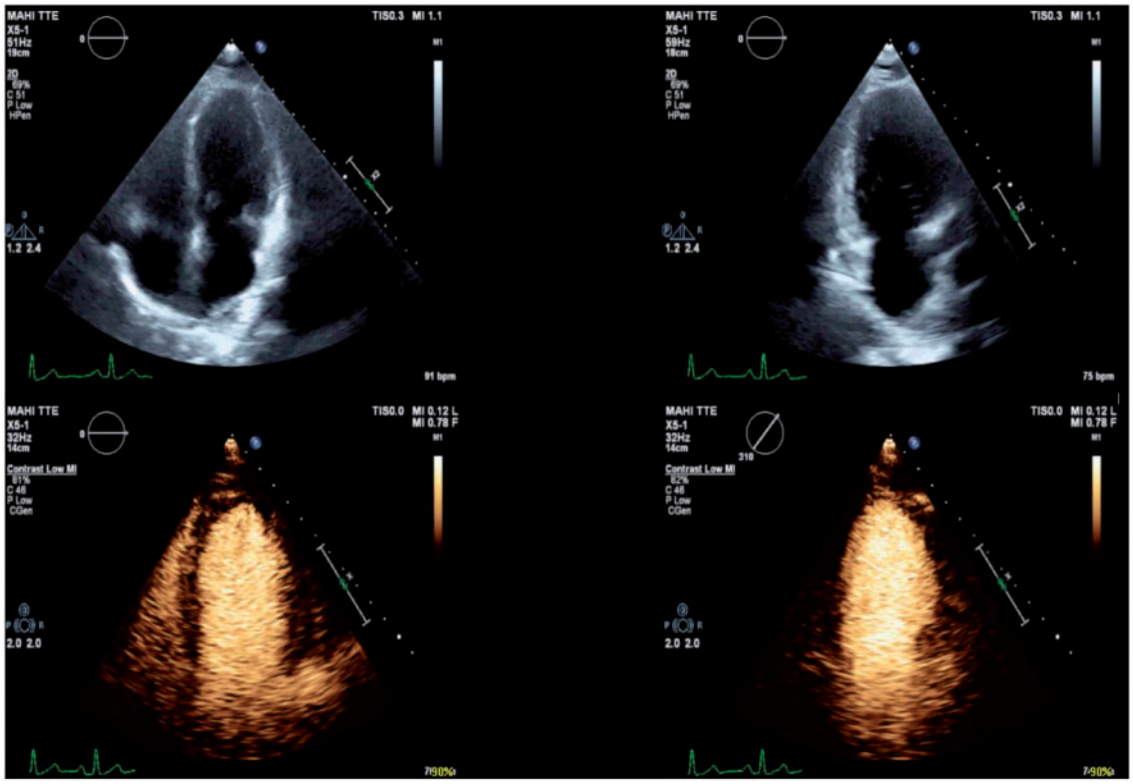

Figure 2 Apical four- and two-chamber views (top left and right) with poorly visualized borders between the compact and trabeculated myocardium. The corresponding recording obtained after injection of contrast agent (0.5 mL SonoVue©) show adequate delineation of the LV cavity from the myocardium (bottom left and right).

Table 3 Efficacy of contrast agents on LV image enhancement

Patients (*n*)	Comparator	Contrast agent	Type of improvement	Author	Year
175	Native echo	Albunex	Endocardial definition improved in 83% patients	Crouse *et al.*[16]	1993
254	Albunex	Echogen	Echogen improved endocardial definition improved in 88% patients; Albunex improved endocardial definition improved in 45% patients	Grayburn *et al.*[17]	1998
203	Albunex	Optison	Optison increased visible endocardial border length by 7.6 ± 4.8 cm; Albunex increased visible endocardial border length by 3.4 ± 4.6 cm	Cohen *et al.*[18]	1998
218	Native echo	SonoVue	Mean improvements in the endocardial border visualization score 3.1–3.7	Senior *et al.*[19]	2000
211	Saline	Definity	Endocardial border visualized in 47% segments without contrast and 81% after contrast	Kitzman *et al.*[20]	2000
70	Native echo	Optison	Harmonic imaging: uninterpretable wall motion in 4.4 segments/patient; Contrast echo: uninterpretable wall motion in 1.1 segments/patient	Reilly *et al.*[21]	2000
50	Native echo	Optison	Conversion of non-diagnostic studies in 85% of patients with contrast in 15% with tissue harmonic imaging compared with fundamental imaging	Kornblut *et al.*[22]	2000

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Table 3 Continued

Patients (*n*)	Comparator	Contrast agent	Type of improvement	Author	Year
40	Native echo	Optison	Segmental score improved from 4.5 to 11.6 in ICU patients with poor acoustic windows	Nguyen *et al.*[23]	2001
100	Native echo	Levovist	Conversion of non-diagnostic image from 33% to 77%	Chen *et al.*[24]	2001
264	Albunex saline	SonoVue	Mean increases in LVEBD 3.8–18.2 for SonoVue, 0.1–4.3 for Albunex	Nanda *et al.*[25]	2002
409	Saline	Imagent	Agreement of segmental wall motion scores; improved from 31% and 39% to 48% and 65%	Nanda *et al.*[26]	2003
92	Native echo	Definity	51% studies salvaged with contrast	Nash *et al.*[27]	2004
30	Native echo	Sonicated albumin	Salvage rate of 77% of non-diagnostic studies in ventilated patients	Costa *et al.*[28]	2005
62	Native echo	Definity Optison	conversion of non-diagnostic to diagnostic study from 11% to 81% when scans are performed by fellows	Makaryus *et al.*[29]	2005
632	Native echo	Definity	Technically difficult studies became contrast adequate 89.9%	Kurt *et al.*[30]	2009
100	Native echo	SonoVue	Inter-observer agreement for wall motion scoring contrast echo (88%, kappa 0.78) non-contrast (76%, kappa 0.60)	Galema *et al.*[31]	2011

LVEBD, left ventricular endocardial definition (modified from Bhatia and Senior).

number of suboptimal studies may vary depending on the mix of patients—in particular on the number of patients scanned on intensive care units. This was confirmed in a large study by Kurt *et al.*[30] who prospectively enrolled 632 patients with technically difficult echocardiographic studies. After contrast echocardiography, the percentage of uninterpretable studies decreased from 11.7% to 0.3% and technically difficult studies decreased from 86.7% to 9.8% ($P < 0.0001$).

Quantitative assessment of LV volumes and function

Volumetric measurements are usually based on tracings of the interface between the compacted myocardium and the LV cavity according to the recent American Society of Echocardiography (ASE)/European Association of Cardiovascular Imaging (EACVI) recommendations for cardiac chamber quantification by echocardiography for adults.[35] However, it can be difficult to differentiate the compact myocardium from the trabeculated layer—in particular in the apical LV segments. Therefore, quantitative assessment of LV volumes is often not feasible using unenhanced echocardiography.[36]

The value of 2D contrast echocardiography for quantification of LV volumes and ejection fraction (EF) was assessed in 17 studies including 2 multicentre studies using cardiac magnetic resonance (CMR), nuclear imaging, electron beam computed tomography or TOE as a reference (*Table 4*).[37–54] No significant difference was found when EF was compared between non-contrast 2D echocardiography, contrast 2D echocardiography and the reference methods. The inter- and intra-observer variability of EF measurements of contrast 2D echocardiography was significantly better than that of non-contrast 2D echocardiography and similar to CMR. Contrast 2D echocardiography is particularly useful in patients who had two or more adjacent poorly visualized segments, which represents the current licensing of the contrast agents. However, a benefit of contrast echocardiography has also been demonstrated in patients in whom image quality was visually judged as adequate. In a study consisting of 110 patients, the accuracy of intravenous contrast echocardiography was found to be significantly better than unenhanced tissue harmonic imaging when compared with cardiac magnetic resonance imaging irrespective of imaging quality.[55] Larsson *et al.*[56] performed contrast echocardiography in 192 patients all with adequate acoustic windows and found better reproducibility for assessment of EF compared with unenhanced echocardiography.[56] The superior reproducibility of 2D contrast echocardiography compared with non-contrast echocardiography becomes clinically relevant when clinical management depends on accurate measurements of LV volumes and EF rather than on a semi-quantitative classification. This is the case in patients assessed for intracardiac defibrillator (ICD) or cardiac resynchronization therapy (CRT) or when serial measurements of EF are performed to monitor cardiotoxic effect of cancer drugs such as trastuzumab. Contrast echocardiography has been recommended in patients in whom assessment of EF is not feasible by non-contrast 3D echocardiography.[57] Measurements of EF by 2D contrast echocardiography have been shown to be feasible and highly reproducible in a large cohort of consecutive patients undergoing chemotherapy with cardiotoxic drugs.[58,59]

During 3D echocardiography, it can be difficult to differentiate between the compact myocardium and the trabeculae. (*Figure 3*).[60] In one multicentre study comparing non-contrast and contrast 3D echocardiography with CMR and several single-centre studies (mostly in comparison with CMR) improved inter-observer variability and better accuracy of EF measurements was demonstrated.[43–46,50,52–54] However, there was inconsistent superiority over 2D contrast echocardiography. There were limitations of 3D contrast echocardiography due to inhomogeneous LV contrast bubble destruction in the near field, which resulted in increased inter-observer variability.[43]

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Table 4 Efficacy of 2D and 3D contrast echocardiography for assessment of LV volumes, EF or regional wall motion abnormalities—comparison with other imaging modalities

Patients (*n*)	Comparator agent	Contrast	Agreement vs. comparator main findings	3D	Author	Year
40	CMR	EchoGen	EF: without contrast 0.85–0.93 contrast, $P < 0.3$ EDV without contrast 0.92–0.95 contrast, $P < 0.02$ ESV without contrast 0.94–0.97 contrast, $P < 0.01$ Correct classification of EF improved From 71% before contrast to 94% after contrast		Hundley *et al.*[37]	1998
50	RNI	Optison	Linear correlation coefficient: 0.84 (EF-non contrast) 0.96 (EF-contrast)		Nahar *et al.*[38]	2000
51	RNI	Levovist	0.89 (EF non contrast) 0.97 (EF contrast) 0.71 (EDV non contrast) 0.93 (EDV contrast) 0.89 (ESV non contrast) 0.97 (ESV contrast)		Yu[39]	2000
26	EBCT	Optison	EDV, ESV and EF: No significant difference between contrast echo and EBCT		Thomson *et al.*[40]	2001
32	TOE	Optison	34% segments visualized with harmonic imaging 87% segments visualized with contrast echo 50% patients EF possible with harmonic imaging 97% patients EF possible with contrast echo Linear correlation coefficient: 0.83 (EF non-contrast) 0.91 (EF contrast)		Yong *et al.*[41]	2002
110	CMR	Luminity	Limits of agreement: SonoVue EF: -18.1% to 8.3% (non-contrast), 7.7% to 4.1% (contrast) EDV: -98.2 to - 11.7 mL (non-contrast) -59.0 to 10.7 mL (contrast) ESV: -58.8 to 21.8 mL (non-contrast) -38.6 to 23.9 mL (contrast)		Malm[42]	2004
46	CMR	Definity	Patients with good acoustic windows, correlation with MRI: 3D echo data sets obtained without contrast (EF, $r = 0.86$, SEE = 8.8%) compared with those obtained with contrast 3D (EF, $r = 0.71$, SEE = 12.3%)	+	Caiani *et al.*[43]	2005
20	CMR	Definity	Triggered imaging (End diastole/end systole) increases accuracy of 3D contrast volume measurements	+	Caiani *et al.*[44]	2005
24	CMR	Definity	In 16 patients with poor endocardial definition correlation with CMR was better on contrast 3D echo ($r = 0.61$) than on native 3D echo ($r = 0.76$)	+	Corsi *et al.*[45]	2006
53	CMR	SonoVue	95% limits of agreement for EF between echocardiography and MRI 2D non-contrast -12.5 to 6.7%, triplane non-contrast -17.2 to 9.9% 2D contrast -7.1 to 5.8%, triplane contrast -9.4 to 6.4%	+	Malm *et al.*[46]	2006
36	CMR	SonoVue	EF classification agreement: 69% (non-contrast; kappa 0.33) and 83% (contrast; kappa 0.66)		Lim *et al.*[47]	2005
120	CMR[a]	SonoVue	RWMA inter-observer agreement CMR: kappa 0.43RWMA inter-observer agreement non-contrast 2D echo: kappa 0.41RWMA inter-observer agreement contrast 2D echo for: kappa 0.77EF inter-observer reliability ICC 0.91 (contrast 2D), 0.86 (CMR), 0.79 (non-contrast 2D echo)		Hoffmann *et al.*[48] Hoffmann *et al.*[49]	2006 2005
50	CMR	Optison Definity	EF classification agreement with CMR non-contrast 2D echo: 68% agreement, kappa 0.45 contrast 2D echo: 62% agreement, kappa 0.20 non-contrast 3D echo 74% agreement, kappa 0.39 contrast 3D echo 80% agreement, kappa 0.56 contrast 3D superior to other techniques in patients with previous infarction	+	Jenkins *et al.*[50]	2009

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Table 4 Continued

Patients (*n*)	Comparator agent	Contrast	Agreement vs. comparator main findings	3D	Author	Year
150	CMR	SonoVue	mean EDV difference: MRI – non contrast 2D echo 54.9 mL MRI – contrast 2D echo 41.7 mL		Mistry *et al.*[51]	2010
41	CMR	SonoVue	contrast 3D echo superior to 2D and 3D non-contrast echo for inter-observer variability and agreement with CMR	+	Saloux[52]	2014
62	CMR[a]	SonoVue	RWMA: accuracy to detect expert panel defined 84% (CMR), 78% (2D contrast echo) 76% (3D contrast echo)	+	Hoffmann *et al.*[53]	2014
			EF: mean percentage of error CMR 7.9%, 2D echo 14.3%, 3D echo 13.6, 14.3% contrast 2D echo 8.0%, contrast 3D echo 7.4, 8.5%	+	Hoffmann *et al.*[54]	2014

[a]Multicentre studies, studies including 3D echocardiography are highlighted with a +.
RNI, radionuclide imaging; EBCT, electron beam computed tomography.

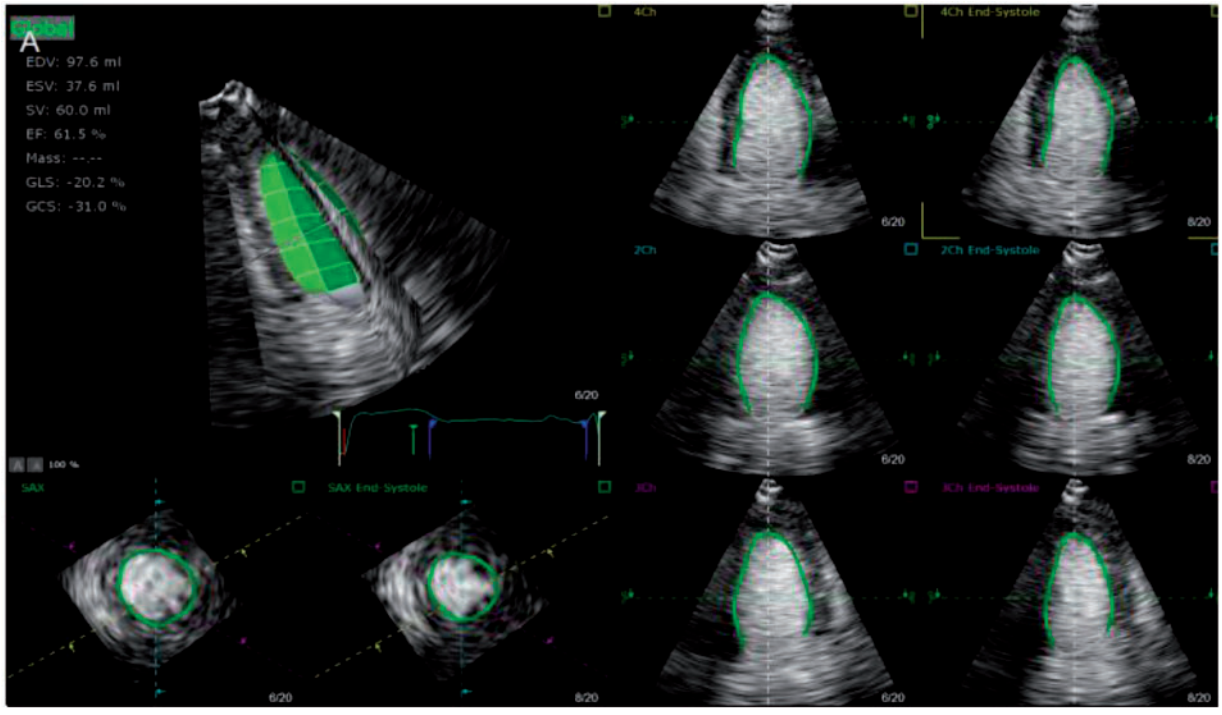

Figure 3 Orthogonal slices obtained from a full-volume data set recorded with 3D contrast echocardiography.

In the 2015 ASE/EACVI recommendations for chamber quantification, normal values for contrast echocardiography have not been mentioned, as there have been no studies designed to address normal values in contrast echocardiography.[35] Contrast echocardiography and non-contrast echocardiography give similar LVEF values compared with CMR. However, both end-diastolic and end-systolic volumes are higher when measured using contrast echocardiography compared with a non-contrast echocardiography for reasons stated before. Thus, LV volumes values—based on non-contrast images—recommended by EACVI/ASE cannot be used interchangeably unlike LVEF with values obtained by contrast echocardiography.

Recommendations

(1) Contrast echocardiography should be used when two or more contiguous LV segments are not clearly visualized (Class I, Level B).

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(2) Contrast 2D echocardiography should be considered irrespective of image quality when clinical management depends on accurate measurements of LVEF such as monitoring of patients treated with cardiotoxic drugs and when implantation of ICD or CRT devices are considered (Class IIa, Level B).
(3) The normal values for EF and grading of reduced EF (mild, moderate or severe) but not LV volumes published in the recent ASE/EACVI recommendations can be used for contrast echocardiography (Class IIb, Level B).
(4) Because of limited number of studies, 3D contrast echocardiography is not yet recommended (Class III, Level B).

Assessment of regional LV function

There is also strong evidence that contrast agents improve the assessment of regional LV wall motion in both 2D and 3D modes. Analysis of regional LV wall motion abnormalities (RWMA) is significantly limited by considerable inter-reader variability even when using high-quality non-contrast 2D and 3D echocardiographic recordings.[48] Two multicentre studies involving a total of 180 patients addressed the inter-reader agreement of unenhanced and contrast-enhanced 2D echocardiography in comparison with CMR and ventriculography.[48,53] One of these studies also included comparisons of non-enhanced and contrast-enhanced 3D echocardiography on 63 patients.[53] For these studies, a standard of truth for the presence of RWMA was obtained by an independent expert panel decision. In both multicentre studies, contrast 2D echocardiography significantly reduced inter-observer variability for the assessment of RWMA and improved the accuracy to detect expert panel-defined RWMA. In the first multicentre study, the accuracy to detect RWMA was highest for contrast 2D echocardiography, followed by CMR, unenhanced 2D echocardiography and cineventriculography.[48] In the second multicentre study, accuracy to diagnose RWMA was highest for CMR (84%), followed by 2D contrast echocardiography (78%) and 3D contrast echocardiography (76%).[53] The use of 3D echocardiography required contrast application similar to 2D echocardiography to reduce inter-observer variability on regional LV function. With 3D echocardiography, the use of contrast increased the inter-reader agreement between two blinded offsite readers from 0.27 to 0.42 (kappa values).

In addition to the two multicentre studies, single-centre studies confirmed the benefit of ultrasound contrast agents for the assessment of regional systolic LV function.[21,41,45,56] It has been shown that contrast echocardiography improved confidence of the interpretation of regional LV wall motion and increased the inter-observer agreement from 80% (non-contrast tissue harmonic imaging) to 95% (2D contrast echocardiography) in intensive care unit patients.[21] In a further evaluation of similar group of patients, comparing the results with TOE, it was concluded that the use of intravenous contrast echocardiography significantly improved the feasibility and accuracy of estimated LVEF over tissue harmonic imaging.[41] Larsson *et al.*[56] compared contrast echocardiography with non-contrast echocardiography in 192 patients with good acoustic windows. They found an increased reproducibility of wall motion score index using contrast 2D echocardiography and that 55% of the patients were reclassified with motion abnormalities by contrast analysis. In patients 7–10 days after acute MI assessment of LV ESV and EF by contrast echocardiography showed incremental prognostic value for predicting hard events beyond clinical and non-contrast determined LV function.[61]

Recommendations

Contrast 2D echocardiography should be considered when two or more contiguous LV segments are not adequately visualized on non-contrast echocardiography and management of the patient will depend on whether there are regional wall motion abnormalities or not (Class I, Level A).

Except for SE (see below), there is not good evidence of using contrast agents in patients with good acoustic windows (Class III, Level B).

Assessment of LV structure and masses

Contrast opacification particularly facilitates the identification of apical abnormalities.[62] This is because native tissue harmonic echocardiography is unable to overcome the noise, clutter and reverberation artefacts in the near field as tissue harmonic signals are weak at the near field (*Figure 4*). Multiple reports are available for using contrast echocardiography for establishing or excluding the presence of apical hypertrophic cardiomyopathy[63–66], non-compaction [67–69], diverticula[70] and life-threatening complications of MI, such as myocardial rupture and LV pseudoaneurysm (*Figure 5*).[71–76] The contrast echocardiographic findings of apical hypertrophy and non-compaction (prominent LV trabeculations and thinned compact myocardium) are specific and usually need no further assessment with CMR. In suspected myocardial rupture, contrast echocardiography is the only bedside method to confirm or exclude myocardial rupture.

The utility of contrast agents to rule out or rule in LV thrombi has been shown in larger cohorts when conventional echocardiography was inconclusive (*Figure 6*).[30,77–79] The obvious implications for management of the patients are further discussed in Clinical impact—cost-effectiveness section. However, smaller mural and apical clots may be missed despite contrast echocardiography.[80,81] However, prognostic implications for small mural thrombi post infarction is uncertain. Cardiac thrombi may be indistinguishable from tumours, especially when occurring adjacent to a normally contracting myocardium. Presence of significant vascularization detected by contrast echocardiography when using the perfusion protocol as described in Myocardial contrast echocardiography section establishes cardiac tumour.[82] However, absence of perfusion does not confirm thrombus as avascular cardiac tumour is also common.

Recommendations

Contrast echocardiography should be considered when apical hypertrophy and diverticula, pseudoaneurysm, myocardial rupture, non-compaction and LV thrombi are suspected but not clearly documented or excluded on non-contrast images (Class I, Level B).

Contrast echocardiography for perfusion may be used in patients with cardiac masses suspicious of a tumour to distinguish it from a thrombus when CMR is not available or inconclusive (Class IIa, Level C).

Left atrial appendage visualization with contrast agent use during TOE

TOE is established for the assessment of thrombi in the left atrium and left atrial appendage (LAA).[83,84] In the LAA, spontaneous echo

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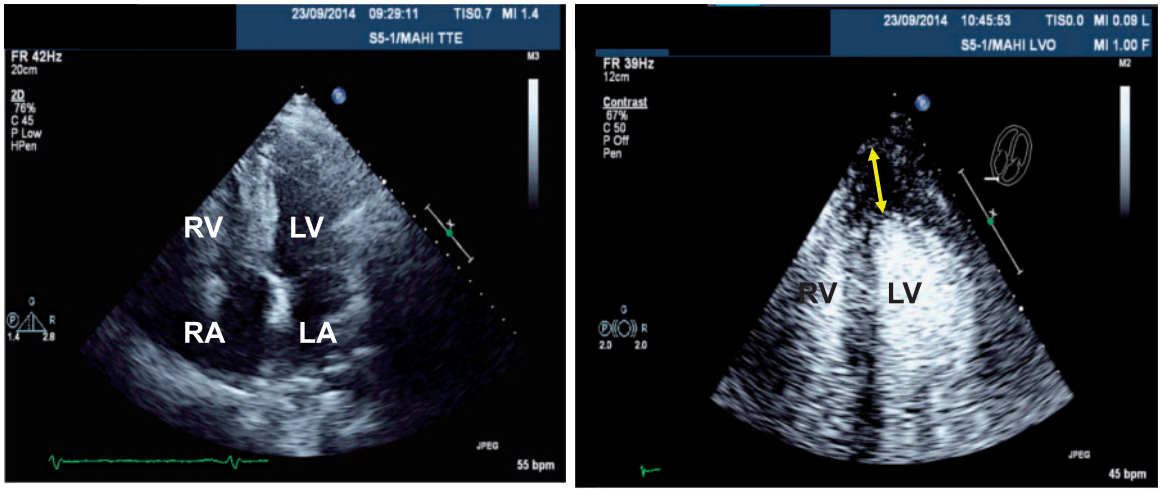

Figure 4 Apical hypertrophy not well displayed on the four chamber view without contrast (left), after injection of ultrasound contrast agent it was possible to measure the thickness of the apical myocardium.

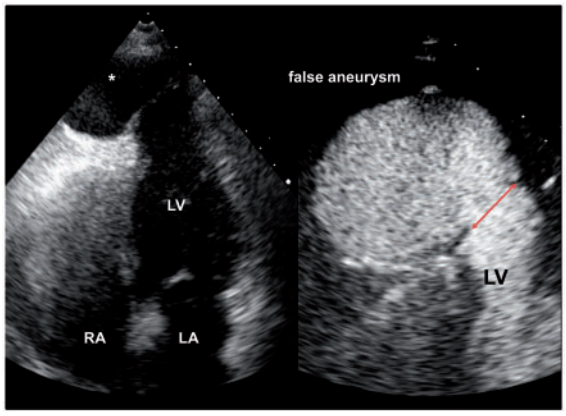

Figure 5 Four-chamber view with incidental finding of a confined echo-free area asterisk denotes adjacent to the LV apex (left). Contrast echocardiography confirms a large false aneurysm, four-chamber view, zoomed apex, and the red arrow shows the neck of the aneurysm.[75]

contrast can impair visualization of thrombi and hypoechogenic thrombi can be missed with standard TOE (*Figure 7*).[85] A study involving 41 patients with atrial fibrillation and dense spontaneous echo contrast delineated contrast free masses characteristic of a clot after injection of Optison®,[86] SonoVue® was used in another study involving 90 patients, and Definity® was administered in 100 patients in a study at the Mayo Clinic.[88] LAA thrombi could be definitely excluded in more patients with contrast-enhanced TOE than with unenhanced TOE (83.3% vs. 66.7%).[88] Jung *et al.*[87] followed their patients after cardioversion; no embolic events were reported during follow-up in patients with contrast-enhanced TOE. However, there were 2 subsequent strokes in a control group of 90 patients in whom only unenhanced TOE was performed prior to cardioversion. Similar to the imaging of LV thrombi, contrast-specific imaging modalities (e.g. contrast LVO using MI < 0.2) are suitable for TOE assessment of LAA thrombi. However, contrast-specific imaging modalities are not available on several TOE scanners, and then harmonic imaging with an MI < 0.3 should be used.

Recommendation

Contrast injection may be considered when native images are inconclusive for the diagnosis of LAA thrombus (Class IIa, Level C).

Assessment of aortic disease

Contrast may have a role in the detection of aortic dissection. Sensitivity and specificity of conventional transthoracic echocardiography in the detection of aortic dissection increased after contrast enhancement.[89,90] Also using the transoesophageal approach, the location of non-visualized entry tear, the correct identification of the true lumen and the diagnosis of retrograde dissection increase after contrast enhancement.[89] Contrast echocardiography also helps to confirm aortic pathology when images are suboptimal or suspicious of being abnormal.[91] Injection of contrast agent has been shown improve display of clots in the aorta.[92] In patients undergoing thoracic endovascular aortic repair procedures, contrast-enhanced TOE has improved endoleak detection.[93]

Recommendations

In patients with acute aortic syndromes and in patients undergoing thoracic endovascular aortic repair procedures, contrast agents may be used to assess the aortic pathology if non-contrast 2D echocardiographic and Doppler images are suboptimal or ambiguous (Class IIa, Level C).

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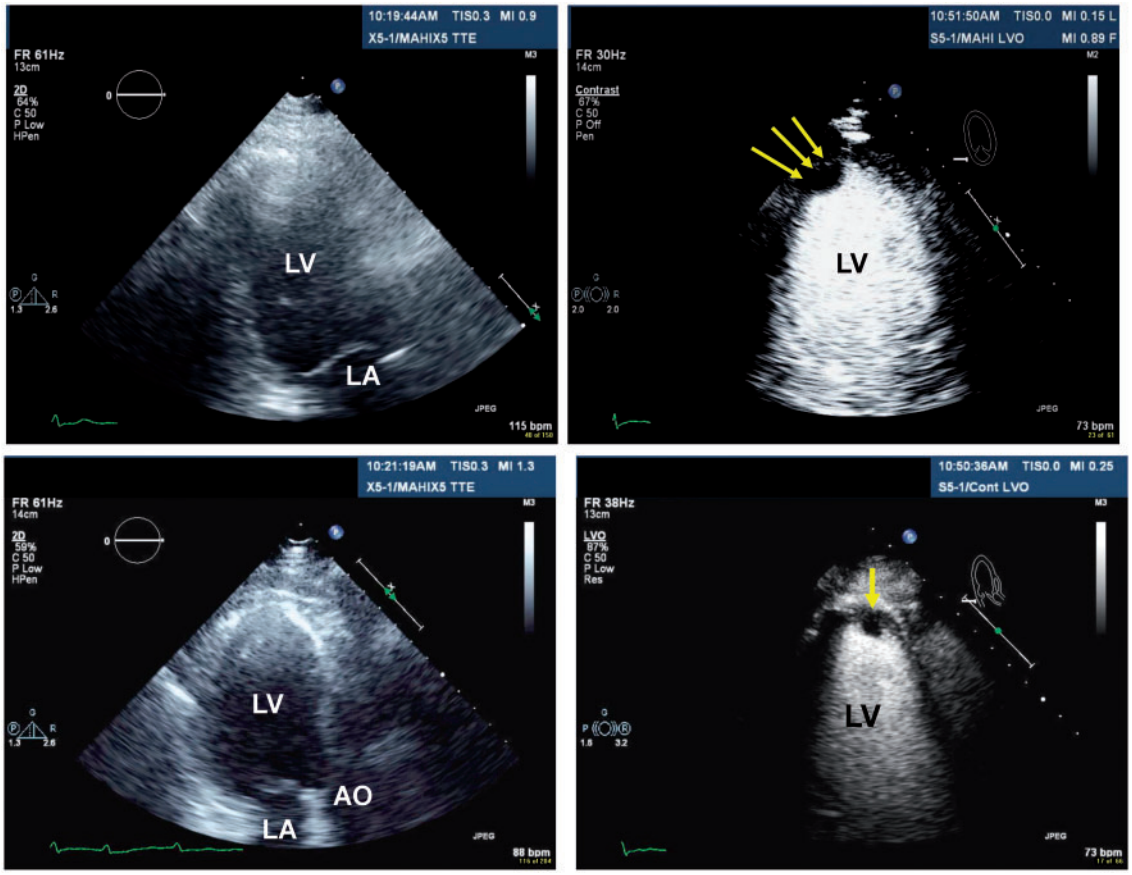

Figure 6 Examples of LV thrombus (arrow) displayed after bolus injection of 0.1 mL Luminity® (right), the corresponding plane (three-chamber view) without contrast did not show the thrombus.

Stress echocardiography

Detection of regional wall motion abnormality for the diagnosis of coronary artery disease

Multiple studies have demonstrated the ability of ultrasound contrast agents to improve visualization of regional wall motion abnormalities, improve study quality, and increase reader confidence in study interpretation (*Table 5*).[94–112] Very low MI techniques add the possibility of assessment of myocardial perfusion to the high quality assessment of regional and global LV wall motion.[12] Myocardial thickening abnormality during stress which is the hall-mark of myocardial ischemia is better appreciated with myocardial opacification and subtle wall-thickening abnormalities are better appreciated when concomitant sub-endocardial perfusion defect is observed[113] Six studies demonstrated better agreement of coronary angiographic findings with contrast SE compared with non-contrast studies and one study was compared with fractional flow reserve.[111] In a randomized crossover study by Plana et al. patients underwent both non contrast and contrast enhanced DSE.[110] When compared with angiography the diagnostic accuracy for the detection of coronary artery disease (CAD) in patients who received contrast was significantly higher than with unenhanced SE for the detection of CAD.[110] A recent single-centre study demonstrated the clinical value of 2D contrast echocardiography in 192 patients with adequate image quality. Contrast echocardiography improved the reproducibility of the wall motion score index and demonstrated regional wall motion abnormalities in 55% of the patients who were diagnosed as normal with non-contrast echocardiography.[56]

There is limited experience using 3D echocardiography with ultrasound contrast agents for SE.[114–118] Despite the current limitations of 3D contrast echocardiography at higher heart rate (need for stitching data sets, lower temporal and spatial resolution when compared with 2D contrast echocardiography), the available studies demonstrated the feasibility of 3D contrast echocardiography. In one of the largest clinical studies, sensitivity and specificity for detecting wall motion abnormalities by 3D DSE was 58% and 75%, respectively, when using 2D DSE results as the gold standard.[115] However, the total number of patients studied and is <200. There is the potential of better results with the newer smaller probes and further advancement of the 3D equipment.

Risk stratification/prognosis

The prognostic information from contrast-enhanced 2D SE appears to be similar to that from non-contrast stress

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echocardiograms in patients with optimal image quality. This has been demonstrated in patients with different reasons for poor acoustic windows for example morbid obesity.[109] A negative contrast stress echocardiogram has an excellent prognosis with an annual event rate <1%.[109] In a study involving 893 patients, the 3-year event-free survival rate was significantly lower in patients with positive contrast dobutamine stress echo results than in those with negative DSE results.[119] In another study, performed in consecutive patients presenting with suspected acute coronary syndrome (ACS) but negative troponin and equivocal electrocardiography (ECG), SE provided diagnostic images in 99% of patients, where contrast was used in over 60% of patients and helped early discharge of patients with excellent outcome but patients with an abnormal SE had worse prognosis.[120]

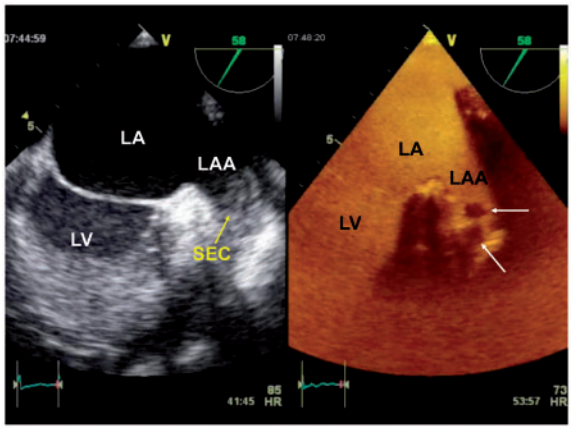

Figure 7 TOE recording of the left atrial appendage (LAA): on the recording without contrast agent (left) spontaneous echo contrast (SEC) is displayed in the LAA but no thrombus can be delineated. With contrast agent (right), two thrombi are delineated as echo-free masses (white arrows) within the LAA. LA, left atrium; LV left ventricle, Courtesy of Dr Andreas Helfen, St.-Marien-Hospital Lünen, Germany.

Limitations of contrast echocardiography

Adequate recordings for assessment of LV function and assessment of LV structure can be achieved in the majority of patients. However, the echocardiographers require training and understanding of the physics of microbubbles as well as the imaging technology (see Training/accreditation requirements in contrast echocardiography section). There are a few artefacts that are unique for contrast echocardiography such as swirling (resulting from bubble destruction or low dosages of contrast), blooming (due to high-contrast dosage or inadequate gain setting) and attenuation, where the contrast agent in the near field shadows the deeper part of the left ventricle. These artefacts could be recognized and eliminated with simple measures (see *Table 12*). One of the most frequent reasons for suboptimal recordings is acquisition of the images too early after bolus injections, when there is a high concentration of microbubbles in the RV and LV cavity, which can cause attenuation and/or blooming. It usually takes more than 20 s to get homogeneous contrast in the entire LV cavity. During stress, this can be shorter. Finally, the microbubbles are very

Table 5 Studies reporting benefit of using ultrasound contrast agents for stress echocardiography

Patients (*n*)	Stress method	Contrast agent	Author	Year
50	Dobutamine	son.Albumin	Porter *et al.*[94]	1994
30	Dobutamine	Albunex	Falcone *et al.*[95]	1995
16	Bicycle	BY 963	Leischik *et al.*[96]	1997
30	Dobutamine	Infoson	Ikonomides *et al.*[97]	1998
36	Dobutamine	BY 963	Schnaak *et al.*[98]	2000
200	Exercise/dobutamine	Optison	Malhotra *et al.*[99]	2000
29	Dobutamine	Optison	Vlassak *et al.*[100]	2002
38	Arbutamine	SonoVue	Brown *et al.*[101]	2004
283	Treadmill	Optison	Yokoyama *et al.*[102]	2004
117	Dobutamine	Optison	Dolan *et al.*[103]	2001
300	Dobutamine	Optison	Rainbird *et al.*[104]	2001
560	Not specified	Definity	Weiss *et al.*[105]	2005
40	Exercise	SonoVue	Rizzo *et al.*[106]	2005
62	Dobutamine	SonoVue	Hu *et al.*[107]	2007
135	Dipyridamole	Definity	Moir *et al.*[108]	2007
611	Dobutamine	Definity/Optison	Lerakis *et al.*[109]	2007
101	Dobutamine	Definity	Plana *et al.*[110]	2008
70	Dobutamine	SonoVue	Jung *et al.*[111]	2008
42	Dobutamine	SonoVue	Cosyns *et al.*[112]	2008

Only those studies are listed in which contrast agents were used to enhance endocardial visualization.

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sensitive to pressure changes, e.g. applying negative pressure during preparation by not following the instructions of manufacturers or scanning with the ultrasound power, which is used for non-contrast imaging, result in poor contrast images.

The additional cost may be a limitation—in particular in institutions where patients have to pay for the contrast additionally. However, alternative imaging methods for SE (e.g. nuclear imaging of CMR) are more expensive, and there is good evidence that suboptimal recordings result in increased downstream costs (see Clinical impact—cost-effectiveness section). This is also true for resting inconclusive or inadequate studies without contrast.[30]

Recommendations

Stress echocardiography for the assessment of RWMA for the detection of myocardial ischaemia should be performed with contrast agents when two or more contiguous segments are not adequately visualized at rest (Class I, Level A) or during deep inspiration mimicking cardiac motion during stress (Class IIa, Level C).[225] In patients with less than 2 segments not well-visualized contrast agents should be given when myocardial perfusion is assessed in addition to LV wall motion using low MI contrast imaging (see Myocardial contrast echocardiography section).

Low MI contrast-specific imaging modalities should be used for SE (see Contrast imaging modalities section), irrespective of whether only wall motion or both wall motion and perfusion are assessed (Class I, Level C).

There is not enough available data to recommend 3D contrast echocardiography for stress testing (Class III, Level B).

Myocardial contrast echocardiography

Principles of myocardial contrast echocardiography

The volume of blood within the entire coronary circulation at rest in diastole is approximately 12 mL/100g of left ventricular myocardium and the predominant (90%) component of this resides within the capillaries.[121] The myocardial signal intensity emanating from the contrast agent reflects the concentration of microbubbles within the myocardium.[122] When the myocardium is fully saturated during a continuous infusion of microbubbles, the signal intensity reflects relative capillary blood volume. Following clearance of microbubbles from the myocardium during brief burst of high-power imaging, microbubble replenishment within the myocardium can be observed (*Figure 8*).[122] The capillary blood velocity is 1 mm/s with an ultrasound beam elevation of 5 mm. Thus, it takes 5 s for complete replenishment of the myocardium. Any decrease in myocardial blood flow (MBF) prolongs replenishment time in proportion to the

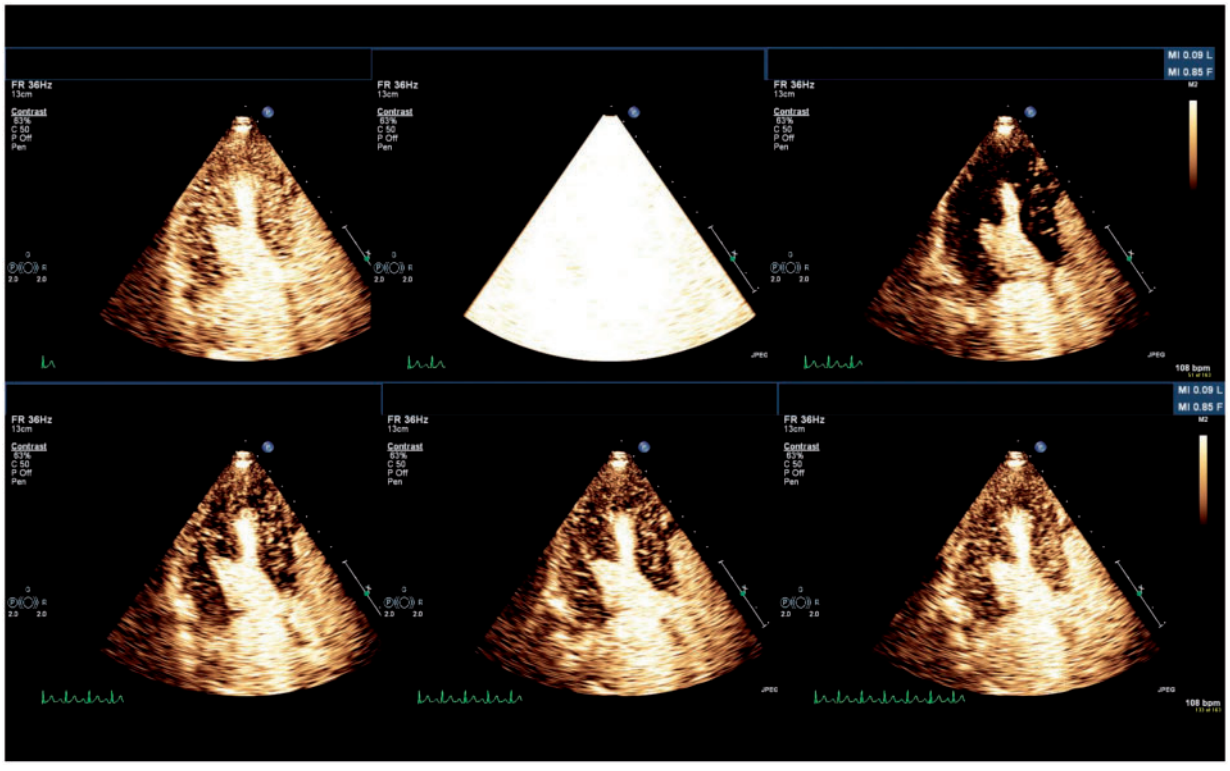

Figure 8 Assessment of myocardial perfusion in the three-chamber view using the flash-replenishment method. Continuous infusion of 1 mL Definity®/min (1.3 mL diluted in 30 mL saline) very low MI contrast-specific imaging (MI for imaging 0.09, for the flash 0.85). Before the flash (top right), the bright LV cavity is well delineated from the myocardium and papillary muscle. During the flash the sector becomes bright (top mid) and in the first cardiac cycle after the flash (top right), the contrast agent in the myocardium has disappeared. The still frames at the bottom are obtained at first (left), second (mid) and fourth (right) cardiac cycle after the microbubbles have been cleared showing progressive replenishment within four cardiac cycles.

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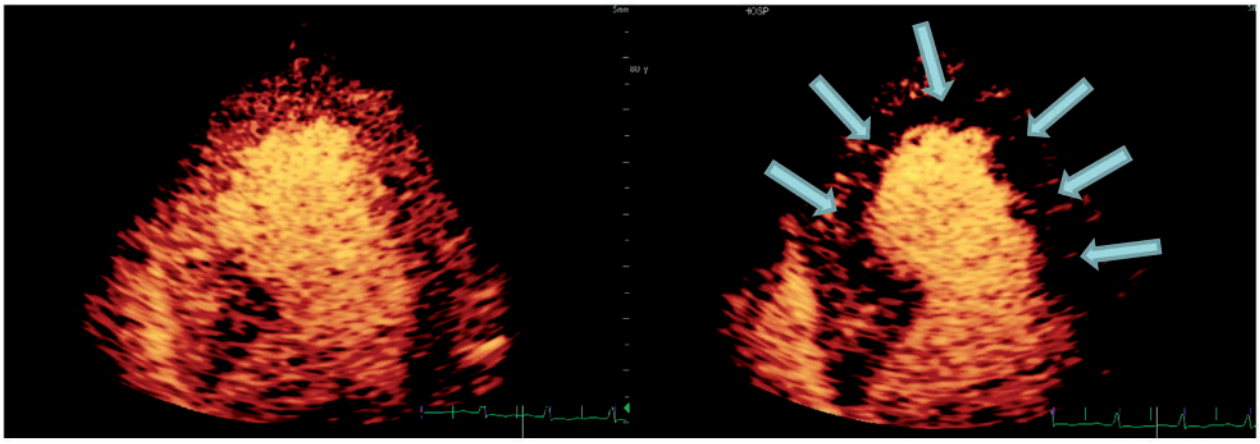

Figure 9 Apical four-chamber view at rest (left) demonstrating normal myocardial perfusion at rest (5 s after myocardial contrast destruction). Right, after stress, four-chamber view displayed 3 s after myocardial contrast destruction. Note sub-endocardial perfusion defect in the septum, apex and transmural defect in the lateral wall. This suggests moderate LAD and severe LCx flow-limiting stenosis, which was confirmed by coronary arteriography.[134]

reduction in MBF.[123] Myocardial perfusion is tissue blood flow at the capillary level. The two components of tissue blood flow are capillary blood volume and red blood cell velocity. As the rheology of microbubbles resemble red blood cell, the product of peak microbubble intensity (relative myocardial blood volume) and their rate of complete replenishment (representative of blood velocity) equals MBF.

Detection and risk stratification of CAD

Following the clearance of microbubbles, in the normal myocardium subtended by normal coronary artery, contrast appears within 5 s (five cardiac cycles if the heart rate is 60 bpm) during replenishment phase at rest; during stress, because MBF increases 4–5-fold normally (normal coronary flow reserve (CFR) is 4–5], replenishment will be achieved by 1–2 s [2–3 cardiac cycles at a heart rate of 120 bpm). A delayed contrast appearance with reduced contrast intensity in the subendocardium due to reduced blood flow velocity and reduced capillary blood volume, respectively, is the hallmark of flow-limiting CAD (*Figure 9*).[122] An updated analysis showed that the sensitivity and specificity of myocardial contrast echocardiography (MCE) for the detection of CAD is 83% and 79%, respectively, for vasodilator MCE (*Table 6*) and for dobutamine/exercise 88% and 77%, respectively (*Table 7*). Single-photon emission computed tomography (SPECT) is the most widely used myocardial perfusion technique for the assessment of CAD. A meta-analysis of eight studies comparing the sensitivity and specificity of MCE with those of SPECT/DSE for the detection of CAD showed that MCE was more sensitive than SPECT for the detection of CAD.[156] In an experimental study, it was shown that microbubble velocity is more sensitive for the detection of stenosis severity than myocardial blood volume, the latter is detected by SPECT, while MCE detects both.[123] The latter property of MCE together with higher spatial resolution may be responsible for the higher sensitivity of MCE compared with SPECT. Subsequently, two large multicentre studies, where all patients underwent coronary angiography, MCE and SPECT and where all imaging modalities were read blindly in sites other than the recruiting sites, showed that MCE demonstrated superior sensitivity to SPECT.[146,153] Both these trials also demonstrated high feasibility of MCE performed in more than 50 centres across Europe and the USA. Specificity of MCE was consistently lower than SPECT. This was also shown in another multicentre study involving CMR vs. SPECT, where CMR showed better sensitivity but specificity was inferior.[157] This was likely because of higher prevalence of microvascular disease in this high-risk population, where all patients underwent coronary arteriography. However, some perfusion defects on MCE may be attributed to artefacts particularly in the apex and the basal segments. These should be recognized and should be corrected by appropriate manoeuvres described in Training/accreditation requirement in contrast echocardiography section of the article.

During demand, SE wall motion assessment remains the cornerstone for the assessment of myocardial ischaemia. MCE, which simultaneously assesses wall motion and perfusion, improves sensitivity of SE by both improving the detection of wall thickening abnormalities and the identification of perfusion defects. Improved assessment in terms of both improved sensitivity and the extent of ischaemia have been corroborated in several independent studies.[126,129,130,147,150,158] A large body of evidence now exist (5679 patients) confirming the improved prognostic value of perfusion when performed simultaneously during SE (*Table 8*). This includes a large (over 2000 patients) randomized study, which showed that perfusion assessment provided improved prognostic information beyond wall motion assessment during SE.[160] A recent study also showed that when MCE was performed routinely during SE in the day-to-day clinical service where MCE was used in decision making provided improved prognostic outcome over wall motion.[159] The incremental prognostic value of MCE in SE was demonstrated in a recent meta-analysis.[172]

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Table 6 Myocardial contrast echocardiography with vasodilator stress in the assessment of coronary artery disease

Patients (*n*)	Stress method (vasodilator)	Patients undergoing coronary angiography	CAD present	Sensitivity	Specificity	Author	Year
123	Adenosine	15	12	75	67	Heinle *et al.*[125]	2000
25	Dipyridamole	12	12	89	100	Rocchi *et al.*[128]	2003
85	Dipyridamole	70	43	91	70	Moir *et al.*[131]	2004
35	Dipyridamole	35	22	85 (qualitative) 97 (quantitative)	79 (qualitative) 82 (quantitative)	Peltier *et al.*[132]	2004
55	Dipyridamole	55	43	86	88	Senior *et al.*[133]	2004
52	Dipyridamole	52	22	82	97	Senior *et al.*[134]	2005
36	Adenosine	36	35	81	67	Winter *et al.*[135]	2004
36	Dipyridamole	16	13	64 (RT imaging) 41 (TR imaging)	92 (RT imaging) 96 (TR imaging)	Tsutsui *et al.*[136]	2005
123	Dipyridamole	123	96	84	56	Jeetley *et al.*[137]	2006
47	Adenosine	47	11	91	92	Karavidas *et al.*[138]	2006
120	Dipyridamole	89	62	83	72	Korosoglou *et al.*[139]	2006
70	Dipyridamole	40	25	84	93	Lin *et al.*[140]	2006
43	Dipyridamole	43	33	77	72	Malm *et al.*[141]	2006
55	Adenosine	50	32	88	89	Aggeli *et al.*[142]	2007
63	Dipyridamole	63	25	92	95	Hayat *et al.*[145]	2008
662	Dipyridamole	457	368	71	64	Senior *et al.*[146]	2009
400	Dipyridamole	116	71	97	74	Gaibazzi *et al.*[147]	2009
48	Adenosine	48	37	89	92	Vogel *et al.*[148]	2009
65	Adenosine	62	41	85	76	Arnold *et al.*[149]	2010
400	Dipyridamole	400	268	96	66	Gaibazzi *et al.*[150]	2010
150	Dipyridamole	150	102	96	69	Gaibazzi *et al.*[151]	2010
100	Regadenoson	98	52	80	74	Porter *et al.*[152]	2011
628	Dipyridamole	512	310	75	52	Senior *et al.*[153]	2013
150	Regadenoson	147	85	77	73	Abdelmoneim *et al.*[155]	2015
Mean (95% CI)	**3571**	**2736**	**1820**	**83 (77–89)**	**79 (72–85)**		

Table 7 Myocardial contrast echocardiography with dobutamine or exercise in the assessment of coronary artery disease

Patients (*n*)	Stress method (dobutamine or exercise)	Patients undergoing coronary angiography	CAD present	Sensitivity	Specificity	Author	Year
45	Dobutamine or exercise	45	32	87	66	Cwaig *et al.*[124]	2000
100	Exercise (treadmill or bike)	44	28	75	100	Shimoni *et al.*[126]	2001
44	Dobutamine	44	44	97	93	Olszowska *et al.*[127]	2003
140	Dobutamine	132	85	81	77	Chiou *et al.*[129]	2004
170	Dobutamine	170	127	91	51	Elhendy *et al.*[130]	2004
5250	Dobutamine	532	413	92	61	Aggeli *et al.*[143]	2008
42	Exercise (bike)	42	25	88	88	Miszalski-Jamka *et al.*[144]	2007
61	Exercise (bike)	61	41	93 (quantitative) 85 (qualitative)	80 (quantitative) 80 (qualitative)	Miszalski-Jamka *et al.*[154]	2013
5852 (total)		1070 (total)	795	Mean(95% CI): 88 (84–91)	Mean(95% CI): 77 (69–85)		

However, it may be added that in most studies MCE was performed in high-risk patients, where beneficial effect of MCE is unequivocally noted. Thus, the benefit of MCE in low-risk patients remains to be shown.

Detection of ACS

The diagnosis of ACS is based on the triad of clinical history, electrocardiography and cardiac markers of myocardial necrosis. The triad could detect only 30% of patients with ACS.[173] In a large multicentre

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Table 8 **Prognostic value of myocardial contrast perfusion SE for the prediction of all events and hard cardiac events (death and non-fatal myocardial infarction) in patients with suspected and/or known coronary artery disease**

Patients (*n*)	Stress method	Contrast agent	Follow-up (months)	Total events (*n*)	Hard events (*n*)	Annual total event rate (%) normal scan	Annual total event rate (%) abnormal Scan	Annual hard event rate (%) normal Scan	Annual hard event rate (%) abnormal Scan	Author	Year
197	Dobutamine and exercise	Sonovue	17 ± 7	35	12	7.76	16.94	2.82	5.64	Shah *et al.*[159]	2015
1024	Dobutamine and exercise	Definity	2.6 years (median)	56	50	1.83	2.82	1.26	3.33	Porter *et al.*[160]	2013
1252	Dipyridamole	Sonovue	25	59	59	0.99	5.90	0.99	5.90	Gaibazzi *et al.*[161]	2012
87	Dipyridamole	Sonovue	50 ± 19	28	28	2.53	11.76	2.53	11.76	Anantharam *et al.*[162]	2011
202	Dipyridamole	Optison	32 ± 11	109	26	3.47	26.35	N/A	N/A	Wejner-Mik *et al.*[163]	2011
545	Dipyridamole	Sonovue	12	25	12	0.86	11.28	0	6.15	Gaibazzi *et al.*[164]	2011
513	Dobutamine	Definity	23	42	42	1.53	14.91	1.53	14.91	Hong *et al.*[165]	2011
261	Dipyridamole	Optison	14 ± 5	22	22	0.98	19.93	0.98	19.93	Dawson *et al.*[166]	2009
84	Exercise	Sonovue	48 ± 8	24	10	1.67	10.19	N/A	N/A	Miszalski-Jamka *et al.*[167]	2009
399	Dobutamine	Optison and Definity	21	46	46	1.85	12.18	1.85	12.18	Tsutsui *et al.*[168]	2008
145	Dipyridamole Dobutamine	Sonovue	8 ± 5	24	4	10.17	88.89	N/A	N/A	Jeetley *et al.*[169]	2007
51	Dipyridamole	Optison and Definity	29	10	2	0	19.70	0	3.94	Basic *et al.*[170]	2006
131	Dobutamine	Optison and Definity	16	25	5	7.79	23.61	N/A	N/A	Tsutsui *et al.*[176]	2005
788	Dobutamine	Optison and Definity	20	75	75	1.50	8.0	1.50	8.0	Tsutsui *et al.*[171]	2005
TOTAL (5679)				580	393	3.02[a]	13.54[a]	1.40[a]	9.12[a]		

[a]Weighted mean percentages.
N/A, not available (not possible to derive total and/or hard event rates from data presented in article or insufficient follow-up period).

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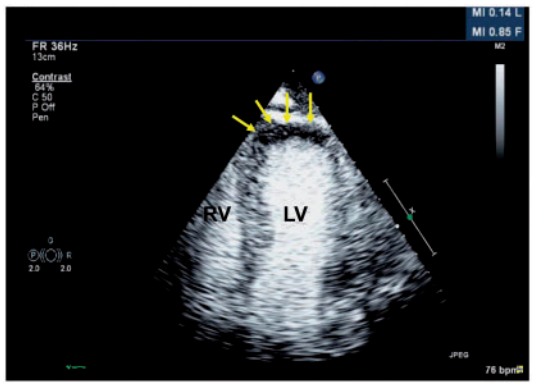

Figure 10 Apical perfusion defect (no reflow) after stenting the proximal LAD because of STEMI. The perfusion defect involves the entire wall thickness (arrows).

study, MCE improved the detection of ACS beyond the triad of clinical, ECG and biochemical markers at presentation and was equivalent to SPECT for the prediction of outcome.[174] However, the advantages of MCE are that it allows both rapid assessment and simultaneous evaluation of wall motion and perfusion at the bedside. Reports also suggest that MCE has higher sensitivity compared with standard echocardiography and SPECT for the detection of ACS.[175,176] In a 1000 patient study, resting perfusion and function with MCE was shown to provide incremental prognostic information beyond clinical, ECG and cardiac biomarker (troponin) parameters in patients with suspected ACS.[177] Normal function and perfusion at rest by MCE demonstrated excellent outcome.[178] In another study, stress MCE with dipyridamole provided strong prognostic information in patients with suspected ACS but normal 12-h troponin and non-diagnostic ECG. A negative stress MCE predicted an excellent prognosis.[169] A larger study involving more than 500 patients in this population confirmed excellent prognosis with no perfusion defect and was superior to wall motion assessment alone.[164]

Detection of myocardial viability

Peak contrast intensity, a measure of capillary blood volume correlates with microvascular density and capillary area, and is inversely related to the collagen content.[194] Animal studies have shown that MCE defect size assessed 10–15 s after contrast administration, corresponded to infarct size.[179,180] This was confirmed in patients following acute MI (AMI).[181] The extent and intensity of contrast defect and the magnitude of resting MBF reduction predicted the transmural extent of myocardial necrosis assessed by late gadolinium CMR imaging (*Figure 10*).[182,183] The ability of MCE to predict functional recovery is comparable to that of cardiac MRI (30 patients).[182] Contractile response during dobutamine infusion depends both on an intact microvascular (important to sustain contractile proteins) and on MBF reserve. Thus, DSE may be less sensitive than techniques that assess microvasculature (MCE) for the detection of hibernating myocardium as MBF reserve may be significantly reduced but the microvasculature may be intact.[184] Therefore, MCE may be particularly useful in the evaluation of myocardial viability in dobutamine non-responsive myocardium.[185] *Table 9* summarizes the accuracy of MCE for the prediction of myocardial viability demonstrating a sensitivity of 85% and a specificity of 70% for the prediction of recovery of function during follow-up. Studies have also shown that among all the clinical, ECG and angiographic parameters of reperfusion after AMI, contrast perfusion is the only independent predictor of reperfusion.[192,197,206] In two studies following AMI, MCE provided incremental prognostic value over clinical and LVEF data for the prediction of hard events[207,208]. In another study, reversed LV remodelling following AMI predicted outcome and myocardial reperfusion assessed by MCE was an independent predictor of reversed LV remodelling.[209] Finally, a recent meta-analysis in a patient population with ischaemic cardiomyopathy, the sensitivity of MCE was similar to that of metabolic markers of hibernating myocardium (*Table 10*).[210] With accumulating evidence of its prognostic value for the detection of myocardial viability over and above clinical markers and LVEF, MCE is evolving as a useful bedside technique for the assessment of myocardial viability.

Table 9 Myocardial contrast echocardiography in the assessment of myocardial viability

Patients (*n*)	Sensitivity	Specificity	Author	Year
23	100	90	Agati *et al.*[186]	1997
34	77	83	Main *et al.*[187]	2001
46	69	85	Main *et al.*[188]	2002
35	94	87	Lepper *et al.*[189]	2002
19	68	88	Swinburn *et al.*[190]	2002
96	62	83	Senior *et al.*[185]	2003
35	80	67	Hillis *et al.*[191]	2003
15	88	74	Greaves *et al.*[192]	2003
50	92	75	Janardhanan *et al.*[193]	2003
18	90	63	Shimoni *et al.*[194]	2003
34	88	61	Aggeli *et al.*[195]	2003
33	86	44	Hillis *et al.*[196]	2003
30	96	18	Bolognese *et al.*[197]	2004
50	95	52	Sbano *et al.*[198]	2005
42	82	83	Janardhanan *et al.*[182]	2005
56	83	78	Hickman *et al.*[199]	2007
34	83	82	Huang *et al.*[200]	2005
31	98	32	Abe *et al.*[201]	2005
32	81	88	Korosoglou *et al.*[202]	2005
26	78	72	Tousek *et al.*[203]	2008
18	95	79	Shentu *et al.*[204]	2008
23	87	67	Hickman *et al.*[184]	2010
24	74	60	Fernandes *et al.*[205]	2011
Total: 804				
Mean	85	70		

Assessment of CFR by MCE

MBF using MCE can be assessed quantitatively.[122] Assessment of MBF during hyperaemia provided an accurate assessment of CFR, which was subsequently replicated by other authors.[211,132] MBF assessed by MCE at rest and during hyperaemia closely correlated with that assessed by positron emission tomography.[212] Further

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Table 10 Comparison of various Imaging techniques for the detection of hibernating myocardium

Technique	No. of studies	No. of patients	Mean EF (%)	Sensitivity (%)	Specificity (%)
Dobutamine echocardiography–total	41	1421	25–48	80	78
Low-dose DbE	33	1121	25–48	79	78
High-dose DbE	8	290	29–38	83	79
Myocardial contrast echocardiography–total	10	268	29–38	87	50
Thallium scintrigraphy–total	40	1119	23–45	87	54
Tl-201 rest-redistribution	28	776	23–45	87	56
Tl-201 re-injection	12	343	31–49	87	50
Technetium scintrigraphy–total	25	721	23–54	83	65
Without nitrates protocol	17	516	23–52	83	57
With nitrates protocol	8	205	35–54	81	69
Positron emission tomography–total	24	756	23–53	92	63
Cardiovascular magnetic resonance–total	14	450	24–53	80	70
Low-dose dobutamine protocol	9	272	24–53	74	82
Late galdolinium-enhancement protocol	5	178	32–52	84	63

studies in various cardiovascular disease conditions showed that CFR assessed by MCE can accurately assess both the presence and the severity of flow-limiting CAD.[132,134,213] This assessment can be performed using both low- and high MI imaging techniques. With high MI, the myocardium is first cleared of microbubbles and subsequent replenishment is assessed in time either using intermittent high MI imaging or by continous low MI imaging (*Figure 11*). Myocardial blood flow is estimated by the product of peak contrast intensity (db) and myocardial flow velocity (db/s) in each of the myocardial segments in the apical views (preferably avoiding the basal segments—see below). The MBF obtained in each segment can then be collapsed into the three vascular territories. The process is repeated during stress myocardial imaging. The ratio of the peak MBF and that of resting MBF indicates CFR. The ratio of peak and resting myocardial blood velocity also provides a robust estimate of CFR.[211].CFR assessed by MCE predicted mortality in patients with heart failure beyond LVEF and CAD.[162] Recently, CFR assessed by MCE was shown to be reduced in patients with hypoglycaemia, which may point towards mechanism of high mortality in such patients.[214]

Assessment of CFR by contrast-enhanced coronary Doppler imaging

In the European Association of Echocardiography SE expert consensus statement of 2008, coronary Doppler imaging has been included as to be added to vasodilator stress protocols. CFR on left anterior descending coronary artery (LAD) territory adds prognostic value when added to conventional wall motion analysis.[215] For measurement of the CFR, the LAD can be visualized using colour Doppler along the anterior interventricular sulcus and the coronary flow can be quantified by pulsed wave (PW) Doppler.[216–218] The ratio of the maximum velocity of diastolic mid-LAD flow during hyperaemia and at rest is measured. Contrast agents have been shown to be useful to enhance the PW Doppler signals of the LAD flow and facilitate PW Doppler recordings of LAD flow.[219] There is no evidence whether the LAD CFR measured by PW Doppler provides incremental information to myocardial perfusion imaging. However, the addition of either CFR–LAD or myocardial perfusion assessment to standard wall motion analysis and clinical parameters improved the prediction of cardiac events.[220]

Limitations of MCE

MCE is the result of interaction between the microbubbles and ultrasound power. Thus, variation in microbubble concentration with each administration may influence the contrast intensity. Lack of uniformity of ultrasound power in the ultrasound field affects the estimation of myocardial blood volume and velocity. Contrast intensity may be reduced at the bases of the heart, because the ultrasound power is weakest in the far field, thereby giving rise to false perfusion defects. Conversely, in the near-field, destruction of contrast may result in false perfusion defects as the ultrasound power is strongest here as it is nearest the transducer. Furthermore, assessing myocardial viability in very thin myocardium may be problematic because of frequent blooming artefacts from the cavity. However, recent advancements in technology and understanding of microbubble and ultrasound interaction and thus recognition of artefacts and techniques to overcome these artefacts has improved interpretation significantly. In a recently concluded multicentre trials involving 50 centres in the USA and Europe, diagnostic images could be obtained in 94–99% of patients. The reproducibility of multiple MCE readers was non-inferior and similar to that of SPECT readers.[146,153]

Recommendations

In SE laboratories with the availability of low MI imaging and expertise of the staff, MCE should be considered in all patients undergoing dobutamine, vasodilator SE and high-risk patients undergoing physiological stress for improved diagnosis and risk stratification of CAD beyond wall motion assessment (Class I, Level A). MCE may also be performed to improve detection of myocardial viability particularly in dobutamine non-responsive segments, where wall thickness is

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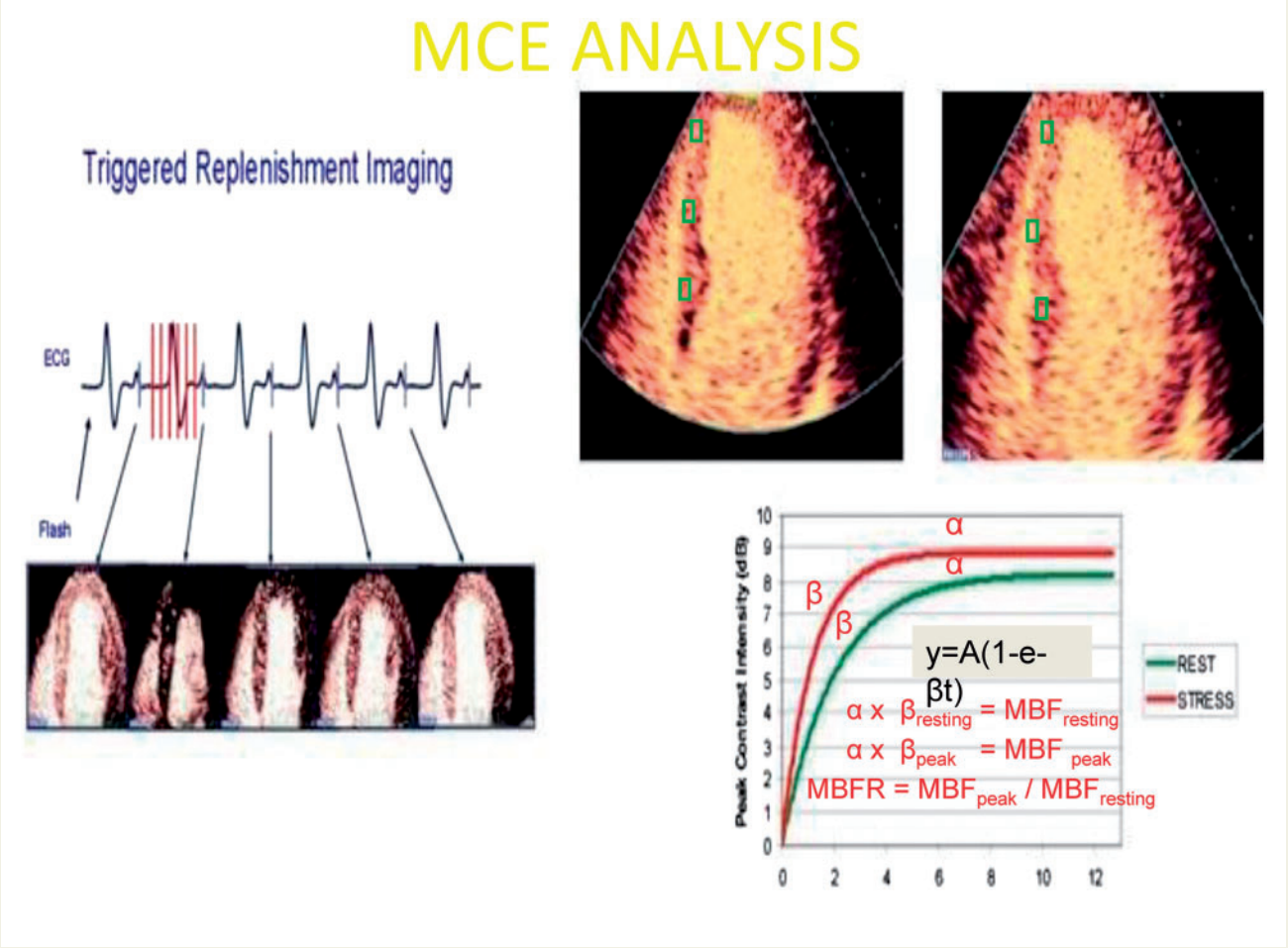

Figure 11 Demonstrating flash-replenishment images describing quantification of myocardial blood flow at rest and during stress and calculation of myocardial blood flow reserve in the septum.

preserved (Class IIa, Level B). The flash-replenishment technique should be used for the assessment of myocardial perfusion (Class I, Level A).

Clinical impact—cost-effectiveness

Kurt *et al.*[30] showed a significant impact of contrast echocardiography on subsequent management of patients with suboptimal echocardiograms: in one-third of patients, diagnostic procedures were avoided and drug management was altered in 10% with cost saving of $122 per patient. In patients assessed for the presence of clots, Siebelink *et al.*[79] reported that oral anticoagulants were started in 68% of the patients with suspected thrombus and unnecessary anticoagulation was avoided in 39%. In technically very difficult patients in the intensive care, echocardiography cost savings of 17% were reported.[41]

Several studies demonstrated cost-effectiveness of using contrast agents for SE: In patients with morbid obesity, non-diagnostic studies were converted to diagnostic images in over 80% of patients with detection of obstructive CAD in approximately 90% of patients with a positive test.[221] An open-label, randomized Phase IV multicentre study evaluated the use of Luminity© for the detection of CAD in 560 patients in whom non-contrast rest echocardiography had given difficult-to-interpret images. Three months after the imaging, 36% of patients with unenhanced imaging had required further diagnostic testing compared with only 17% of those with enhanced images.[105] Stress ECG remains the test of choice in patients who can exercise with no resting ECG changes with no previous history of CAD [American College of Cardiology (ACC)/ American Heart Association (AHA) guidelines and European Society of Cardiology (ESC) guidelines)].[222,223] However, in several studies, SE using contrast agents was significantly better than Ex-ECG for risk-stratifying patients to low-, intermediate- and high-risk groups. Non-diagnostic tests were less frequent, resulting in fewer referrals for other tests compared with stress ECG and these translated to superior cost efficacy of SE compared with Ex-ECG.[224–227] The use of contrast in all patients undergoing SE seems to be not cost-effective, if contrast agents are used for the assessment of LV wall motion only.[108] A recent current opinion paper by some authors of the ESC guidelines for stable angina concluded from the evidence provided as above that SE should be the initial test of choice in patients presenting with suspected stable angina.[228]

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Clinical safety of contrast agents in echocardiography

Over 10 years of use of contrast on millions of patients established the safety of contrast. In a large retrospective analysis of 18 000 patients, of which one-third received contrast agent in the acute setting, there was no significant difference in mortality in patients who received contrast vs. those who did not.[229] This was despite the fact that patients in the contrast group were at increased risk compared with non-contrast group. A subsequent observational study showed that in the contrast group, patients are 24% less likely to die compared with the non-contrast group in over 4 million patients.[230] This is likely because diagnosis of life-threatening conditions is made when contrast is used and action taken. In a latest propensity-matched study of >16 000 patients in each group the study showed: (i) patients undergoing echocardiography with a ultrasound contrast agent had lower mortality at 48 h compared with patients undergoing non–contrast-enhanced echocardiography (1.70% vs. 2.50%), with an odds ratio 0.66, 95% confidence interval (CI) 0.54–0.80; (ii) patients undergoing echocardiography with a contrast agent had lower hospital stay mortality compared with patients undergoing non-contrast echocardiography (14.85% vs. 15.66%), with an odds ratio 0.89, 95% CI 0.84–0.96.[231] A European SE study included patients receiving Optison®, SonoVue® or no contrast and found that the overall incidence of adverse events was not different between the three groups.[232] Another UK study involving 4000 patients showed no difference in acute complication rate in patients who received contrast vs. those who did not during SE, and this is despite the fact that the patients in the contrast group were in the higher risk group.[233]. In a study over 10 000 patients receiving contrast vs. similar numbers not receiving contrast during SE were compared. No difference in serious adverse events were noted between the two groups.[234] Similarly MCE during SE was found to be safe.[143,235] A study in the USA included 523 receiving Optison® and 523 receiving Luminity® during SE and analysed adverse cardiovascular and pulmonary effects.[236]. The incidence of side effects did not differ significantly between the two groups. Safety in patients with pulmonary disease and severe pulmonary hypertension has been demonstrated in several studies.[237–241].These data firmly establish the use of contrast agents in severe pulmonary artery hypertension. Side effects have been noted with contrast agents, but they are usually mild and transient. Serious allergic reactions have been observed, at a very low incidence (estimated to be 1:10 000). *Table 11* lists risk categories observed during usage of competing investigations.[242] Therefore, the evidence shows that contrast echocardiography is very safe in clinical practice. The only absolute contraindications for administration of contrast agents available in the market today, i.e. Sonovue® (Lumason® in USA), Luminity® (Definity® in USA) and Optison® are in patients with known or suspected intracardiac cardiac shunting of significant degree or known hypersensitivity to the agent. The contraindications in the former scenario have been questioned.[243] Meanwhile, the FDA has lifted the contraindication of intracardiac shunts for Definity®. Intracoronary administration is also not approved and is considered contraindicated, although it has been performed without complications in thousands of patients with hypertrophic cardiomyopathy undergoing septal ablation. Adverse events are rare (seen in between 1 in 1000 and 1 in 10 000 patients) and usually mild (headache, nausea, dizziness, taste disturbances, paraesthesia, chest discomfort and reactions at the injection side). They are usually transient and do require any treatment apart from reassuring the patients. Back pain has been reported after injections of Definity and may need treatment with analgesics, this is rare with other other contrast agents. All staff in the echo laboratory should be familiar with the symptoms of anaphylactoid reactions such as skin erythema, urticaria, rash, dyspnoea, throat tightness, flushing and difficulty swallowing) and know where the drugs (allergy box) are located. Allergic reactions have been reported within 30 min. Most of the severe adverse events are probably due to complement activation-related pseudo allergy. However, the treatment is the same as for immunoglobulin E-mediated allergic reactions. Early diagnosis and treatment can positively affect the severity and course of the anaphylactic reaction: IV injection of antihistaminics and steroids and small dosages of epinephrine for symptomatic hypotension can prevent the anaphylactic shock.

Table 11 Incidence of Severe Anaphylaxis by Substance Class as Defined by the International Collaborative Study of Severe Anaphylaxis(adapted from reference 242)

Risk Category	Incidence	Substance Class
Low	0.005% - 0.015%	Analgesics
		Antibiotics
		MRI-Contrast Media
		Echo contrast agents
Medium	0.03% - 0.1%	Penicillin IV
		Blood Dextrane
		Pentoxyphylline
		Iodine-Contrast Media
High	> 0.1%	Plasma
		Streptokinase

Recommendations

Although serious adverse events are very rare, echocardiography laboratories using ultrasound contrast agents should have a policy to deal with adverse events. The echocardiography laboratories performing contrast echocardiography should be equipped with the appropriate drugs to treat severe adverse events. Echocardiographers injecting ultrasound contrast media should be trained to recognize adverse events and to provide the adequate treatment (see Training/accreditation requirements in contrast echocardiography section.)

Training/accreditation requirements in contrast echocardiography

The EACVI has updated the standards and processes for accreditation of echocardiographic laboratories in 2014.[244] Contrast agents have to be available for LVO in SE (basic standard). Contrast-

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specific imaging modalities should be available (see Contrast agents section). According to the ESC Core Curriculum for the General Cardiologist 2013, the trainees should acquire knowledge in contrast echocardiography, but this has not been further specified.[245] Considering the growing use of ultrasound contrast agents and availability of suitable echocardiography scanners, there is a need for following procedures for training. There have been no systematic studies on how many studies using contrast agents have to be performed to provide a reliable service. Taking the experience from other advanced echocardiographic imaging techniques such as TOE, the writing group proposes the following procedures for all physicians undergoing training in transthoracic echocardiography:

(1) Physicians should participate in a course on contrast echocardiography to learn the performance, interpretation, pitfalls and adverse effects in contrast echocardiography.
(2) They should have basic life support (BLS) training.
(3) They should perform and interpret at least 25 contrast echo studies under supervision.
(4) They should maintain competency by performing at least 50 contrast studies per year.

The training of physicians who apply contrast agents in SE aligns to recommendations in the Stress Echocardiography Expert Consensus Statement of the European Association of Echocardiography.[215] It is recommended to perform at least 50 examinations with contrast agent under the supervision of an expert reader in a high-volume laboratory, and ideally with the possibility of angiographic verification, before starting SE on a routine basis. For perfusion, SE the committee recommends 100 examinations supervised in a high-volume centre. For demonstration of maintenance of competence at least 50 stress echo examinations per year should be performed. The trainees should also attend a course on contrast SE.

An important topic for training is to assess the adequacy of image quality of contrast echocardiograms. The trainees should become familiar with the criteria of an adequate contrast echocardiogram as well of pitfalls and artefacts. In principle, the same rules apply for studies that are performed for LVO and those performed to assess myocardial perfusion, which is usually assessed in addition to LV wall motion. In apical views, the focus is usually set at the mitral valve level. The contrast in the LV should be visible in the entire cavity with no or minimal swirling in the near field and no attenuation in the far field (see *Figure 2*).[246] Myocardial opacification is usually less intensive than LVO and should not obscure the delineation of the endocardial border (see *Figure 8*). The basal anterior and lateral myocardial segments may be attenuated specially during myocardial perfusion. A troubleshooting guide for suboptimal images has been developed to optimize contrast images before recording (*Table 12*).

Table 12 Troubleshooting for contrast recordings obtained in apical views: the echocardiographer assesses the opacification in the apical third and basal third of the LV cavity for swirling and attenuation

Problem	To do
• Apical swirling good basal contrast	Reduce MI
• Basal attenuation no apical swirling	Increase MI (contrast infusion) wait longer after bolus injection
• Apical blooming and basal attenuation	Reduce infusion rate of contrast wait longer after bolus injection
• Apical swirling and inhomogeneous contrast in the entire cavity	Increase infusion rate of contrast or higher volume of the bolus

This guide is also useful in MCE. A homogeneous LV opacification of the LV cavity without attenuation or swirling is the prerequisite for adequate display of contrast in the myocardium (modified from Becher and Helfen).[246]

Perspectives/expectations

3D technology plays only a minor role in the current recommendations for contrast echocardiography. However, we expect further hardware and software development in the future that will allow to investigate more patients using 3D technology. Ultrasound agents have been used for quantitative analysis of intraventricular flow dynamics and assessment of LV vortex, which may provide new parameters to assess heart failure patients.[247] New ultrasound contrast agents are being developed for molecular imaging—e.g. to detect expression of myocardial cell membrane receptors in myocardial ischaemia.[248] Recently, therapeutic applications of ultrasound contrast media are being investigated.[249] A recent study demonstrated the ability of diagnostic ultrasound impulses to restore microvascular flow in patients with ST-elevation myocardial infarction.[250] These new diagnostic and therapeutic applications utilize MCE. The latter developments in therapeutics will encourage the manufacturers to further improve the assessment of myocardial perfusion.

Protocols for contrast echocardiography

Check lists can be helpful for quality control in the echocardiography laboratory. *Table 13* shows the steps to perform contrast echocardiography. The protocols in Perspectives/expectations section provide the details of contrast dosages and image settings for the different indications.

The following protocols have been found to be useful in clinical practice. They were selected, because they represent the basic requirements and limit the amount of ultrasound contrast which is given. Laboratories may use modifications including additional steps or recordings in particular for the protocols in SE based on local experience and preferences.

Rest 2D echocardiography

LV volumes and EF, regional wall motion

Use intermediate MI or low MI contrast imaging mode (see *Table 2*) if both modalities are available first choice should be low MI technique; use the presets of the manufacturers, which work in most patients (*Figure 2*).

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Table 13 Checklist for contrast echocardiography

(1)	Check indication
(2)	Assess patient for contraindications of contrast agents
(3)	Inform patients about the risk/benefit and obtain consent
(4)	Insert IV (right arm preferable) or check available IV access – central lines may be used – in SE both the contrast agent and pharmacologic stress agent (eg dobutamine or adenosine) can be administered via a three-way tap through the same IV
(5)	Prepare contrast agent – follow instructions of the manufacturer for preparation – avoid negative pressure when transferring the contrast agent from the vial into the syringe
(6)	Check whether the adequate contrast setting is active on the echocardiography scanner (see Contrast imaging modalities section), this depends on the indication
(7)	Slow bolus injection (see Contrast administration section) infusion should be considered for SE
(8)	Check whether images are adequate if necessary optimize images before recording (see Table 12)
(9)	Ask and observe the patient for possible adverse events
(10)	Document the indication for contrast use and the total contrast dosage which was administered in the echo report

– bolus injection of *0.5 mL* SonoVue®/*0.2–0.3 mL* Optison®, *0.1 mL* Luminity® or SonoVue® infusion 0.7–1.2 mL/min;
– acquire apical four- and two-chamber views;
– start acquisition not before 20 s after contrast injection;
– adjust MI/gain/focus to ensure good endocardial definition in all segments;
– inject additional contrast or increase infusion rate, if insufficient contrast and
– use biplane Simpson method as for non-contrast echocardiography.

3D echocardiography (limited experience) (*Figure 3*):

- same procedure but usually higher dosage of contrast needed;
- infusion of the contrast agent facilitates adjustment of machine settings;
- the semi-automated analysis software for LV analysis cannot be used and
- use biplane Simpson method on reconstructed, unforshortened views.

Myocardial perfusion

Myocardial perfusion needs low MI contrast imaging mode (see *Table 2*), use the presets of the manufacturers:

– infusion of the contrast agent recommended, SonoVue® 0.7–1.5 mL/min, Luminity® 1.3 mL vial diluted in 30 mL saline, start with 1 mL/min;
– acquire flash-replenishment sequences (15 cardiac cycles) of the apical 4-, 2- and 3-chamber views with the flash delivered after the second cardiac cycle (*Figure 8*)

The cardiac cycles following the flash show very good endocardial definition and can be used to measure LV volumes and ejection fraction (see rest 2D echocardiography).

Doppler echocardiography

Doppler echocardiography use same PW- or continuous-wave Doppler settings as for non-contrast studies:

– no extra contrast injection needed, when performed after recordings for assessment of LV volumes and EF (section 8.1.1), the small amounts of contrast agent still present during washout after image acquisition for LV volumes or perfusion are enough
– reduce emission power (MI) until Doppler spectrum shows regular grey levels

TOE for assessment of LAA

Use harmonic imaging or contrast-specific modality, which are available in some TOE scanners, reduce MI to <0.3, reduce penetration depth and/or use Zoom mode.

– same dosages as for TTE (rest 2D echocardiography);
– can take >30 s to opacify the LAA;
– record in at least 2 imaging planes and
– flash replenishment sometimes helpful to assess flow into LAA.

For all SE methods, low MI contrast imaging modalities are recommended (*Table 2*). Usually, the presets provided by the manufacturers are applicable in most patients.

Exercise SE

Supine bicycle

Rest	– contrast bolus injection or infusion like in rest 2D echocardiography (see LV volumes and EF, regional wall motion); – acquire apical four, two and three chamber and parasternal short axis views; – start acquisition not before 20 s after contrast injection and – when infusion is used, pause infusion after image acquisition.
25 Watts	– bolus injection or infusion (same dosage as at rest); – acquire apical four, two and three chamber and parasternal short axis views and – when infusion is used, pause infusion after image acquisition.

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Peak stress	– bolus injection or infusion (same dosage as at rest); – acquire apical four, two and three chamber and parasternal short axis views and – when infusion is used, continue infusion until recovery.
Recovery	– bolus injection or continue infusion (same dosage as at rest) and – acquire apical four, two and three chamber and parasternal short axis views.

Optional: Assessment of myocardial perfusion in addition to LV wall motion, see Myocardial perfusion section

The flash-replenishment sequences can be performed at rest and in the early recovery period (should complete by 90 s after cessation of exercise), when the patient can hold the breath. The stress echo protocols on most ultrasound scanners allow acquisition of the flash-replenishment sequences in addition to the standard loops for assessment of wall motion by pausing the regular stress protocol (*Figure 12*).

Treadmill

Rest	– patient on the imaging bed; – bolus injection of contrast or infusion like in rest 2D echocardiography (LV volumes and EF, regional wall motion section); – acquire apical four, two and three chamber* and parasternal short axis views and – then patient is moved to the treadmill.
Stress	– repeat bolus injection or restart infusion when patient is exercising at; – maximum effort or usual criteria for termination of exercise; – move the patient to the imaging bed; – start acquisition immediately as soon as possible and acquire same views and as during rest.

*For additional perfusion imaging (optional), see Myocardial perfusion and Supine bicycle sections

Dobutamine stress echocardiography

Assessment of myocardial ischaemia

Rest	– contrast bolus injection or infusion like in rest 2D echocardiography (LV volumes and EF, regional wall motion section) – acquire apical four, three and two chamber and parasternal short-axis views; – start acquisition not before 20 seconds after contrast injection and – when infusion is used, pause infusion after image acquisition.
10 μg/kg/min	– bolus injection or infusion (same dosage as at rest); – acquire apical four, two and three chamber and parasternal short-axis views and – when infusion is used, pause infusion after image acquisition.
Peak stress	– bolus injection or infusion (same dosage as at rest); – acquire apical four, two and three chamber and parasternal short-axis views and – when infusion is used, continue infusion until recovery.
Recovery	– bolus injection or continue infusion (same dosage as at rest) and – acquire apical four, two and three chamber and parasternal short-axis views.

For assessment of myocardial perfusion in addition to LV wall motion, see Myocardial perfusion section.

The flash-replenishment sequences can be performed in addition or instead of to the single beat recordings performed in the early recovery period in most stress imaging protocols. The stress echo protocols on most ultrasound scanners allow acquisition of the flash-replenishment sequences in addition to the standard loops for assessment of wall motion by pausing the regular stress protocol (*Figure 13*).

Assessment of myocardial viability

Rest	– contrast bolus injection or infusion like in rest 2D echocardiography (LV volumes and EF, regional wall motion section); – acquire apical four, two and three chamber and parasternal short-axis views; – start acquisition not before 20 s after contrast injection and – when infusion is used, pause infusion after image acquisition.
5 μg/kg/min	– bolus injection or infusion (same dosage as at rest); – acquire apical four, two and three chamber and parasternal short-axis views and – when infusion is used, pause infusion after image acquisition.
10 μg/kg/min	– bolus injection or infusion (same dosage as at rest); – acquire apical four, two and three chamber and parasternal short-axis views and – when infusion is used, pause infusion after image acquisition.
20 μg/kg/min	– bolus injection or infusion (same dosage as at rest); – acquire apical four, two and three chamber and parasternal short-axis views; – when infusion is used, pause infusion after image acquisition.

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For assessment of myocardial perfusion in addition to LV wall motion, see Assessment of myocardial ischaemia section.

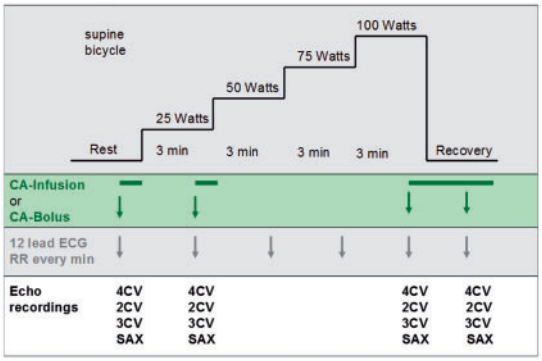

Figure 12 Protocol for supine bicycle stress and using contrast agent (CA) infusion or injections. In this example, the patient was able to exercise at 100 W. The load is increased by 25 W every 3 min. Cessation of exercise according to the EAE consensus for stress echocardiography.[217] In this example, the patient exercised at maximum effort at 100 W. Additional images may also be acquired at intermediate stress (70% of target heart rate). 4CV,four-chamber view; 2CV, two-chamber view; 3CV, three- chamber view (parasternal long axis view can be used instead); SAX, parasternal short axis view.

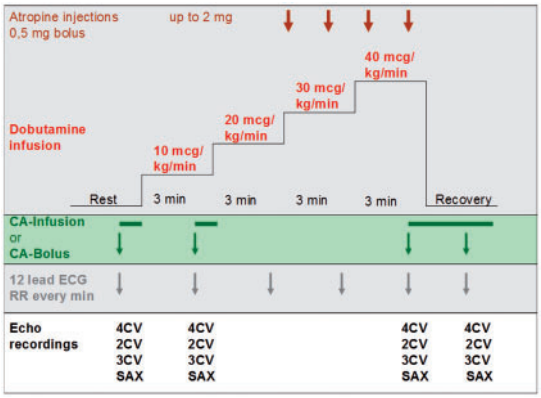

Figure 13 Protocol for dobutamine stress/assessment of ischaemia and using contrast agent (CA) infusion or injections. In this example, the dobutamine infusion had to be increased up to 40 µg/kg/min and atropine was injected to reach target heart rate. To minimize the time of the examination, atropine can be started already at the 30 µg/kg/min stage when the heart rate has not increased by at least 20% from baseline. Cessation of exercise according to the EAE consensus for stress echocardiography.[217] For abbreviations, see *Figure 10*. Additional recordings may also be acquired at intermediate stress (70% of target heart rate).

Homogeneous myocardial contrast enhancement at rest suggests viability. However, demonstrating contractile reserve and/or biphasic response with dobutamine stress are further supporting findings for viability (*Figure 14*).

Vasodilator SE using contrast agents

Dipyridamole SE—high dose

rest	- Contrast bolus injection or infusion like in rest 2D echocardiography (LV volumes and EF, regional wall motion) - Acquire apical four, two and three chamber and parasternal short-axis views - Start acquisition not before 20 s after contrast injection - When infusion is used, pause infusion after image acquisition
0.84 mg/kg Dipyridamole infusion in 6 min	
3 minutes after start of Dipyridamole infusion	- Acquire apical four, two and three chamber and parasternal short-axis views - Start acquisition not before 20 s after contrast injection - When infusion is used, pause infusion after image acquisition
6 minutes after start of Dipyridamole infusion	- Contrast bolus injection or infusion (same dosages as at rest) - Acquire apical four, two and three chamber and parasternal short-axis views - When infusion is used, pause infusion after image acquisition
10 minutes after start of Dipyridamole infusion	- Contrast bolus injection or infusion (same dosages as at rest) - Acquire apical four, two and three chamber and parasternal short-axis views - Aminophylline 120-240 mg IV

Measurement of LAD flow using PW Doppler at rest and during dipyridamole infusion (6 min) is recommended (*Figure 15A*).

For assessment of myocardial perfusion in addition to LV wall motion, see Myocardial perfusion section.

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Dipyridamole SE—low dose

Rest	– infusion of contrast (SonoVue 0.7–1.2 mL/min) recommended; – acquire apical four, two and three chambers as flash-replenishment sequences; start acquisition not before 20 s after contrast injection and – pause infusion after image acquisition.
Over 4 min Dipyridamole infusion 0.56 mg/kg	
2 min after the end of Dipyridamole infusion	– start infusion of contrast agent (same dosage as at rest) and – acquire apical four, two and three chambers as flash-replenishment sequences (*Figure 15B*).

Adenosine SE

Rest	- Infusion of contrast agent recommended (see section Myocardial perfusion) - Acquire apical four, two and three chamber views - Start acquisition not before 20 s after contrast injection - Record LAD flow using PW-Doppler (RCA, LCX if possible)
Adenosine infusion 140µg/kg/min) for maximum 6 minutes	
1 minute after start of Adenosine infusion	- Record LAD flow using PW-Doppler (RCA, LCX if possible)* - Adjust adenosine infusion if needed** - Acquire apical four, two and three chamber views as flash-replenishment sequences (see figure 16)
Recovery	- Acquire apical four, two and three chamber views as flash-replenishment sequences

*The contrast infusion may be paused, when systems with sensitive coronary Doppler are used.

**Increase adenosine dosage by 20 µg/kg/min (up to 220 µg/kg/min) when the patients show no signs of an adenosine effect such as flushing, change in heart rate, increase in LAD velocity and angina or worsening LV wall motion (*Figure 16*).

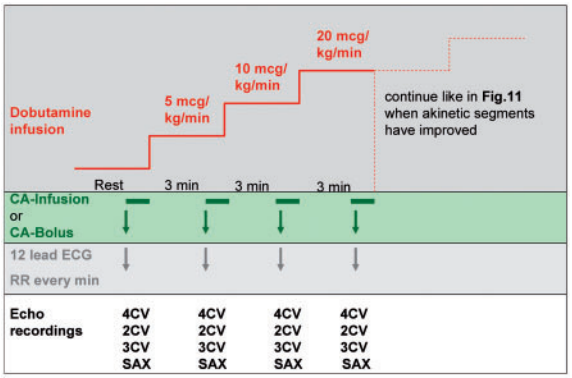

Figure 14 Protocol for low-dose dobutamine stress/assessment of viability and using contrast agent (CA) infusion or injections. For abbreviations, see *Figure 10*. When there is no improvement in contractility in the akinetic segments up to 20 µg/kg/min, the test can be terminated. High-dose dobutamine infusion may be added to demonstrate a biphasic response (see dobutamine protocol for assessment of myocardial ischaemia, *Figure 10*) in those patients who show improvement in contractility of akinetic segments or when there is a suspicion of ischaemia in other segments with preserved contractility at rest. Perfusion assessment in dobutamine non-responsive segments improves sensitivity for the detection of myocardial viability.

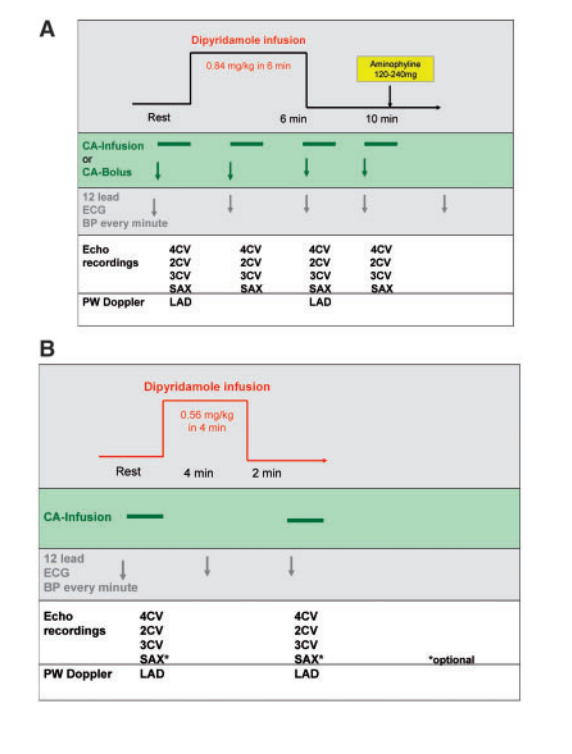

Figure 15 Protocol of state-of-the-art high-dose dypyridamole SE suggested by the EAE[215]. In addition to 2D echocardiographic recordings measurement of the blood flow in the LAD is recommended at rest and at the end of the dipyridamole infusion. (*B*) Protocol for low-dose dypyridamole SE, which is suitable assessment of myocardial perfusion.

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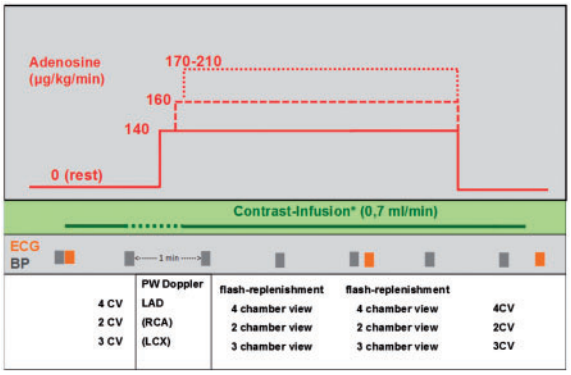

Figure 16 Protocol of adenosine SE; for abbreviations see *Figure 10*. Acquisition of flash-replenishment sequences are recommended for the assessment of myocardial perfusion. Coronary flow measurement in the LAD and if possible in other coronary arteries using PW Doppler are recommended at rest and 1 min after start of the adenosine infusion.

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