

# Indian Academy of Echocardiography Guidelines and Manual for Performance of Stress Echocardiography in Coronary Artery Disease

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## Abstract

Stress echocardiography is one of the most useful non-invasive diagnostic modalities for detection and evaluation of coronary artery disease (CAD). It is also very useful for assessment of cardiac response to hemodynamic stress in a variety of other cardiac and non-cardiac disorders. Given its cost-effectiveness, stress echocardiography is particularly suited for Indian scenario where the incidence of CAD is rising at an alarming rate and the astronomical expenditure required for its management is borne largely by the patients themselves. However, despite its unequivocal diagnostic value, stress echocardiography remains underutilized, particularly in India, due to the lack of adequate exposure and training in this modality. Unfortunately, while there is extensive literature available to document diagnostic accuracy of stress echocardiography, there are very few texts that actually describe how to perform stress echocardiography in real life. This Indian Academy of Echocardiography guideline document aims to fill this very void. This is a comprehensive 'how to do' document prepared with the objective of providing detailed description of the steps involved in performance and interpretation of stress echocardiography so that there is increased adoption of this important and clinically useful diagnostic modality in daily clinical practice. However, while stress echocardiography has several clinical applications, the present document is restricted to its main application, which is evaluation of CAD.

**Keywords:** Treadmill stress test, dobutamine echocardiography, myocardial viability

## INTRODUCTION

Stress echocardiography is a combination of real-time echocardiographic imaging with conventional electrocardiographic stress testing. Stress echocardiography is arguably the most cost-effective test, as compared to nuclear imaging or coronary angiography, for diagnosis, prognosis, and therapeutic decision-making in coronary artery disease (CAD).<sup>[1,2]</sup> Due to its cost-effectiveness, it is best suited for Indian scenario where the incidence of CAD is rising at an alarming rate, and the astronomical expenditure required for its management is borne largely by the patients themselves due to poor insurance and social security cover.

Stress echocardiography uses either exercise or pharmacological stressors depending on the patient profile and the clinical

situations. Harmonic imaging and ultrasound contrast use in stress echocardiography have improved the sensitivity, specificity, accuracy, and prognostic power of the test. Newer modalities such as tissue Doppler and two-dimensional (2D) strain analysis can be creatively and strategically integrated with stress echocardiography to potentially help further enhance its diagnostic accuracy. In terms of the diagnostic and prognostic performance and the outcome data, stress echocardiography is comparable to other functional imaging

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modalities, and in fact, has some unique advantages over them, as discussed subsequently.

## SCOPE OF THE DOCUMENT

The predominant reason why stress echocardiography is so underutilized in India is the lack of adequate exposure and training in this modality. While there is extensive literature available to document diagnostic accuracy of stress echocardiography, there are very few texts that actually describe how to perform stress echocardiography in real life. This Indian Academy of Echocardiography (IAE) guideline document aims to fill this very void. This is a comprehensive “how to do” document prepared with the objective of providing detailed description of the steps involved in assessing the performance of stress echocardiography so that there is an increased adoption of this important and clinically useful echocardiographic modality. However, while stress echocardiography has several applications beyond just evaluation of CAD, the present document is restricted to its application in CAD, using the two most commonly used stressors, namely, exercise and dobutamine.

## INDICATIONS FOR STRESS ECHOCARDIOGRAPHY AND APPROPRIATE USAGE CRITERIA

### Clinical indications for performing stress echocardiography

There are broadly three settings in which a referral for stress echocardiography is considered.<sup>[3,4]</sup>

- Patients without known CAD who present with symptoms suggestive of myocardial ischemia,
- Patients with known stable CAD who present with new onset of symptoms or change in symptom pattern or in whom functional significance of a coronary lesions needs to be determined for prognostic or therapeutic purpose, or
- Patients requiring assessment of myocardial viability.

The objective of stress echocardiography in these settings is to ascertain whether the symptoms are due to the presence or progression of CAD, to determine the extent of CAD, to assess the likelihood of functional recovery following revascularization, and to permit prognostic risk stratification to guide the treatment. Thus, common indications for stress echocardiography can be summarized as follows:

1. Positive stress electrocardiogram (ECG) test in a patient with low pretest probability and stress ECG data showing low or intermediate Duke score
2. Patients not known to have CAD but require cardiac stress test and have intermediate pretest probability for CAD
3. Resting ECG showing nonspecific ST/T changes, left bundle branch-block (LBBB), left ventricular hypertrophy (LVH) with strain pattern, preexcitation, baseline ST-segment depression >1 mm in patients postrevascularization, or those on digoxin
4. Troponin-negative acute chest pain or asymptomatic rise in troponin
5. High coronary calcium score by computed tomography (CT)

6. Assessment of myocardial viability and reversible ischemia in patients with previous myocardial infarction (MI) who received lytic therapy but coronary angiography was not performed
7. CT or catheter coronary angiography showing coronary stenosis of borderline severity
8. Previous percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery with new onset of symptoms (i.e., suspected stent restenosis, graft occlusion, or progression of native coronary disease)
9. Inability to exercise due to any reason (e.g., respiratory, orthopedic, neurological impairments or obesity and deconditioning)
10. Risk stratification before noncardiac surgery
11. Evaluation of dyspnea on exertion
12. Evaluation of change in symptomatic status of patients with chronic stable CAD
13. Assessment of myocardial viability in chronic stable CAD.

### Appropriate uses of stress echocardiography

Routine use of stress imaging to detect CAD in asymptomatic patients is inappropriate and leads to unnecessary downstream invasive procedures without improving the outcomes.<sup>[5]</sup> Appropriate use criteria (AUC) have been developed for various diagnostic tests that are derived from systematic voting and discussion by a panel of experts about the value of that test in a wide range of clinical scenarios. Table 1 summarizes the clinical situations in which the choice of stress echocardiography over stress ECG is considered appropriate in ambulatory patients. Similarly, Table 2 summarizes the clinical scenarios in which the performance of stress echocardiography, in general, is considered highly appropriate<sup>[5]</sup> (as per the expert panel defining AUC) for diagnostic or prognostic purpose or for guiding therapeutic decisions.

### Estimating pretest probability of coronary artery disease

In patients without known CAD referred for stress echocardiography, it is advisable to estimate pretest probability

**Table 1: Clinical situations in which the choice of stress echocardiography over stress electrocardiogram is considered appropriate in ambulatory patients**

- Intermediate-to-high pretest probability of CAD
- Uninterpretable baseline ECG (ST-segment depression, preexcitation, LBBB). However, in patients with atrial fibrillation or paced rhythm, vasodilatory myocardial perfusion imaging is indicated instead of stress echocardiography
- Presence of LV RWMA at rest
- Patients with established CAD with
  - Coronary stenosis of uncertain significance
  - Previous PCI or CABG, now presenting with anginal symptoms, and stress echocardiography is being performed to identify the “culprit” lesion
  - Post incomplete re-vascularization
  - When simultaneous assessment of myocardial viability is required

CABG: Coronary artery bypass graft, CAD: Coronary artery disease, ECG: Electrocardiogram, LBBB: Left bundle branch block, LV: Left ventricular, PCI: Percutaneous coronary intervention, RWMA: Regional wall motion abnormality

**Table 2: Clinical scenarios in which the performance of stress echocardiography is considered highly appropriate for diagnostic or prognostic purpose or for guiding therapeutic decisions**

- Initial evaluation for diagnosis and prognosis in a patient without known CAD presenting with symptoms suggestive of angina or angina equivalent
- Asymptomatic patients with high global CAD risk score (e.g., those with LV systolic dysfunction, arrhythmia, syncope, etc.)
- Suspected symptoms of acute coronary syndrome with negative or equivocal troponin and low-risk "thrombolysis in myocardial infarction" score
- Positive results of other noninvasive tests (asymptomatic raised troponin; obstructive disease on CT coronary angiography; CT calcium score >400; positive stress ECG with intermediate-to-high duke score; or borderline, equivocal results of nuclear stress imaging)
- Established CAD for initial evaluation and prognosis assessment to guide optimal medical treatment or revascularization to improve survival
- When there is a change in the clinical status of a patient with established CAD (except new-onset heart failure or previous left main coronary angioplasty), for re-evaluation for symptom validation, prognostication, and for guiding management (re-vascularization to improve survival or symptoms despite optimal medical treatment)
- Presentation with STEMI or non-STEMI when coronary angiography is not performed at the time of index event and there is no post-MI angina or heart failure

CAD: Coronary artery disease, CT: Computed tomography, ECG: Electrocardiogram, MI: Myocardial infarction, STEMI: ST-elevation myocardial infarction, LV: Left ventricular

of CAD. There are various methods for estimation of pretest probability of CAD based on age, gender, type of symptoms, concomitant cardiovascular risk factors, history of MI, ECG changes, etc.<sup>[5-8]</sup> A practical approach is described below:<sup>[6]</sup>

- Low pretest probability (0%–25%):
  - No chest pain: All women and men with <3 risk factors, men with >3 risk factors if <50 years old
  - Atypical chest pain: Women <60 years old, men <40 years old.
- Intermediate pretest probability (26%–69%):
  - No chest pain: Men with >3 risk factors if >50 years old
  - Atypical chest pain: Women >60 years old, men >40 years old
  - Typical angina: Women <50 years old, men <30 years old
- High pretest probability (>70%):
  - Typical angina: Women >50 years old, men >30 years old.

### Contraindications to stress echocardiography

All standard contraindications to a cardiac stress test are applicable to stress echocardiography also. Thus, the following would constitute contraindications to stress echocardiography:

#### Absolute contraindications

- Acute MI (within 2 days)
- High-risk unstable angina
- Uncontrolled cardiac arrhythmia with hemodynamic compromise

- Active endocarditis
- Symptomatic severe aortic stenosis
- Decompensated heart failure
- Acute pulmonary embolism or pulmonary infarction
- Acute myocarditis or pericarditis
- Physical disability precluding safe and adequate testing.

#### Relative contraindications

- Known left main coronary artery stenosis
- Tachyarrhythmias with uncontrolled ventricular rates
- Acquired complete heart block
- Hypertrophic cardiomyopathy with a significant left ventricular (LV) outflow gradient at rest
- Mental impairment with limited ability to cooperate.

In addition, stress echocardiography would also be contraindicated in patients with poor acoustic window that precludes satisfactory LV endocardial visualization, despite contrast use or when contrast is not available.

## FUNDAMENTAL PRINCIPLES OF STRESS ECHOCARDIOGRAPHY

### Pathophysiology of stress-induced myocardial ischemia

Stress echocardiography relies on the recognition of regional wall motion abnormality (RWMA) induced by regional mismatch between myocardial oxygen demand and myocardial blood flow (MBF) due to either epicardial coronary stenosis or microvasculature dysfunction. Stressors such as exercise or dobutamine-atropine infusion increase myocardial oxygen demand by increasing myocardial contractility and heart rate, with or without increase in afterload. In contrast, vasodilators such as dipyridamole or adenosine induce myocardial ischemia by causing coronary steal.

During exercise or catecholamine infusion, coronary blood flow increases by 3–5 folds as a result of dilatation of epicardial coronary arteries (conductance vessels) and intramyocardial arterioles (resistance vessels) as well as opening of (i.e. recruitment of) a more number of intramural capillaries. However, in the perfusion bed of epicardial coronary artery with significant stenosis, there is already maximal dilatation of downstream arterioles and de-recruitment of capillaries at rest to maintain resting MBF. As a result, there is virtually no coronary flow reserve (CFR) remaining to augment blood flow during stress, leading to reduced capillary blood volume, perfusion defects, and metabolic abnormalities.

### Principles of functional imaging of myocardial ischemia

Nuclear imaging, gadolinium-contrast magnetic resonance imaging (MRI), and myocardial contrast perfusion imaging detect regional perfusion and/or metabolic defects. These abnormalities appear early in the course of myocardial ischemia. When ischemia is sufficiently prolonged, the affected myocardial region develops diastolic dysfunction followed by systolic dysfunction. The ischemic myocardial dysfunction initially affects subendocardial layers and then becomes transmural.<sup>[9-11]</sup> Stress echocardiography detects ischemia at



this stage qualitatively by visual assessment of regional wall systolic thickening and endocardial excursion manifesting as RWMA. Postsystolic thickening is the earliest wall motion abnormality (WMA) in response to ischemia. It is followed by reduced thickening and finally no thickening, akinesia, or even systolic thinning, depending on the transmurality of ischemia.

RWMAs disappear fast after cessation of stress. Therefore, to maintain optimal diagnostic sensitivity, rapid and efficient echocardiographic image acquisition is required within a window period of 60–90 s after cessation of exercise. However, ischemia-induced myocardial diastolic stunning as detected by strain imaging (postsystolic shortening or failure of relaxation in early diastole) may last for as long as 15–30 min following stress, making it possible to detect ischemia even when there has been some delay in image acquisition.

## SETTING UP A STRESS ECHOCARDIOGRAPHY LABORATORY

The stress echocardiography laboratory consists of stress ECG console interfaced with a treadmill and/or bicycle ergometer and a high-end echocardiography system loaded with software applications for stress echocardiography, tissue Doppler and 2D strain imaging, and contrast LV opacification (LVO) with or without perfusion imaging. A commercially available or customized imaging bed with a semicircular mattress and bed cut out at the patient's chest position should be available to facilitate acquisition of diagnostic quality images. The commercially available supine bicycle comes with the echocardiography imaging bed.

There should be a provision for two syringe infusion pumps for pharmacological stress and a permanently stationed resuscitation trolley equipped with defibrillator, Ambu bag, laryngoscopes, tracheal tubes, and all emergency medications. The medications should necessarily include adrenaline, atropine, sublingual nitroglycerine, metoprolol, hydrocortisone, aminophylline, dextrose, and saline. The echocardiography laboratory should have piped oxygen supply, piped suction connection, pulse oximeter, a nebulizer, and a bronchodilator inhaler. A kidney tray should also be available, in case vomiting occurs. A weight-based dobutamine infusion rate chart should be prepared and kept in the stress echocardiography room for easy reference.

The layout of the stress echocardiography laboratory should be such that there is a good proximity between treadmill and imaging bed so that the patient can have easy exit from the treadmill and an unhindered rapid access to the imaging bed [Figure 1]. This should be achieved without disconnection or entanglement of the ECG cables from both the echocardiography machine and the treadmill console. In addition, the physician performing scanning should have a clear view of the ECG console. The emergency trolley should have unobstructed movement to the treadmill or the imaging bed. Unnecessary personnel or equipment should not clutter the space for the patient's and the escorting technician's



**Figure 1:** Suggested layout of a stress echocardiography laboratory. (a) Exercise stress echocardiography; note the proximity of treadmill to echocardiographic examination bed for exercise echocardiography. (b) Dobutamine stress echocardiography

movement. The height of the imaging bed should preferably be kept low so that the patient can quickly lie down.

Due to paucity of space in most of the hospitals, a single stress echocardiography room can be used for both exercise and pharmacological stress tests with few quick rearrangements. The syringe infusion pump and the treadmill ECG console (for simultaneously monitoring 12-lead ECG) can be rearranged closer to imaging bed when performing pharmacological stress test.

There should preferably be a provision for a recovery area when prolonged observation is needed poststress. In addition, an emergency response protocol should be in place to shift a patient to intensive care unit in the event of an emergency.

## Training of stress echocardiography laboratory personnel

Minimum personnel required in the stress echocardiography laboratory include one physician (who does scanning also), one stress test technician, and one nursing staff. We do not recommend sonographers to perform the test independently without physical presence of the physician in the echocardiography laboratory. The physician should be at least IAE level II echocardiography certified, experienced in handling cardiac emergencies, and should have had advanced cardiac life support training. Before the physician starts performing stress echocardiography independently, he/she should first observe fifty stress echocardiograms, then perform at least fifty exercise stress and fifty dobutamine stress echocardiography (DSE) studies under the supervision



of an expert and should additionally read 100 stress echocardiography studies with the expert. In a high-volume stress echocardiography laboratory, this can be accomplished within 3–4 weeks. Thereafter, the competency should be maintained by performing at least 100 stress echocardiography studies per year. The technician and the nursing staff should be trained and instructed by the physician. It is extremely beneficial if they can undertake observership for a week in one of the high-volume echocardiography laboratories which is regularly performing stress echocardiography and LV contrast opacification studies.

## PERFORMANCE OF STRESS ECHOCARDIOGRAPHY

A thorough 2D and Doppler echocardiography study conforming to the IAE guidelines for transthoracic echocardiography<sup>[12]</sup> should be performed, if not done earlier, before undertaking the stress study.

Stress echocardiography uses two types of stressors - exercise or pharmacological.<sup>[13]</sup> The actual process involved in the performance of stress echocardiography differs according to the stress modality.

### Performance of exercise stress echocardiography

Exercise is the preferred stress modality, as it is physiological, allows symptoms correlation, and permits assessment of functional capacity. Exercise can be performed in different ways as follows:

- Treadmill exercise: The exercise protocol is similar to that of conventional stress ECG. Bruce protocol is used most commonly. In patients with limited functional capacity, modified Bruce protocol may be used. When using treadmill exercise, postpeak stress imaging for RWMA assessment should be completed within 90 s of cessation of exercise. Some experts have shown improved sensitivity for ischemia detection by performing imaging at peak stress while the patient is still on treadmill.<sup>[14]</sup> However, it is technically challenging.
- Supine bicycle ergometry: It has the advantage of allowing simultaneous echocardiographic imaging while the patient is performing exercise. As a result, not only peak exercise imaging is possible, but imaging can also be performed at every stage during exercise which helps in recognizing the onset of ischemia.<sup>[13,15]</sup> Breathholding and control of body position are also easier compared to treadmill exercise. However, the overall workload achieved on supine bicycle is lower than that achieved on treadmill.<sup>[16]</sup>
- Handgrip, leg raising, squatting: Handgrip and leg raising are often combined with pharmacological stressors but not used as the sole stress modality. Squatting has been used as the primary stress modality in the past but has now been given up due to technical challenges.

### Patient preparation

A written informed consent should be obtained from every patient prior to performing stress echocardiography. A template

for consent form is included at the end of this document [Appendix 1a].

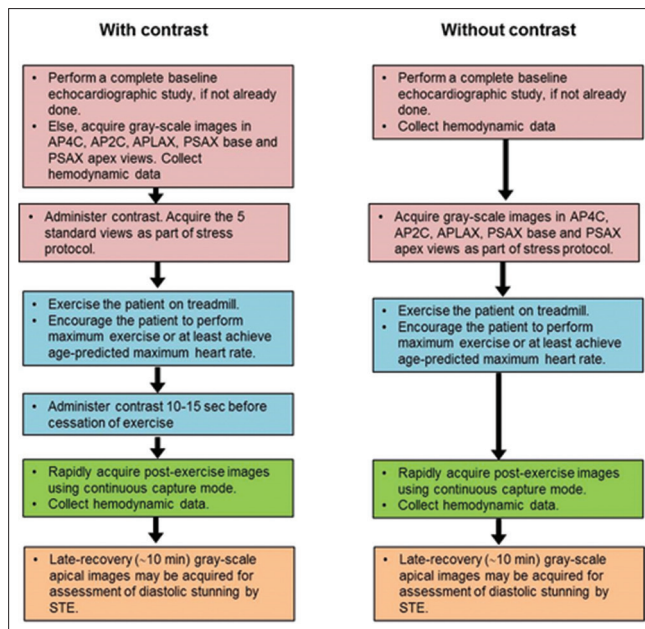
Patients scheduled for stress echocardiography usually have prior appointment and should receive detailed instructions from the laboratory staff about medications, need for fasting, etc. When the test is being performed for diagnosing CAD in a patient not previously known to have CAD, it is advisable to withhold antianginals and heart rate-controlling medications for 3–4 half-lives (usually omitting only on the day of the test is sufficient) and resume them few hours after the test is completed. However, these medications should not be discontinued when the objective of the stress test is to detect the severity of inducible ischemia despite optimal medications. Fasting for 3–4 h is required prior to stress testing (particularly with dobutamine as dobutamine-induced nausea and vomiting occur frequently). The echocardiographer should go through all relevant medical records and ascertain the clinical query to be answered by the planned stress test. He/she should also look for anemia, hypokalemia, significant back pain or leg pain, or any other factor that could interfere with the performance of stress echocardiography. Following this, the patient's vital parameters, height and weight, should be recorded. If the patient has high blood pressure, ongoing angina, and/or dynamic changes in ECG, it may be advisable to postpone or even cancel the test.

Chest shaving and skin preparation should be meticulously done to get pristine ECG signals at peak stress for acquiring ECG-gated peak stress images. Electrodes are connected in the same manner as for conventional stress ECG, except for chest leads V2 and V5. These leads can interfere in acquiring parasternal and apical echocardiographic images, respectively. Therefore, these leads may have to be shifted one space below or the sticker part of the V2 and V5 electrodes may be cut out to create extra space for imaging. Additional three electrodes need to be secured for connecting the ECG cable of the echocardiography machine. If contrast is going to be used, an intravenous (IV) cannula needs to be placed, preferably in the left forearm.

After explaining the procedure to the patient, it is advisable to do a mock trial with the patient. The patient can practice a fast and swift exit from the treadmill to the imaging bed and lying down immediately in the left lateral decubitus position with the chest positioned over the cutout portion of the bed. The technician should help with the attached ECG cables during patient movement to avoid entanglement or lead detachment. Such mock practice trials greatly help in minimizing time delay between the cessation of exercise and initiation of image acquisition.

### Imaging during exercise stress echocardiography

The imaging protocol depends on the capabilities and the customizability offered by the echocardiography equipment and whether contrast will be used or not [Figure 2]. A proper stress echocardiography application with facility for continuous ECG-gated capture at peak stress is the minimum requirement. In addition, ideally, the echocardiography machine should also



**Figure 2:** Imaging protocols for exercise stress echocardiography, with or without using ultrasound contrast for left ventricular opacification. AP2C - apical two chamber; AP4C - apical four chamber; APLAX - apical long axis; PSAX - parasternal short axis; STE - speckle tracking echocardiography

have the option for customizing the imaging protocol and the technical capabilities for contrast LVO, color tissue Doppler imaging (TDI), and 2D strain imaging.

Resting imaging is done with the patient lying in the left lateral decubitus position with ECG cables of treadmill and echocardiography machine connected. Stress echocardiography application on the machine should be turned on. The adequacy of access to apical and parasternal echocardiography windows should be checked; if inadequate, some of the ECG electrodes may need to be repositioned. The patient should be asked to take deep breaths so that the echocardiographer gets an idea of the translational motion of the heart during tachypnea at peak exercise and can plan strategy for imaging at peak stress. If contrast is not going to be used, a fresh set of five standard views of the left ventricle, namely, apical 4-chamber (AP4C), apical 2-chamber (AP2C), apical long axis (APLAX), parasternal short axis (PSAX) at base, and PSAX at apex should be acquired and stored as part of the protocol. The 2D images must be optimized using the appropriate transducer frequency, gain, and focus. Harmonic imaging is mandatory. In stress echocardiography, the focus of imaging is entirely on the left and right ventricles. Apical views should be acquired in such a way that the atria (but not the annuli) are predominantly excluded from the image (by adjusting depth) and sector width optimized so that both the endo- and epi-cardial borders of the left and right ventricle are seen. These adjustments facilitate tissue Doppler and 2D strain analysis. Care should be taken to ensure that these baseline settings are not changed after this stage and that the images at each subsequent stage of acquisition are similar to baseline images.

If contrast is to be used, the above noncontrast images are needed only if 2D strain analysis is planned later on for detection of diastolic stunning which would require baseline and delayed poststress images (described later in Myocardial Strain Imaging Section). In such case, the baseline noncontrast images are acquired outside the stress protocol. Following this, the IV contrast bolus (usually 0.3–0.5 ml of reconstituted Sonovue®) is administered with a 5–10 ml saline flush till the contrast appears in the right ventricle. Image acquisition is commenced when optimum LVO is achieved. The contrast-enhanced images in the afore-mentioned five standard views are acquired and stored in the stress echocardiography protocol.

Finally, hemodynamic data (LV filling pressures, mitral regurgitation, tricuspid regurgitation, right ventricular [RV] function, etc.) should also be collected, if not already done so. This should be done prior to administration of contrast.

The patient is then exercised on treadmill using Bruce or modified Bruce protocol with stage-wise record of ECG and blood pressure. All patients are encouraged to perform maximum exercise, even if they have already achieved age-predicted maximum heart rate (MPHR, 220-age in years). However, in patients with reduced exercise capacity, effort should be made to at least achieve the target heart rate, but without compromising the patient safety. The patients should be instructed to communicate their desire to stop the test at least 10–15 s in advance so that IV contrast can be administered while they are still on the treadmill [Figure 2]. As mentioned above, on-treadmill echocardiographic imaging can be performed to detect the onset of RWMA and to improve the diagnostic sensitivity of the test. Although it is feasible in most patients, it is technically challenging. Once the patient has finished exercise, the treadmill should be stopped at peak stress using the emergency button and the patient is rapidly escorted to imaging bed. The postpeak exercise imaging should be started within 10 s of cessation of exercise and the echocardiographer should aim at finishing the first set of all views by 45 s mark. In case of borderline ischemia at peak stress, the rapid adoption of supine position by the patient for imaging increases venous return and preload, thereby favorably accentuating ischemia and its imaging manifestation. Some researchers have administered IV 0.6 mg atropine at peak stress to avoid rapid drop in the heart rate during postexercise imaging. However, we do not recommend this strategy.

Completing posttreadmill exercise imaging in a time window of roughly 60 s in a hyperventilating patient requires training, practice, and mastering imaging skills. The patient should be lying in steep left lateral decubitus position. The cutout in the imaging bed helps the echocardiographer to access far lateral echocardiographic window beyond the anterior axillary line. The transducer position should be rapidly adjusted to get true long-axis images of AP4C, AP2C, and APLAX from this apical window. This is followed by quick acquisition of the PSAX images at base and apex. The first set of these five images should be acquired within 45 s of cessation of exercise.

This is followed by a second round of apical and parasternal imaging which should be finished by 90 s time point after cessation of exercise. The continuous capture mode in the stress echocardiography application stores ECG-gated images continuously for approximately 120 s. These images can be reviewed at the end of the test to choose the best diagnostic quality peak exercise images of AP4C, AP2C, APLAX, and PSAX base and PSAX apex views. The immediate postexercise imaging for RWMA should be followed by acquisition of the same hemodynamic data as at baseline. Another set of gray-scale images of the five primary views may also be recorded late into recovery (10–15 min) for 2D strain analysis for assessing diastolic stunning.

In case of bicycle ergometry, workload is increased in step-wise manner and images are obtained at multiple stages. Typically, baseline, prepeak (75% of MPHR), peak and recovery images are acquired as minimum. The views and rest of the imaging principles are same as for treadmill exercise echocardiography.

### **End points for exercise stress echocardiography**

The indications for terminating stress echocardiography are similar to those for stress ECG test. The test can be terminated on reaching MPHR and patient's perception of extreme effort as semiquantitatively assessed by the Borg scale or rise in systolic blood pressure >220 mmHg. In case of bicycle ergometer stress echocardiography or treadmill stress echocardiography with "on treadmill" imaging protocol, continuous echocardiography imaging surveillance allows detection of onset of ischemia. In these situations, appreciation of unambiguous RWMA in two or more segments or LV/RV dilatation should prompt termination of the test. Stress test should also be terminated prematurely if the patient reports significant angina, giddiness, or severe breathlessness disproportionate to the level of exertion or if the ECG shows asymptomatic horizontal or down-sloping ST depression >3 mm or ST elevation >1 mm in a noninfarct lead without an abnormal Q-wave. A fall in systolic blood pressure, signs of decreased peripheral perfusion, nonsustained ventricular tachycardia, or multi-focal ventricular premature beats are some of the other indications for immediate termination of exercise and close monitoring during the immediate postexercise period. Patients showing severe ischemia in the form of symptoms, ST-segment changes on ECG, or extensive RWMA should be very briefly imaged at peak stress in the supine position and then should be instructed to immediately sit upright at the edge of the bed to reduce venous return and preload of the heart to relieve angina and any pulmonary congestion.

### **Postprocedural observation**

A 30-min waiting period, usually in the echocardiography laboratory waiting room, is mandatory if either IV contrast or a pharmacological agent was used or if the test showed extensive ischemia. When the stress test is positive, it is a good practice to stop ECG monitoring only after the wall motion is normalized and the ST-segment depressions have returned back to baseline. An ECG performed 30 min after completion

of the study should preferably be recorded in case of a strongly positive stress test.

### **Performance of pharmacological stress echocardiography**

Pharmacologic stress testing is required for patients who are unable to exercise or when assessment of myocardial viability is the main objective of the study. It has the advantage that, unlike treadmill exercise, continuous and good quality imaging can be done throughout the test and at peak heart rate without motion or breathing artifacts. This permits assessment of myocardial viability and recognition of onset of myocardial ischemia. However, the peak workload (double product) achieved during DSE is generally lower than treadmill stress.<sup>[17]</sup>

Pharmacologic stress testing is performed using either dobutamine or a vasodilator such as dipyridamole or adenosine. IV atropine boluses are used with dobutamine infusion to increase the sensitivity of the pharmacological stress testing.<sup>[18-21]</sup>

- **Dobutamine:** It is a relatively inexpensive, easily available, and easy to use drug with a good safety profile. Dobutamine is administered IV as a continuous infusion, starting at a dose of 5 mcg/kg/min and is increased every 3 min to 10, 20, 30, and 40 mcg/kg/min.<sup>[13]</sup> Atropine boluses of 0.3–0.6 mg with a maximum dose of 1.8–2.0 mg are often required to achieve target heart rate, especially in patients on beta-blockers.<sup>[19]</sup> IV metoprolol (2–10 mg) is usually administered at the end of the test to rapidly reverse tachycardia and dobutamine side effects. It also unmasks subtle RWMA and improves the sensitivity of DSE, especially in patients with single-vessel disease.<sup>[22]</sup>
- **Adenosine or dipyridamole:** These agents are potent epicardial coronary vasodilators. They produce ischemia by causing coronary steal from the vascular beds supplied by the stenosed coronary arteries.<sup>[23]</sup> Dipyridamole is administered IV at a dose of 0.84 mg/kg over 10 min and the vasodilatory effect persists for approximately 30 min. Adenosine is an ultra-short-acting agent and requires continuous IV infusion at a rate of 140 mcg/kg/min for 3–5 min. Most patients complain of flushing, dyspnea, and chest discomfort. Other less common side effects are sinus bradycardia, atrioventricular block, or bronchospasm. These side effects usually subside within few seconds of stopping the infusion, but IV aminophylline may be needed to reverse the bronchospasm.
- **Ergonovine:** It is used to provoke coronary vasospasm in patients with suspected vasospastic angina.

Pacing stress echocardiography is an option in patients with an implanted permanent pacemaker. In such patients, the heart rate is increased progressively in a step-wise manner using the external programmer. It is often combined with dobutamine infusion to simultaneously increase myocardial contractility and therefore, the myocardial workload.

### **Patient preparation**

The preparation for DSE is similar to that for exercise echocardiography with some differences. Fasting for 3–4 h prior to the test must be ensured to minimize the chances of

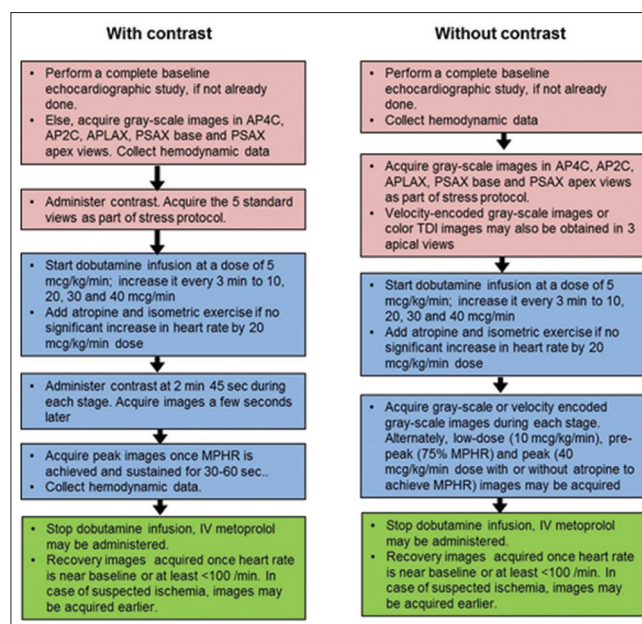


dobutamine-induced nausea and vomiting. Some laboratories also prefer to administer IV ondansetron before DSE. The patients should be asked to empty urinary bladder before the test is started.

Unlike exercise echocardiography, an IV cannula is must for DSE. If imaging is performed with echocardiographer on the right side of the patient, the IV line should be secured in the left arm of the patient, both for the patient's comfort and for the ease of contrast administration. The IV line site should be easily visible to detect bleeding, leakage, or swelling at local site or if it gets accidentally disconnected. A three-way stopcock with 5–10 cm extension with an additional 200 cm extension line is suggested. Patency of line should be checked before starting the infusion. Blood pressure cuff should be placed on the other arm. The dobutamine infusion is prepared by dissolving 250 mg of dobutamine in 50 ml of normal saline and is administered using an infusion pump. The infusion rates corresponding to 5, 10, 20, 30, and 40 mcg/kg/min dose should be calculated beforehand by taking into account patient's weight. As mentioned above, a weight-based dobutamine infusion rate chart should be prepared and kept in the stress echocardiography room for easy reference. IV metoprolol, IV atropine, and IV saline flush syringes should always be kept ready, and similar to any other form of stress echocardiography, the laboratory must also have permanently stationed defibrillator and resuscitation trolley. It should be remembered that patients receiving medications such as angiotensin-converting enzyme inhibitors, angiotensinogen receptor blockers, diuretics, or nitrates are more likely to have prolonged hypotension during or immediately after DSE.

### Imaging during pharmacological stress echocardiography

The imaging at rest is same as for exercise echocardiography. Five primary views with or without contrast are recorded in the customized pharmacological stress protocol. The baseline image settings including depth and sector width must not be changed thereafter. Dobutamine infusion is started at a dose of 5 mcg/kg/min and is increased every 3 min to 10, 20, 30, and 40 mcg/kg/min [Figure 3]. Twelve-lead ECG is monitored continuously using the treadmill console. The ECG print outs are taken at rest, at every intermediate stage, at peak dose, during early and late recovery, and in case of any arrhythmia. Blood pressure and symptoms are also monitored. The same set of five images, ideally in the same orientation as baseline, should preferably be acquired during each stage. Alternately, images can be obtained at low dose (10 mcg/kg/min), prepeak (~75% MPHR), peak dose (40 mcg/kg/min with or without atropine to achieve MPHR), and during recovery. As each stage lasts for 3 min, it is a good practice to start recording the set of five images of the corresponding stage at 2 min 45 s time point in the stage. If contrast is planned, a small bolus (0.2–0.3 ml) of the prepared contrast solution with saline flush is administered just before acquisition of the images during each stage. Pharmacological stress echocardiography has the advantage that, at each stage, the corresponding baseline image is available for comparison and the image



**Figure 3:** Imaging protocols for dobutamine stress echocardiography, with or without using ultrasound contrast for left ventricular opacification. AP2C - apical two chamber; AP4C - apical four chamber; APLAX - apical long axis; IV - intravenous; MPHR - maximum predicted heart rate; PSAX - parasternal short axis; TDI - tissue Doppler imaging

can be optimized to resemble the baseline image as much as possible prior to acquisition. This is essential to ensure accurate interpretation of segmental wall motion changes.

For peak stress imaging, MPHR should be maintained for at least 30–60 s without compromising the patient's safety. To augment the heart rate and blood pressure rise, the patient can be asked to perform repeated right handgrip exercise, by squeezing on a rubber ball, or to perform active leg raising against resistance. As mentioned above, atropine is commonly used to achieve desired heart rate during dobutamine echocardiography. Two different strategies are used for this purpose. In the first strategy, after reaching dobutamine dose of 40 mcg/kg/min, small aliquots (0.3 mg) of IV atropine followed by saline flush are administered every 1 min till the heart rate reaches the target. In the second strategy, which is usually preferred, small aliquots (0.3–0.6 mg) of atropine are given at the end of each stage starting from dobutamine 20 mcg/kg/min dose itself.

At higher dosages of dobutamine, some patients complain of throbbing headache, palpitations, generalized anxiety or distress, nausea, and urge to pass urine. Chest pain (due to dobutamine-induced forceful cardiac contraction), hypotension, and arrhythmias such as ventricular ectopics and nonsustained ventricular tachycardia may also occur. Stopping dobutamine infusion and administering IV metoprolol are sufficient to reverse all these side effects. Serious side effects such as ventricular fibrillation and MI are very rare (<1 in 2000 patients) and no death has ever been reported during DSE.<sup>[24]</sup>

### End points for pharmacological stress echocardiography

The indications for terminating the pharmacological stress test are similar to those described for exercise stress test. Some patients with LVH and/or hypovolemia may develop hypotension due to LV intracavity dynamic obstruction or due to peripheral vasodilation caused by dobutamine. This can be countered by handgrip, passive leg raising, and stopping dobutamine infusion. IV fluid administration may be needed if hypotension persists. After reaching any of the end points, the test is terminated and IV metoprolol may be administered to bring back the heart rate to baseline. It should be noted that, for the same degree of ischemia, the ST-segment depression and angina are much less frequent with dobutamine as compared to exercise stress. Accordingly, ST-segment depression during DSE has low sensitivity for detection of inducible ischemia. The primary role of ECG during DSE is to detect arrhythmias or ST-segment elevation.

### Postprocedural observation

It is advisable to have the patients rest for ½ h in the echocardiography laboratory recovery or waiting room after completion of the test. The IV cannula should be removed only after 30 min, when the patient is already mobilized (bedside), is asymptomatic, and all vital parameters are stable. This ensures that an IV access for administration of medicines is available in case of any late emergency. In some patients who have concentric LVH, neurocardiogenic syncope may occur as they assume upright position immediately after the test. Having the patient lie supine again is generally sufficient to treat it, but IV fluid administration may sometimes be required. An ECG should be repeated at 30 min in all patients with strongly positive test. The patients should also be warned about the persistence of atropine effect on visual accommodation for those who want to read and about the chances of urinary retention in elderly patients.

### Interpretation of stress echocardiography

Qualitative visual assessment of regional wall thickening and motion at rest, during stress, and following stress is the basic method for interpretation of stress echocardiograms. This needs good quality image acquisition, systematic approach for reading, and considerable operator experience. Digital quad screen format for side-by-side display of images is strongly recommended.<sup>[25]</sup> Routine use of harmonic imaging,<sup>[26]</sup> more frequent use of contrast, and use of strain imaging in special circumstances may help in reducing nondiagnostic studies, improving confidence of reporting, and reducing inter-reader variability.

The interpretation of stress echocardiogram should begin with evaluation of the technical adequacy of the test [Table 3]. Digital images should be checked to ensure adequate image quality, appropriate triggering, and comparability of views at each stage. After confirming technical adequacy of the images, an assessment should be made of LV size and shape following stress as they often provide useful clues to the presence or absence of ischemia. In normal stress response, end-systolic

**Table 3: Important steps for comprehensive interpretation of stress echocardiography**

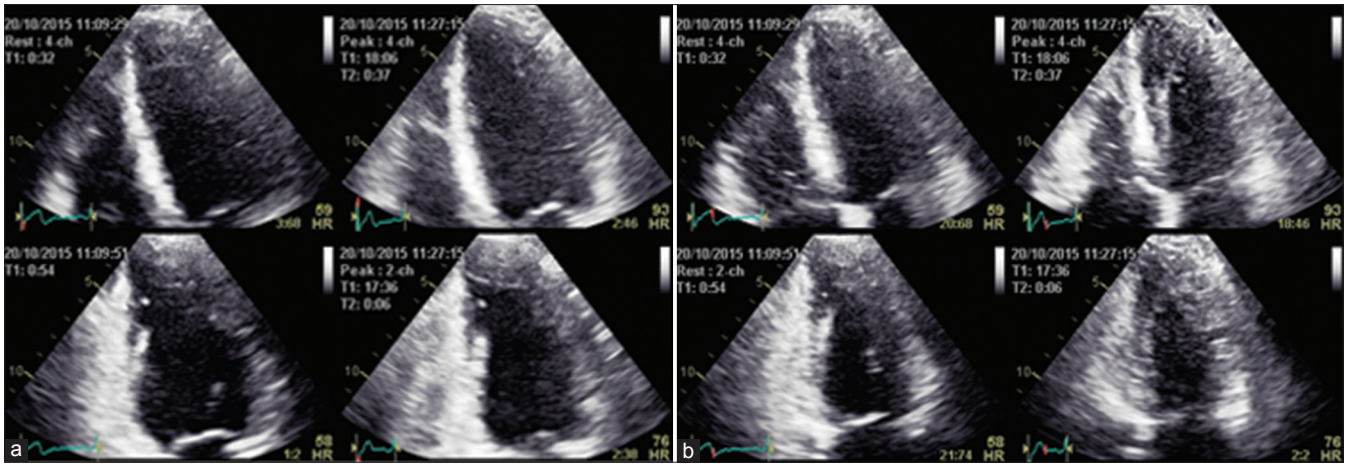
- First, evaluate the technical adequacy of the images
- Perform global function assessment - look for any changes in LV size and shape following stress
- Perform segmental wall motion analysis
- Focus on wall thickening rather than wall motion
- Reviewing only the systole instead of complete cardiac cycle improves the ability to recognize RWMA
- Assess endocardial excursion “take off” in the first half of systole (freeze the image and scroll through early systole frame by frame)
- When looking for ischemic response during DSE, it is best to compare peak dose images with low-dose images instead of rest images
- It is also important to carefully review recovery images. The presence of even subtle impairment of contractility during recovery in comparison to baseline should be considered as an evidence of ischemia at peak dose
- Try to correlate distribution of inducible RWMA with coronary vascular distribution; however, atypical patterns may occur, especially in patients with previous coronary bypass surgery
- Isolated RWMA involving basal inferior wall or basal inferoseptum are likely to be false positive if the adjacent segments supplied by the same vascular territory show normal function
- After completing segmental wall motion analysis, review hemodynamic data obtained at peak stress
- Also, correlate with stress-induced electrocardiographic changes to avoid missing any subtle RWMA which may have gone unnoticed during initial review of images

DSE: Dobutamine stress echocardiography, LV: Left ventricular, RWMA: Regional wall motion abnormalities

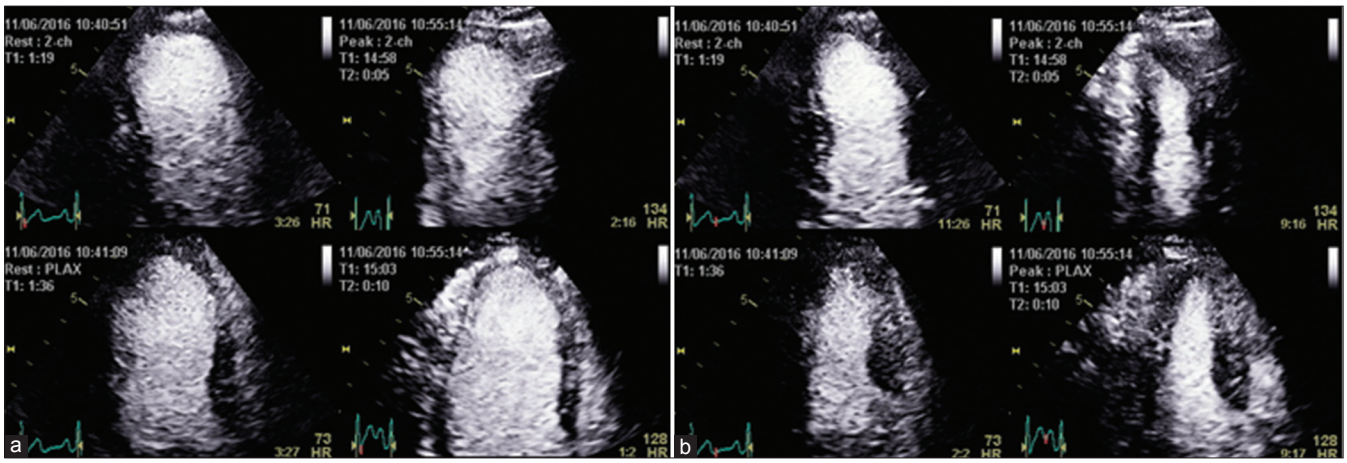
LV cavity at peak stress is small and looks like a narrow base triangle [Figures 4a, b, 5a, b, 6a, b and Videos 1a, b, 2, 3a-e]. Focal RWMA may cause outward bulging resulting in distortion of LV end-systolic cavity shape at peak stress [Figures 7a, b, 8a, b and Videos 4a, b, 5]. A more extensive RWMA will result in dilatation of LV cavity, manifesting initially as failure to reduce end-systolic volume and eventually as actual increase in end-systolic cavity size [Figures 9a, b and Videos 6a-c, 7, 8a, b]. Thus, regional LV shape change should always alert the interpreter to the possibility of CAD whereas an increase in LV size with stress, in the absence of concomitant valvular or myocardial disease, is usually indicative of multivessel ischemia.<sup>[27]</sup> These LV cavity shape changes, particularly global LV dilatation, are more common with exercise echocardiography as reduction in afterload with dobutamine often masks these changes.<sup>[27]</sup>

After the global evaluation of the images, segmental wall motion analysis is undertaken [Table 4]. In case of exercise stress, dual screen format is used for side-by-side display of ECG-synchronized rest and peak stress images of each view. In case of dobutamine echocardiography, a quad screen format is used for simultaneous comparison of rest, low-dose, peak-dose, and recovery images. For segmental wall motion analysis, the 16-segment model (not including apical cap) for LV myocardial segmentation is used, as recommended by the American Society of Echocardiography.<sup>[28]</sup> Wall motion of each myocardial segment at rest is carefully analyzed and compared with peak stress “one segment” at a time. For each segment,





**Figure 4:** An example of normal stress echocardiogram without using ultrasound contrast. (a) End-diastolic frame. (b) End-systolic frame. Upper images show apical 4-chamber view and the lower images show 2-chamber view. Rest images are on the left side and the immediate postexercise images are on the right side. There is no left ventricular dilatation or wall motion abnormality in the postexercise images



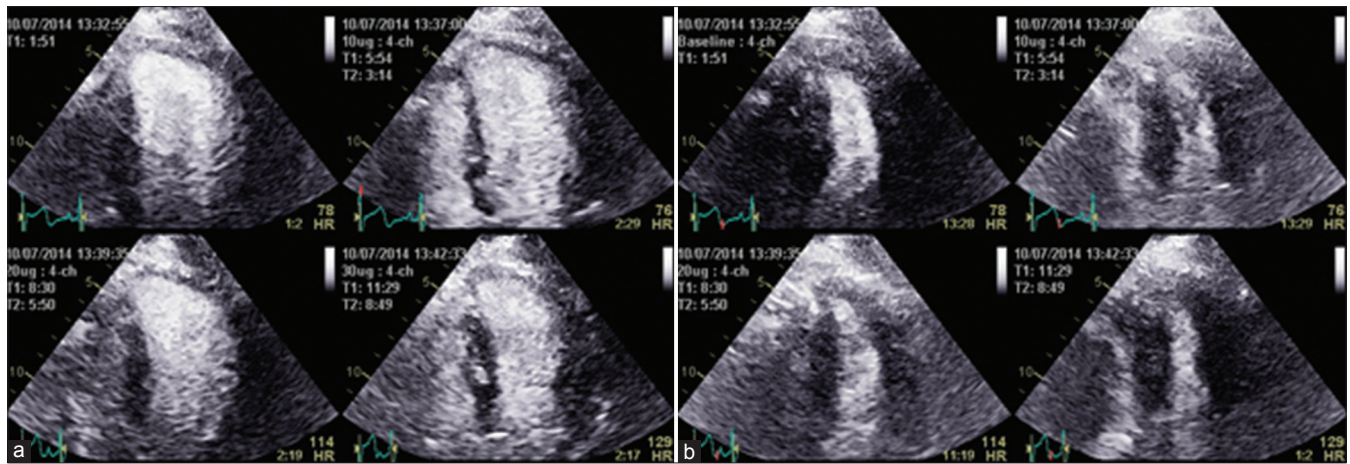
**Figure 5:** Contrast-enhanced images from a normal stress echocardiogram. (a) End-diastolic frame. (b) End-systolic frame. Upper images show apical 2-chamber view and the lower images show apical long-axis view. Rest images are on the left side and the immediate postexercise images are on the right side. There is no left ventricular dilatation or wall motion abnormality in the postexercise images

Table 4: Interpretation of regional wall motion changes during stress echocardiography			
Resting function	Low dose	Peak stress/immediate poststress	Interpretation
Normal	Normal	Hyperkinetic	Normal response
Normal	Normal	Tardokinesis (delayed contraction)	Ischemia
		Worse than rest	
		Worse than adjacent segments	
Normal	Worse	Even worse	Severe ischemia
Rest WMA	Improvement at low dose	Worsening (compared with low dose)	Biphasic response; suggests viability with ischemia (i.e., hibernation)
Rest WMA	Improvement at low dose	Sustained improvement	Uniphasic response; suggests viability without ischemia (stunning, remodeled segment, myopathic segment, or subendocardial infarct)
Rest WMA	Worse	Even worse	Severe ischemia
Rest WMA	No change	Improved contraction	Tethering effect or subendocardial infarct
Rest WMA	No change	No change	Nonviable, scar tissue

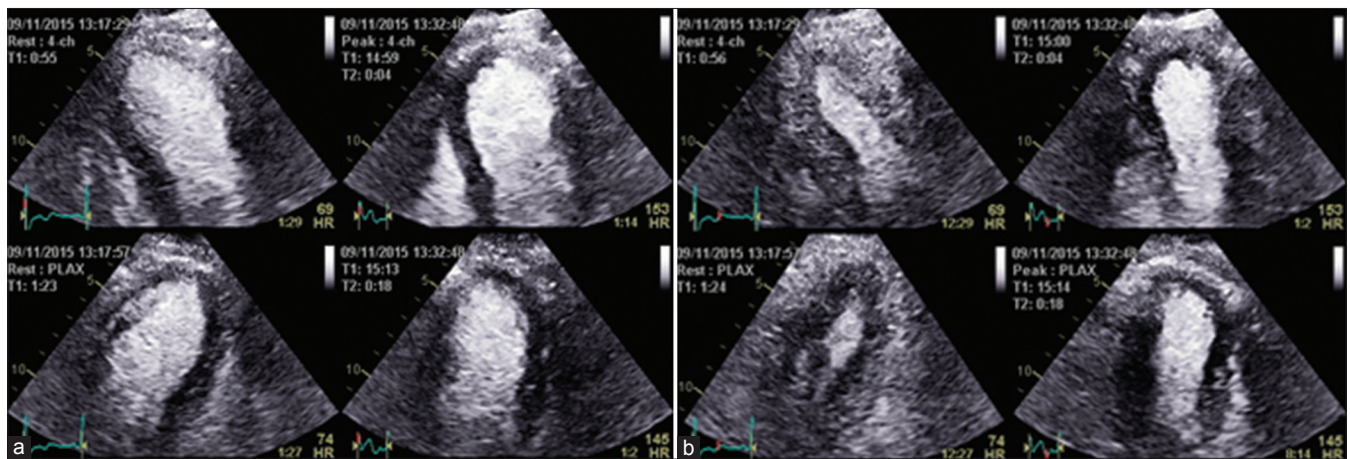
WMA: Wall motion abnormality (hypokinesia, akinesia, dyskinesia)

wall motion should be classified as normal, hypokinesia, akinesia, or dyskinesia and the same should be recorded in the reporting template [Appendix 1b]. Segmental wall motion can also be scored semiquantitatively (1 - normal, 2 - hypokinetic,

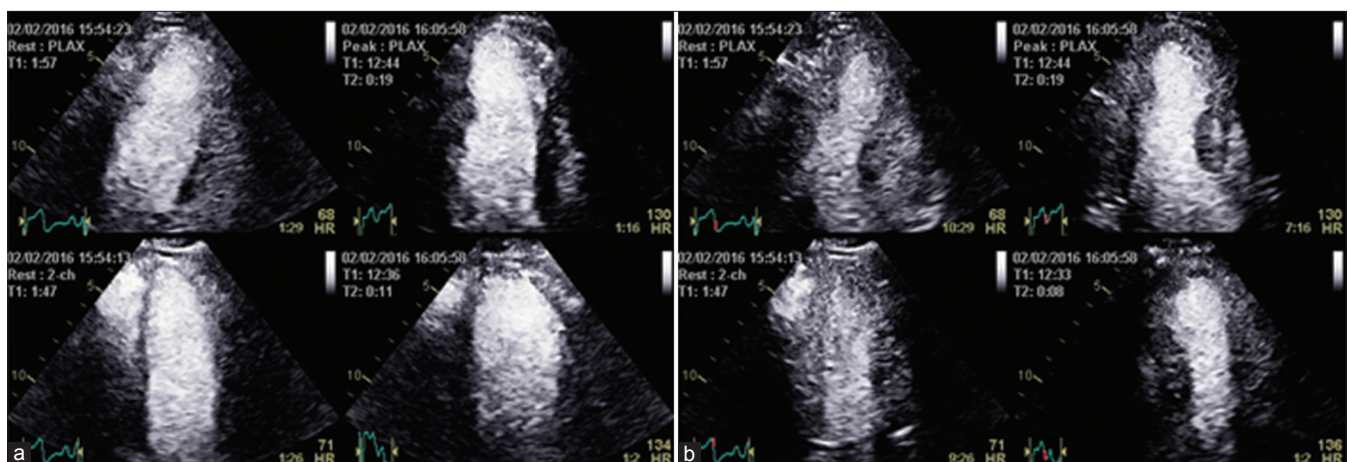




**Figure 6:** Contrast-enhanced images of apical 4-chamber view in a normal dobutamine stress echocardiogram. (a) End-diastolic frame. (b) End-systolic frame. Upper left - baseline, upper right - 10 mcg/kg/min, lower left - 20 mcg/kg/min, and lower right - 30 mcg/kg/min. There is no left ventricular dilatation or wall motion abnormality at any stage

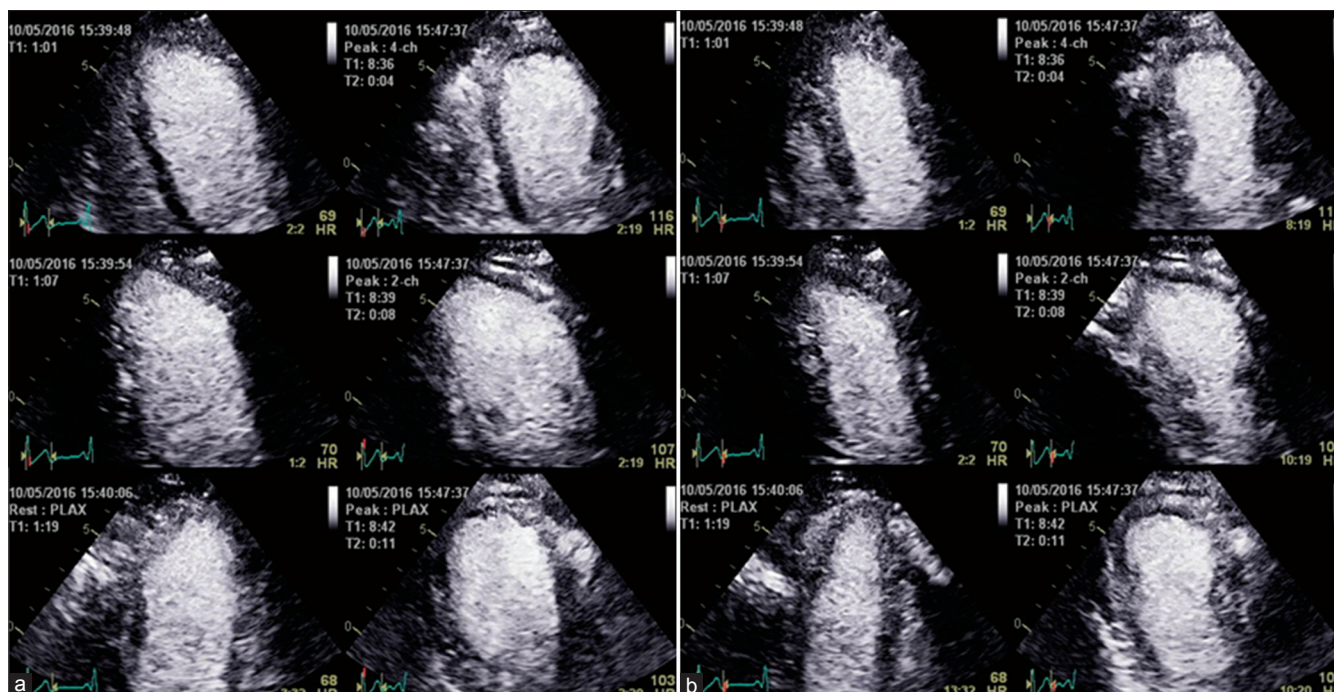


**Figure 7:** An abnormal exercise stress echocardiogram. (a) End-diastolic frame. (b) End-systolic frame. Upper images show apical 4-chamber view and the lower images show apical long-axis view. Rest images are on the left side and the immediate postexercise images are on the right side. There is no visible abnormality in end-diastolic images but end-systolic frames show bulging of apex and distal part of anteroseptum postexercise suggestive of inducible ischemia in the territory of left anterior descending artery



**Figure 8:** An abnormal exercise stress echocardiogram. (a) End-diastolic frame. (b) End-systolic frame. Upper images show apical long-axis view and the lower images show apical 2-chamber view. Rest images are on the left side and the immediate postexercise images are on the right side. There is no visible abnormality in end-diastolic images but end-systolic frames show bulging of apex and distal part of anteroseptum postexercise suggestive of inducible ischemia in the territory of left anterior descending artery





**Figure 9:** Another example of an abnormal exercise stress echocardiogram. (a) End-diastolic frame. (b) End-systolic frame. Upper images show apical 4-chamber view, middle images show apical 2-chamber view, and the lower images show apical long-axis view. Rest images are on the left side and the immediate postexercise images are on the right side. End-diastolic images show global left ventricular dilatation whereas end-systolic images show multiple regional wall motion abnormalities. These findings are suggestive of multivessel coronary artery disease

3 - akinetic, and 4 - dyskinetic or aneurysmal), and wall motion score index (WMSI) can be calculated by dividing the total score with the number of segments scored.

A normal stress response is defined as an increase in endocardial excursion and thickening of each myocardial segment resulting in >5% increase in LV ejection fraction (LVEF) and reduction in LV end-systolic volume.<sup>[29]</sup> Ischemic response is defined as either delayed systolic (i.e., later half of systole) endocardial take off (tardokinesia), reduced systolic thickening (hypokinesia), absent systolic thickening (akinesia), or even paradoxical systolic stretching (dyskinesia), depending on the severity, duration, and transmural extent of ischemia [Videos 9a, b and 10-16].

When analyzing RWMA, more emphasis should be put on the assessment of wall thickening rather than wall motion (or endocardial excursion). The wall motion may spuriously occur even in an ischemic segment due to the following two reasons:

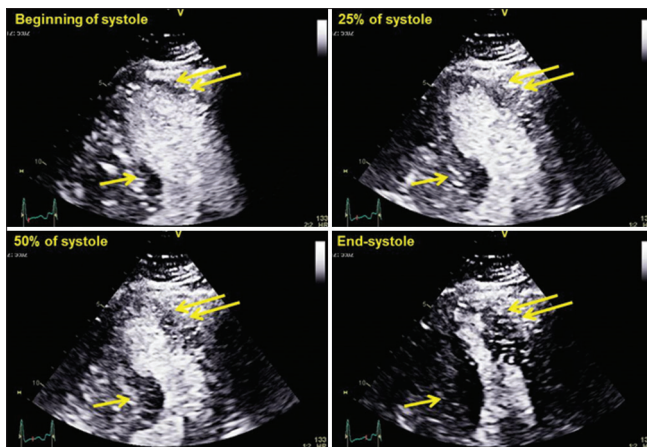
1. Tethering effect of the adjacent hyperkinetic normal segments.
2. Translational movement of the heart through the imaging plane in long- or short-axis views. Since LV cavity is tapering on either side of the long-axis imaging plane, a through-plane cardiac motion may give wrong perception of endocardial excursion.

Reviewing only the systole instead of complete cardiac cycle improves the ability to recognize RWMAs [Video 17a and b]. It is also advisable to assess endocardial excursion “take off” in the first half of systole, as this phase is relatively independent of

translational motion and tethering.<sup>[29]</sup> Moreover, the occurrence of endocardial “take off” in later half of systole also helps in recognizing tardokinesia [Figure 10]. Freezing the image and scrolling through early systole frame by frame is very helpful for this purpose.

When looking for ischemic response during DSE, it is best to compare peak-dose images with low-dose images instead of rest images. At low dose, the myocardial segments generally have much better contractility as compared to baseline and therefore any worsening of contractile function, and thus recognition of ischemia, becomes much easier if low-dose images are used as the reference. It is also important to carefully review recovery images. In patients undergoing dobutamine echocardiography, ischemic response is often masked at peak dose due to reduction in LV cavity size leading to reduction in LV wall stress. Once dobutamine infusion is stopped, rapid increase in LV cavity size increases wall stress and precipitates ischemia [Video 18a and b]. In addition, recovery images also help in the appreciation of ischemic response when the same cannot be reliably assessed at peak dose due to tachycardia. Since ischemia often persists for a few minutes, contractility may remain compromised during recovery phase also. As there is no reason why a normal myocardial segment should have worse wall motion during recovery as compared to baseline, the presence of even subtle impairment of contractility during recovery in comparison to baseline should be considered an evidence of ischemia at peak dose.

Ischemic RWMAs follow a coronary vascular distribution and this helps in recognizing true wall motion abnormalities.



**Figure 10:** An example of tardokinesia. Basal inferoseptum (single arrow) starts to contract early in systole whereas apical lateral wall contracts very late (double arrows)

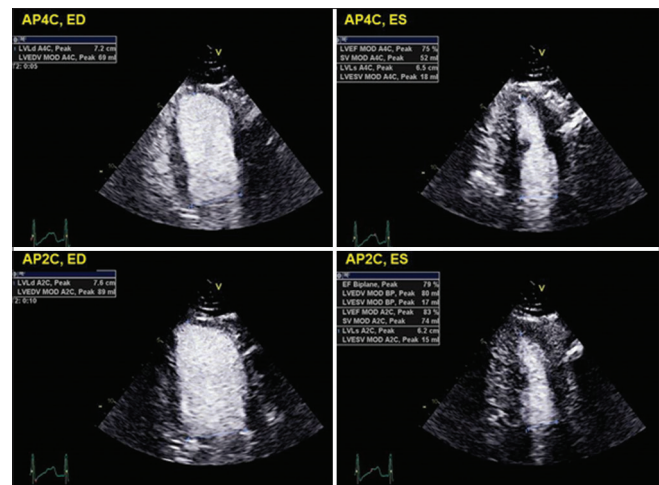
False-positive results are common in basal inferoseptal wall and basal inferior wall whereas false-negative results are common in basal anterolateral wall. Therefore, isolated abnormalities in basal inferior wall or basal inferoseptum can be disregarded if the adjacent segments supplied by the same vascular territory show normal function.<sup>[30]</sup> One should also corroborate and confirm RWMA in a particular coronary perfusion territory in corresponding long- and short-axis views. However, atypical patterns (e.g., proximal-to-mid-septal RWMA with apical sparing) may be seen in patients with patent coronary bypass graft to distal segment of left anterior descending artery with severe disease in proximal segment. Occasionally, a generalized global LV wall hypokinesia (cardiomyopathic response) may be seen in patients with hypertension or diabetes without obstructive CAD. It has been shown that these patients have higher incidence of heart failure, vascular events, or atrial fibrillation in the future.

After completing segmental wall motion analysis, the rest and peak WMSI, WMSI change, rest and peak LV volume, and LVEF can be formally calculated offline [Figure 11]. Hemodynamic data obtained at peak stress imaging are also reviewed. Increase in the severity of mitral regurgitation, rise in LV filling pressure, increase in pulmonary artery systolic pressure, or RV dilatation, either alone or in combination, may provide useful corroborative evidence of myocardial ischemia.

Finally, it is also important to review stress-induced ECG changes. If there are significant ECG changes but there is no apparent RWMA on echocardiography, it would be worthwhile to review the echocardiographic images once again, especially if the patient also had chest pain during the stress test. This may help recognize any subtle RWMA which may have gone unnoticed during the initial review of images.

## DIAGNOSTIC ACCURACY OF STRESS ECHOCARDIOGRAPHY

Stress ECG is known to have sensitivity and specificity in the range of 63%–68% and 74%–77%, respectively.<sup>[31]</sup> Stress echocardiography has much higher sensitivity and specificity



**Figure 11:** Estimation of left ventricular volumes and ejection fraction using modified biplane Simpson's method in postexercise images. AP2C - apical two chamber; AP4C - apical four chamber; ED - end diastole; ES - end systole

as compared to stress ECG. In a large meta-analysis, average sensitivity and specificity of exercise echocardiography were 83% and 84%, respectively, whereas the same for DSE were 80% and 85%, respectively [Table 5].<sup>[32]</sup> In women, exercise echocardiography has higher specificity (80% vs. 64%) and overall diagnostic accuracy (81% vs. 64%) for detection of CAD than exercise ECG.<sup>[2]</sup> For dobutamine echocardiography, average sensitivity for one-, two-, and three-vessel disease has been reported to be approximately 74%, 86%, and 92%, respectively.<sup>[24]</sup> The sensitivity is higher for detection of stenosis in the left anterior descending (72%) and right coronary arteries (76%), as compared to left circumflex artery (55%).<sup>[24]</sup> The overall sensitivity and specificity are 71% and 92% for dipyridamole echocardiography and 68% and 81% for adenosine stress echocardiography, respectively.<sup>[32]</sup>

Compared with nuclear imaging (exercise or pharmacological), stress echocardiography (exercise or dobutamine) has been shown to have better specificity (77%–82% vs. 36%–71%, respectively) but lesser sensitivity (80%–88% vs. 86%–98%, respectively), resulting in nearly similar overall diagnostic accuracy (80%–84% for both).<sup>[33–36]</sup> For detection of multivessel CAD, both nuclear imaging and stress echocardiography have similar sensitivity (94%) and specificity (88%).<sup>[24,37]</sup> Stress echocardiography is better than nuclear stress tests in patients with LBBB, microvascular disease, or LVH<sup>[36]</sup> whereas nuclear imaging performs better in the presence of single vessel disease, low workload stress test, and in patients on beta-blockers.<sup>[38]</sup> Stress MRI has higher sensitivity (90%), specificity (81%), and diagnostic accuracy (87%).<sup>[39]</sup>

## Factors affecting diagnostic accuracy of stress echocardiography

### Operator expertise

Operator expertise in performance and interpretation of stress echocardiography is perhaps the most important determinant of the



**Table 5: Diagnostic accuracy of stress echocardiography as reported in meta-analyses**

For detection of myocardial ischemia*		
Stress modality	Sensitivity (%)	Specificity (%)
Exercise	82.6	84.4
Dobutamine	79.6	85.1
Adenosine	68.4	80.9
Dipyridamole	71.0	92.2
Atrial acing, transthoracic	90.7	86.1
Atrial acing, transesophageal	86.2	91.3
For detection of myocardial viability (i.e., functional recovery following revascularization)**		
Imaging modality	Sensitivity	Specificity
Low-dose dobutamine echocardiography	84	81
Thallium-201 rest-redistribution SPECT	90	54
Thallium-201 rest-redistribution-reinjection SPECT	86	47
Technetium-99m-sestamibi SPECT	83	69
Fluorine-18 fluorodeoxyglucose PET	88	73

\*Source: Noguchi Y, Nagata-Kobayashi S, Stahl JE, Wong JB. A meta-analytic comparison of echocardiographic stressors. *Int J Cardiovasc Imaging*. 2005;21:189-207. \*\*Source: Bax JJ, Wijns W, Cornel JH, Visser FC, Boersma E, Fioretti PM. Accuracy of currently available techniques for prediction of functional recovery after revascularization in patients with left ventricular dysfunction due to chronic coronary artery disease: Comparison of pooled data. *J Am Coll Cardiol* 1997;30:1451-60. PET: Positron emission tomography, SPECT: Single-photon emission computed tomography

accuracy of the results.<sup>[40,41]</sup> Operator experience of performing and reading at least 100 studies under expert supervision is necessary to improve the accuracy of the beginner to expert level.<sup>[42]</sup>

### Workload achieved

WMA develops at a later stage in the ischemic cascade and recovers fast. Therefore, stress echocardiography loses its sensitivity if sufficiently high rate-pressure product is not achieved on treadmill and/or if there is a delay in imaging after cessation of stress.

During dobutamine echocardiography, one should try to achieve MPHR and maintain it for at least 30–60 s before image acquisition. Addition of atropine helps in achieving target heart rate and improves sensitivity of the test by 5%.<sup>[43]</sup> If MPHR cannot be achieved for any reason, every effort should be made to achieve at least 85% of MPHR (also termed as target heart rate).

### Delay in imaging

Delay in postexercise imaging is an important consideration in patients undergoing treadmill stress echocardiography. To avoid any delay, some investigators have also suggested performing scanning at peak stress itself, while the patient is still on treadmill.<sup>[14,44]</sup> On-treadmill peak stress imaging has higher sensitivity (84%) compared to peak supine bicycle imaging (75%) and posttreadmill imaging (60%). The quality of images is similar between on-treadmill versus posttreadmill imaging.<sup>[44]</sup> However, “on-treadmill” scanning is technically difficult.

### Beta-blockers and antianginals

On beta-blockers and antianginals, the rate-pressure product achieved is lower and the postexercise heart rate drop occurs faster. Both these factors reduce the sensitivity of the test. Addition of atropine helps improve sensitivity of the test in these situations.<sup>[19]</sup>

### Hypertension and left ventricular hypertrophy

Accelerated blood pressure response during exercise causes LV afterload mismatch and can result in RWMA even in the absence of obstructive CAD. Further, in the presence of LVH, hypercontractility with reduced afterload in response to dobutamine infusion can result in dynamic LV outflow tract or mid-cavity obstruction. This may lead to LV apical ballooning, which recovers spontaneously. Conversely, the presence of significant concentric LVH with small LV cavity size may make it difficult to appreciate the extent of endocardial excursion and to recognize WMA. However, despite all these challenges, stress echocardiography is still superior to stress ECG or nuclear imaging in patients with LVH.<sup>[36,45]</sup>

### Resting regional wall motion abnormality

Detection of inducible ischemia in segments with resting hypokinesia is challenging due to difficulties in recognizing subtle deterioration in contractility. Dobutamine echocardiography permits assessment of biphasic response to detect ischemia in hypokinetic or akinetic segments. Resting RWMA can also interfere with the assessment of normal wall motion response in adjacent segments due to tethering effects.

### Acoustic window

Stress echocardiography is highly dependent on image quality. When acoustic window is not good, the use of contrast for LVO may help improve diagnostic accuracy and reproducibility of stress echocardiography. Rarely, when adequate acoustic window is not available and the images are suboptimal even with the use of contrast, the test should be cancelled.

### Extent of coronary artery disease and functional significance of the stenotic lesion

The ability of stress echocardiography to detect inducible ischemia increases with increasing severity of CAD (severity

of coronary stenoses as well as the number of vessels involved). However, it should also be recognized that the extent of inducible ischemia depends on the functional significance and not on anatomic severity of the coronary stenosis. Functional significance of a coronary lesion is determined by the size of the coronary artery, vasodilatory reserve in the distal perfusion bed, and the presence of collateral circulation. While coronary angiography shows anatomic severity of stenosis, fractional flow reserve (FFR) shows the functional significance of the lesion. The sensitivity of DSE for detection of myocardial ischemia increases to 90% for vessels with a diameter of >2.6 mm and FFR <0.75.<sup>[46]</sup>

The affected coronary artery also influences the diagnostic accuracy of stress echocardiography. Sensitivity of stress echocardiography is generally lower for ischemia in left circumflex artery territory, whereas it is highest for left anterior descending artery lesions.

Table 6 summarizes common causes responsible for false-positive and false-negative stress echocardiography.

ROLE OF NEWER MODALITIES IN STRESS ECHOCARDIOGRAPHY

As discussed above, stress echocardiography depends primarily on the visual assessment of segmental wall motion, which is a subjective process. This leads to significant interobserver variability in the results. Gaining required expertise in performance of stress echocardiography and following standardized protocol for image acquisition and interpretation significantly improve the diagnostic accuracy of the test<sup>[25,26]</sup> and are strongly recommended. In addition, several newer techniques have also been used to enhance the diagnostic accuracy of stress echocardiography. However, the

role of these modalities at present is only as adjunct to and not as a substitute for visual wall motion analysis.

Three-dimensional echocardiography

The tri-plane simultaneous acquisition mode with a three-dimensional (3D) echocardiography transducer provides good frame rate and image quality comparable to 2D imaging. Tri-plane imaging is beneficial during DSE because it reduces time and effort of the operator for acquiring three apical images at every stage, without compromising the accuracy of the test.<sup>[47]</sup>

Conceptually, single-beat 3D volume acquisition at rest and peak can greatly reduce acquisition time, reduce the operator’s effort, and can also overcome the problems of off-axis imaging. However, the present-generation 3D echocardiography machines lack sufficiently high frame rates and line density (in single-beat acquisition mode) required for peak stress imaging.

Use of contrast

The detection of endocardial excursion and wall thickening at peak heart rate during stress echocardiography requires adequate endocardial visualization. The use of contrast for LVO uniformly improves endocardial visualization in almost every patient [Figure 12 and Video 19].<sup>[48]</sup> In addition, the low mechanical index used for contrast imaging also provides clear epicardial visualization, resulting in much better appreciation of segmental wall thickening.<sup>[49]</sup> As a result, the number of nondiagnostic studies is reduced considerably. The use of contrast has been demonstrated to significantly improve diagnostic accuracy of the studies with difficult acoustic window and to improve the reader’s confidence in reporting such studies.<sup>[50]</sup> Contrast also improves accuracy of measurement of LVEF and LV volumes at rest and peak stress. The American Society of Echocardiography recommends use of LV cavity contrast in all stress studies in which at least two consecutive LV myocardial segments are not clearly visualized.<sup>[13]</sup>

Technical aspects of contrast use require understanding of instrumentation and physical dynamics of microbubbles and ultrasound waves. The acquisition mode is set at low

Table 6: Causes of false-negative and false-positive stress echocardiograms
<b>False negatives</b>
Inadequate stress
Delayed poststress imaging
Beta-blocker usage, antianginal therapy
Coronary stenosis in smaller perfusion territory
Left circumflex disease
Ischemia in segments with preexisting RWMA
Significant LV hypertrophy
Poor image quality
<b>False positives</b>
Isolated basal inferior septum or basal inferior wall RWMA
Unmasking of subclinical cardiomyopathy (diabetes, hypothyroidism, or idiopathic)
Segments with subendocardial infarcts (RWMA despite patent coronary artery)
Exaggerated hypertensive response during stress
LV midcavity dynamic obstruction during dobutamine echocardiography
Abnormal septal motion (LBBB, previous coronary bypass surgery)
LBBB: Left bundle branch block, RWMA: Regional wall motion abnormality, LV: Left ventricular

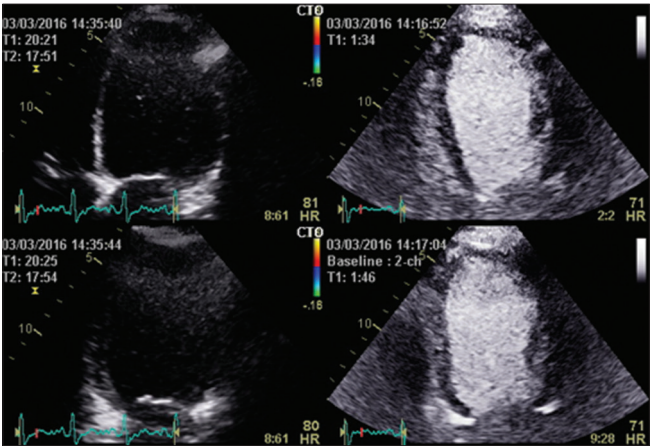


Figure 12: Significant improvement in endocardial visualization with left ventricular cavity contrast in a patient with poor acoustic window

mechanical index, a low ultrasound power mode, to prevent destruction of bubbles. However, low mechanical index prevents visualization of regular LV structures due to poor penetration and low intensity backscatter. During the rest images, the gain setting is adjusted to visualize only outer shell of the epicardium/pericardium which is a relatively stronger reflector [Figure 13 and Video 20].

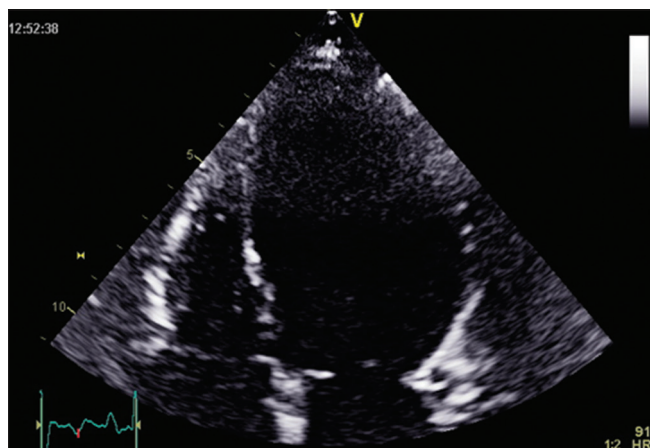
The only commercially available ultrasound contrast in India is Sonovue®, a sulphur hexafluoride inert gas with lipid shell. It is available in powder form which is reconstituted by mixing with 5 ml saline. Small aliquot of 0.2–0.3 ml of the prepared solution is injected IV using insulin syringe followed by a constant flush with 5–10 ml saline, till the contrast appears in right ventricle, when the saline flush should be stopped. A uniform white LVO should be achieved with crisp endocardial delineation and black myocardial wall thickness in all LV myocardial segments [Figure 14 and Video 21]. There should not be shadowing at base which would mean too much of contrast bolus volume or too rapid injection or flushing [Figure 15]. In that case, one needs to wait till the ultrasound-mediated bubble destruction leads to uniform opacification. Conversely, visible swirling of contrast means less volume of bolus injected too

slowly or excess destruction of bubbles due to higher mechanical index. Swirling of contrast in LV cavity should be avoided as it gives a false perception of endocardial motion [Figure 16 and Video 22]. In this situation, further lowering of mechanical index, administering additional bolus of contrast, and quickly finishing acquisition of images to prevent prolonged insonation are the strategies used to achieve uniform LVO.

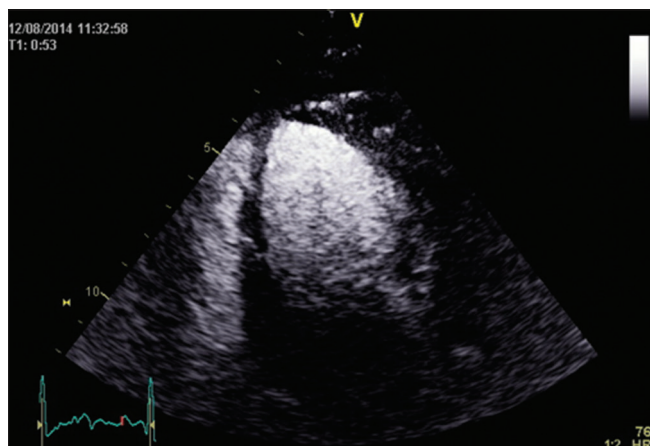
At peak stress during exercise echocardiography, 0.3–0.5 ml contrast bolus is administered with quick saline flush approximately 10–15 s before stopping the treadmill. Due to fast circulation time at peak exercise, the contrast is always seen in the left ventricle with good LVO by the time patient returns to the imaging bed and the postpeak stress imaging is started. In case of DSE, a smaller quantity of contrast bolus (0.1–0.2 ml) is required during dobutamine infusion due to accumulation of contrast from previous stages. It is advisable to administer contrast bolus at 2 min 45 s time point in the stage so that the images for that stage can be acquired in the last 10 s of the stage.

### Myocardial strain imaging

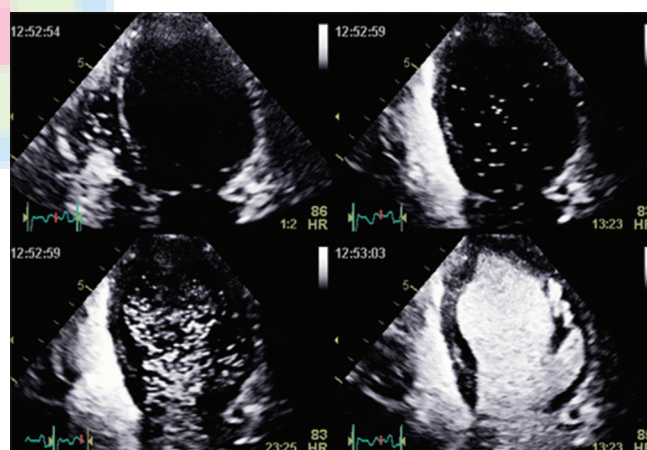
Given the ability of strain imaging to quantify myocardial contractile function and detect subtle changes in contractility, strain imaging has been used as an adjunct to wall motion analysis during stress echocardiography. The objective is to enhance diagnostic accuracy of the test and to minimize interobserver variability.



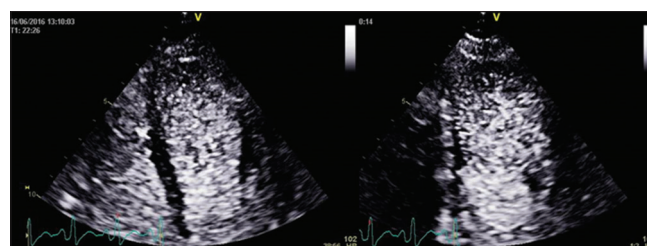
**Figure 13:** Imaging at low mechanical index. Gain settings are adjusted such that epicardium is clearly visualized



**Figure 15:** Shadowing due to excessive or too rapid contrast administration



**Figure 14:** Technique for left ventricular contrast opacification. The contrast bolus is followed from initial appearance on the right side to complete left ventricular cavity opacification. Saline flush is stopped as soon as contrast appears in the right ventricle



**Figure 16:** Swirling artifact due to too little or too slow contrast administration



There are two methods for myocardial strain imaging - the Doppler based and the gray scale based (also known as 2D strain or speckle tracking echocardiography [STE]). The Doppler-based strain imaging allows sampling at high frame rates suitable for stress echocardiography, but has poor signal-to-noise ratio. With STE, signal-to-noise ratio is robust at rest, but deteriorates considerably at faster heart rates. For Doppler-based strain measurement, velocity-encoded images or color TDI images need to be acquired, whereas standard gray-scale images are used for STE. The results of offline analysis are displayed as parametric imaging using curved anatomic M-mode or segmental strain/strain rate waveforms. Dobutamine echocardiography is more suited for strain imaging because it is relatively free of respiratory and motion artifacts.

Since crossover from end systole to early diastole is the phase most vulnerable to ischemia, strain imaging reveals several abnormalities in this phase during ischemic response. These include delayed onset of relaxation, reduced early diastolic strain rate, increased postsystolic shortening, delayed peak systolic strain rate, reduction in peak systolic strain rate, and reduced end-systolic strain values.<sup>[51-53]</sup> In early studies exploring the utility of strain imaging during dobutamine echocardiography, Voigt *et al.* demonstrated that magnitude of postsystolic shortening measured using Doppler strain could detect myocardial ischemia with good accuracy.<sup>[51,54]</sup> A cutoff value of >35% for the ratio of postsystolic shortening to maximum shortening had a sensitivity of 82% and specificity of 85% for the detection of CAD. In a subsequent study, Hanekom *et al.* found that Doppler-based peak systolic strain rate measured at peak stress was an excellent predictor of CAD and was superior to postsystolic shortening for this purpose.<sup>[55]</sup> This study also compared the diagnostic accuracy of Doppler-based strain with STE for the detection of inducible ischemia. It was found that STE-based strain had an acceptable accuracy for the detection of ischemia only in left anterior descending artery territory but not in other vascular territories. However, despite the above studies demonstrating the value of strain imaging for the detection of myocardial ischemia, segmental strain analysis has considerable variability which limits its routine application in clinical practice. The variability increases significantly at peak stress which further affects its clinical utility.

An important observation from animal studies is that the abnormalities of early diastolic relaxation often persist for a significant period after cessation of stress.<sup>[56]</sup> This phenomenon has been termed as “diastolic stunning” and may help in the detection of transient myocardial ischemia by obviating some of the limitations inherent to peak stress imaging. Gray-scale images can be acquired at ~10 min after cessation of exercise when the heart rate and hyperventilation have already settled. STE-based strain analysis of these images can reveal markedly impaired diastolic strain recovery in ischemic segments. In a study involving 162 patients with stable angina, segmental transverse strain was obtained at 5 and 10 min after cessation of exercise.<sup>[53]</sup> Impairment of segmental transverse strain decay during the initial 1/3<sup>rd</sup> of diastole was almost uniformly seen

in ischemic segments and persisted for up to 10 min. This was termed as “ischemic memory” sign and was very sensitive for the diagnosis of obstructive CAD.

## PROGNOSTIC VALUE OF STRESS ECHOCARDIOGRAPHY

Stress echocardiography provides a considerable amount of prognostic information that is far greater than just the diagnosis of inducible ischemia conveyed in a dichotomous fashion (i.e., positive or negative stress echocardiogram). This is in line with recent large-scale studies demonstrating that functional tests have superior prognostic power than the anatomical imaging for predicting cardiovascular mortality and major adverse cardiac events (MACEs).<sup>[57]</sup> The overall prognostic information provided by stress echocardiography is comparable to nuclear stress imaging using the same stress (exercise or dobutamine) modality.<sup>[58,59]</sup>

Patients with normal exercise stress echocardiogram have better event-free survival than age- and sex-matched population.<sup>[6]</sup> A negative exercise or dobutamine stress echocardiogram predicts low cardiac mortality and MACE rates (<1% per year) over the next 4–5-year follow-up.<sup>[60-62]</sup> This prognostic information is incremental to the Framingham risk score,<sup>[63]</sup> Duke treadmill score,<sup>[60]</sup> and even coronary angiographic findings.<sup>[62]</sup> However, the excellent prognostic value of a negative stress echocardiogram is adversely influenced by submaximal workload and antianginal medications.<sup>[64,65]</sup> Patients with normal stress echocardiography but submaximal peak heart rate have higher risk of cardiac events and incidence of revascularization compared to those who achieve maximal peak heart rate.<sup>[64]</sup>

Conversely, the patients with a positive stress echocardiogram have a high risk of MACE even if there is no hemodynamically significant CAD. The risk of cardiac events in patients with the so-called “false-positive” stress echocardiogram approaches that with true-positive stress echocardiograms.<sup>[66]</sup> The pathophysiological mechanisms underlying such false-positive stress echocardiograms include unmasking of underlying subclinical cardiomyopathy, coronary endothelial dysfunction leading to abnormal CFR or microvascular dysfunction, and in some cases, transient takatsubo-like stress cardiomyopathy response.

The risk of MACE in patients with true-positive stress echocardiograms is unequivocally high. The prognostic value of a positive stress echocardiogram has been demonstrated in a wide variety of patient subgroups including women,<sup>[67]</sup> elderly patients,<sup>[68]</sup> patients with diabetes,<sup>[69]</sup> patients with or without LV systolic dysfunction,<sup>[70,71]</sup> and those with previous MI<sup>[72]</sup> or previous CABG. This prognostic power of stress echocardiography is incremental to the patient’s baseline clinical data, resting ECG, stress ECG, and resting LV systolic function. Among patients with normal stress ECG, those who show stress-induced RWMA have twice the annual rates of all-cause mortality and cardiac events than those who have normal stress echocardiogram.<sup>[73]</sup> The prognostic value of

a positive stress echocardiogram is further enhanced by incorporating data about WMSI, resting WMA, and peak stress LV end-systolic volume and LVEF.<sup>[6,62,68,74,75]</sup> The lack of reduction or an actual increase in LV end-systolic volume at peak stress and failure to increase peak exercise LVEF are independent predictors of cardiac death or nonfatal MI.<sup>[68]</sup>

## ADDITIONAL BENEFITS OF STRESS ECHOCARDIOGRAPHY

The choice between stress echocardiography and nuclear stress test mainly depends on cost, local availability, and local expertise.<sup>[76]</sup> However, stress echocardiography has numerous advantages over nuclear imaging. Stress echocardiography provides additional information, at no extra cost, about LV systolic and diastolic function, valvular hemodynamics, pulmonary pressures, etc., at rest and at peak stress, which is clinically useful in guiding patient management. Furthermore, in many patients without previously known cardiac illness, resting echocardiography performed before initiation of exercise often shows incidental finding of RWMA, significant valvular disease, pericardial effusion, pulmonary hypertension, cardiomyopathies, or aortic dissection which itself answers the clinical query. This obviates the need for performing the stress test and prevents serious potential complications. Safety, rapidity, repeatability, and lack of exposure to radiation or nephrotoxic drugs are further advantages of stress echocardiography.

## CLINICAL RELEVANCE OF ISCHEMIA DETECTION WITH STRESS ECHOCARDIOGRAPHY

In stable chronic CAD, several large-scale randomized trials have failed to show incremental benefit of routine revascularization in reducing cardiac mortality or nonfatal MI in comparison to optimized medical therapy alone.<sup>[77-79]</sup> Although revascularization has been shown to reduce angina more effectively, this benefit too is not durable beyond the first few years. Therefore, the challenge before stress imaging is to accurately identify the high-risk subgroup of asymptomatic or minimally symptomatic stable CAD patients in whom revascularization is likely to reduce the risk of death/MI in the present era of optimized medical therapy. Traditionally, it is believed that the evidence of moderate or severe ischemia on cardiac stress test signifies large area of jeopardized myocardium and high risk of adverse cardiac event rates that justify coronary revascularization. The definition of moderate-to-severe ischemia for various stress tests is based on their respective thresholds for predicting annual cardiac event rates of 4%–6%. This amounts to >10% ischemic myocardium on nuclear imaging, >3/16 new akinetic segments on stress echocardiography, and >4/32 perfusion defects or >3/16 new akinetic segments on stress cardiac MRI.<sup>[80]</sup>

## ASSESSMENT OF MYOCARDIAL VIABILITY

### Pathophysiological considerations

A dysfunctional myocardial segment is considered viable if it shows improved contractility over time after restoration

of adequate coronary blood flow. Myocardial dysfunction can occur due to transient severe ischemia with reperfusion (myocardial stunning) or due to chronically reduced coronary blood flow with several ultrastructural changes in myocytes (myocardial hibernation).<sup>[6]</sup> Repeated episodes of stunning due to demand–supply mismatch resulting from coronary stenosis not severe enough to cause reduction in resting MBF can also lead to myocardial hibernation without myocardial ultrastructural changes.

In case of ST-elevation MI (STEMI), myocardial damage extends from endocardium to epicardium as the advancing wave front of necrosis with its net extent depending on the rapidity of reperfusion. The regional myocardial systolic thickening depends on the extent of preservation of helically-oriented subendocardial fibers and the circumferentially-oriented mid-myocardial fibers. The transmural extent of myocyte loss and replacement with fibrosis decide the recovery of wall motion and its contribution to global LV systolic function.<sup>[81]</sup>

In patients with stable CAD and chronic LV systolic dysfunction, multiple factors contribute to the regional myocardial dysfunction apart from the acute myocyte loss from previous STEMI or non-ST-elevation MI. In early phase, transmural MBF (TM-MBF) may be near normal or mildly reduced, but the CFR is significantly compromised. The subendocardial layer-MBF (SE-MBF) is also significantly reduced, even at rest.<sup>[82]</sup> During any episode of acute ischemia, SE-MBF is reduced further. It is noteworthy that reduction in SE-MBF is out of proportion to reduction in TM-MBF with a 25% reduction in TM-MBF resulting in ~50% reduction in SE-MBF. When there is a 50%–75% reduction of SE-MBF, segmental akinesia occurs. After relief of an ischemic episode, the hyperemia due to vasodilation is also maldistributed to mid and epicardial layer so that SE-MBF remains reduced for a considerable period.<sup>[81]</sup> Therefore, demand–supply mismatch in a setting of significant coronary stenosis may cause repetitive stunning and persistent akinesia, even if TM-MBF is not significantly reduced at rest.

In chronic ischemic dilated cardiomyopathy, advanced regional myocardial remodeling process occurs as a consequence of increased wall stress, exposure to systemic neuro-humoral activation, and myocyte adaptation to chronically reduced capillary blood flow. The microvasculature significantly shrinks to form sparse capillary network and reduced capillary blood volume.<sup>[83]</sup> The myocytes undergo ultrastructural changes by shutting down energy-intensive cellular processes, and the sarcomeres, myofilaments, and sarcoplasmic reticulum degenerate over time. The myofilament space gets filled with glycogen and the cytoskeletal proteins and mitochondria also show structural alterations. Eventually, the myocytes undergo apoptosis. The extracellular matrix expands and shows increased amounts of type I collagen, type III collagen, and fibronectin. These histopathological changes occur to a variable extent in both ischemic and nonischemic remote territories in chronic ischemic dilated cardiomyopathy.<sup>[84,85]</sup>

Hence in chronic ischemic LV systolic dysfunction, regional myocardial dysfunction may reflect a spectrum of pathological processes including variable extent of transmural scarring, remodeled myocardium, variable myocardial capillary blood flow and volume, and variable amount of interstitial fibrosis. Segments with less fibrosis and with less severe myocytic ultrastructural changes are more likely to improve in function on low-dose dobutamine echocardiography (LDDE) and after revascularization. The time to myocardial recovery in such hibernating myocardium postrevascularization would depend on the baseline severity of myocardial ultrastructural changes.<sup>[81]</sup>

### Low-dose dobutamine echocardiography for assessment of myocardial viability

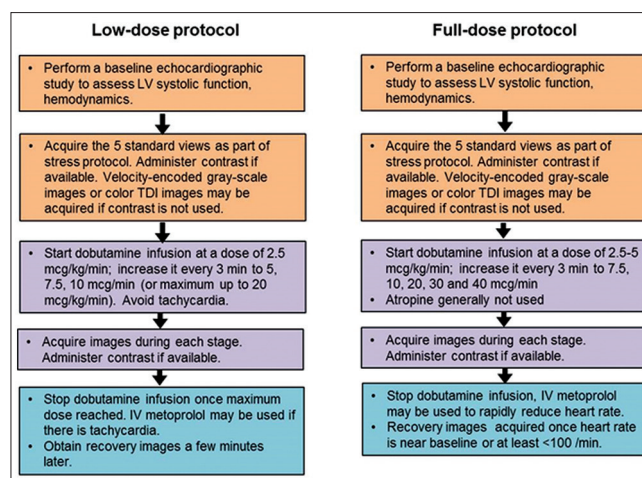
LDDE is the primary echocardiography modality for the assessment of myocardial viability. It is also the simplest and the least expensive among all the currently available imaging modalities for this purpose (with the exception of end-diastolic wall thickness [EDWT] assessment).

For viability assessment, LDDE relies on the ability of the dysfunctional myocardial segments to improve their contractility in response to low dose (i.e., 2.5–10 mcg/kg/min) dobutamine infusion. At this dose, dobutamine produces an inotropic effect without increasing the heart rate. In addition, there is mild systemic and coronary vasodilatation causing reduction in afterload and increase in myocardial perfusion and myocardial blood volume. As a result, there is no increase in myocardial workload or myocardial oxygen demand. Therefore, a dysfunctional myocardial segment is likely to show augmentation in wall motion and systolic thickening at this dose. The visually discernible improvement in the contractile function, however, depends on the transmural quantity of the surviving myocytes and the intact contractile apparatus in the myocytes as well as the recruitable residual coronary vasodilatory reserve. For this reason, dobutamine-induced augmentation of contractile response is a highly specific predictor of viability.<sup>[6]</sup> However, absence of contractile response can occur in spite of having sufficient viable myocytes and can be explained by absent recruitable coronary vasodilatory response, dobutamine-induced ischemia in tachycardic patients, and complete loss of subendocardial layer (which contributes to systolic thickening). Thus, while a positive LDDE result is useful to “rule in” viability, a negative LDDE result cannot be used to “rule out” viability with certainty.

### Performing dobutamine stress echocardiography for myocardial viability

Patient preparation and baseline imaging for myocardial viability assessment are same as for DSE performed for ischemia detection. However, the dobutamine infusion protocol differs [Figure 17].<sup>[13,81]</sup>

For viability assessment, dobutamine infusion is started at a dose of 2.5 mcg/kg/min and the dose is increased every 3 min to 5, 7.5, 10, and 20 mcg/kg/min. Further increase in the dose to 30 and 40 mcg/kg/min remains debatable. Since most of the patients undergoing viability assessment have



**Figure 17:** Imaging protocols for dobutamine echocardiography performed for myocardial viability assessment. IV - intravenous; LV - left ventricular; TDI - tissue Doppler imaging

significant LV systolic dysfunction with multivessel CAD, higher dose is associated with a certain risk of arrhythmias or cardiac decompensation. Moreover, it can be argued that showing augmentation of contractile response at low-dose dobutamine is all that is needed to detect viability and there is really no need to go up to full-dose dobutamine. However, using full-dose dobutamine protocol permits recognition of biphasic response which is the most specific predictor of functional recovery following revascularization. Additionally, worsening of contractile function at high dose also makes it easier to appreciate subtle improvements in contractile function at low dose. Finally, a full-dose protocol also permits detection of inducible myocardial ischemia in normally contracting segments at baseline. Thus, both the protocols have their own advantages and disadvantages. The choice between the two should depend on the overall patient profile, availability of the infrastructure to deal with any cardiac emergency if arises, and the expectations from the stress test in a given patient. In general, in low-resource settings, low-dose dobutamine protocol is preferable, especially if assessment of myocardial viability is the dominant clinical query.

The imaging principles are almost similar to that for ischemia detection. First, a baseline echocardiogram is performed to assess for LV systolic function and hemodynamics. Good quality images in the five standard views as described for ischemic protocols should be acquired. In addition, as strain imaging seems to be useful for viability assessment, it is also advisable to obtain velocity-encoded gray-scale images or color TDI images (depending on the echocardiography equipment) of the three apical views (AP4C, AP2C, and APLAX). The stress protocol is then turned on and contrast-enhanced images in the five standard views are acquired as part of the protocol. Dobutamine infusion is then started. Regardless of the infusion protocol, it is advised that the same set of standard gray-scale images are recorded at the end of each step. Having multiple sets of images enhances



the ability to detect viability as improvement in contractile function may sometimes be only transient. The contrast bolus (0.5–1 ml) should be administered at 2 min 45 s time point during each stage and the images can be acquired 10–15 s later. The ability to administer contrast as IV infusion permits uniform LVO and makes it easier to obtain good quality images, but the requisite type of infusion pumps is currently not available in India.

It should be noted that contrast interferes with strain imaging, and hence if strain imaging at low dose is required, an appropriate protocol would be to acquire both noncontrast- and contrast-enhanced images at baseline, followed by only noncontrast images during subsequent stages. The acquisition of contrast-enhanced images at baseline is important as it would allow qualitative assessment of myocardial perfusion also. If contrast is not available, then of course there is no dilemma and only velocity-encoded gray-scale images or separate gray-scale and color TDI images need to be acquired at each stage.

Atropine boluses of 0.3–0.6 mg are rarely required in this patient population to achieve target heart rate. IV metoprolol (2–10 mg) may be administered at the end of the test to rapidly reverse dobutamine-induced tachycardia and arrhythmia.

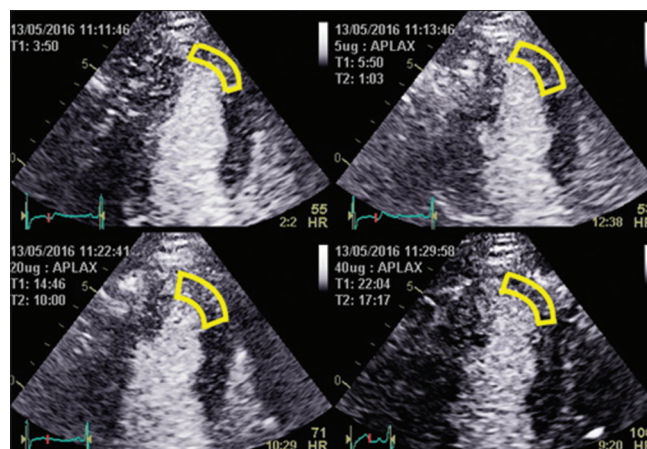
#### *Interpretation of dobutamine echocardiography for viability*

As mentioned above, at low dose (5–10  $\mu\text{g/kg/min}$ ), dobutamine augments cardiac contractility without any appreciable increase in myocardial oxygen demand. However, when the dose is increased further, there is progressive increase in heart rate and myocardial oxygen demand. As a result, a hibernating segment will improve at low dose but worsens again at peak dose [Table 4, Figure 18 and Video 23a-c].

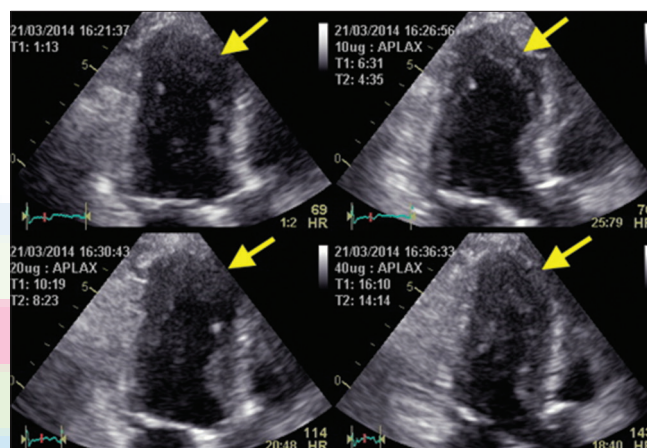
In contrast, a stunned myocardial segment or nonischemic, myopathic, or remodeled segment will demonstrate a sustained improvement in contractility at low- and peak-dose [Figure 19 and Video 24]. Tethering may also produce a similar response, but more often the augmentation in contractility is visible only at peak dose with no appreciable increase in contractility at low dose. When there is no change in contractility at low dose, it indicates lack of myocardial viability [Figure 20 and Video 25]. Rarely, a dysfunctional segment may deteriorate at low dose itself indicating the presence of critically reduced MBF at rest and no CFR. Viable segments without contractile reserve on LDDE usually have lower or completely exhausted CFR than viable segments with contractile reserve. Apart from the exhaustion of CFR, other factors, such as severity of ultrastructural changes in cardiomyocytes or downregulation of beta-adrenoreceptors, may also contribute to the lack of contractile reserve in viable segments.

Accordingly, four different types of responses can be seen in dysfunctional myocardial segments during DSE as follows [Table 4]:<sup>[86]</sup>

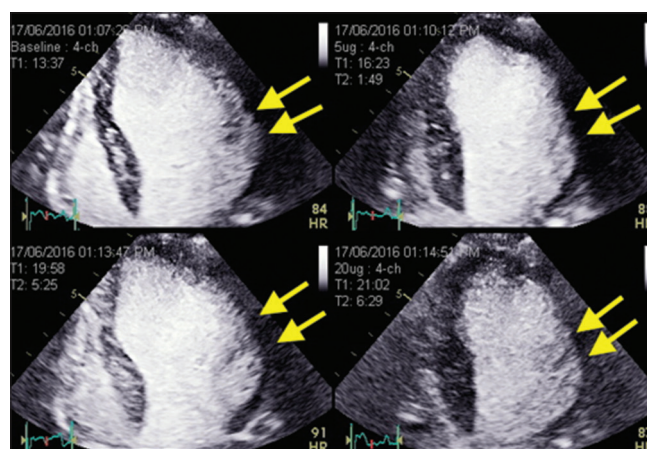
- Biphasic: Improvement in contractility at low dose and worsening at higher dose suggesting viable and ischemic



**Figure 18:** Biphasic response during dobutamine stress echocardiography. A dysfunctional apical segment improves at 5 and 20 mcg/kg/min but worsens again at 40 mcg/kg/min dose



**Figure 19:** Uniphasic response during dobutamine stress echocardiography. The apical segment (arrow) shows sustained improvement at 10, 20, and 40 mcg/kg/min dose



**Figure 20:** Lack of contractile response to dobutamine suggestive of lack of viability

segment [Figure 18 and Video 23a-c]. This type of response is the most accurate predictor of functional recovery after revascularization.<sup>[87]</sup>

- Sustained improvement: Continued improvement in contractility with increasing dobutamine dose [Figure 19 and Video 24]. It suggests viable, stunned, remodeled, myopathic, or tethered segment or segment with subendocardial infarct but without ischemia. It has lower specificity to predict improvement postrevascularization. However, in practice, both biphasic and sustained responses are reported as indicative of viability to improve sensitivity. Sustained improvement should be differentiated from improvement occurring only at peak dose without any improvement at low dose. This type of response does not indicate myocardial viability.
- Deterioration at low dose: Hypokinetic segments becoming akinetic to dyskinetic with low-dose dobutamine itself. These are the segments with critically reduced resting MBF. Such segments have variable chances of recovery with revascularization.
- No response: Akinetic segments that show no improvement in contractile function at low dose [Figure 20 and Video 25]. These are nonviable, scarred segments. These segments usually have low myocyte mass and more transmural extent of fibrosis and are unlikely to improve with revascularization.

Additionally, in ischemic dilated cardiomyopathy, LV end-diastolic volume index  $>170$  ml/m<sup>2</sup>, LV end-systolic volume index  $>90$  ml/m<sup>2</sup>, and LV end-diastolic diameter index  $>55$  mm/m<sup>2</sup> indicate an advanced LV remodeling with very low likelihood of global LVEF recovery postrevascularization.<sup>[81]</sup>

### **Sensitivity and specificity of dobutamine stress echocardiography for myocardial viability**

LDDE shows average sensitivity of 75%–80% and a specificity of 80%–85% for the prediction of functional recovery, both early after MI or in the setting of ischemic dilated cardiomyopathy.<sup>[81]</sup> Biphasic response is the most specific for myocardial viability and is the most accurate predictor of functional recovery after revascularization (specificity 89% and sensitivity 74%).<sup>[87]</sup> Sustained response, though highly sensitive, has a much lower specificity. Generally, both biphasic and sustained responses are reported as evidence of viability, which improves sensitivity (86%) but reduces specificity (68%) for prediction of functional recovery.<sup>[88]</sup> Combining any response on dobutamine (biphasic, sustained, or worsening) further improves sensitivity (88%) but with a significant drop in specificity (61%).<sup>[88]</sup>

The global LV functional recovery postrevascularization depends on the number of myocardial segments showing viability on baseline LDDE. The improvement in LVEF postrevascularization is expected to be in the range of 5%–6% for 2–5 viable segments at baseline and  $>10\%$  for 6 or more viable segments.<sup>[89]</sup> Patients showing significant LVEF improvement with LDDE are likely to show global functional recovery and reverse remodeling after CABG.<sup>[90]</sup>

### **Comparison with other imaging modalities**

Preserved EDWT in an infarcted segment indicates the presence of sufficient mass of recruitable myocytes to effectively cause systolic thickening. Thus, EDWT  $>6$  mm has high sensitivity ( $>90\%$ ) to predict postrevascularization functional recovery but specificity is poor (40%–50%).<sup>[91]</sup> Conversely, reduced diastolic wall thickness ( $<5$  mm) is highly accurate in identifying resting regional myocardial dysfunction that is unlikely to improve after revascularization.<sup>[81]</sup>

Combining EDWT with LDDE significantly improves the diagnostic accuracy of the latter by excluding segments showing tethering effect.<sup>[91]</sup> A combination of EDWT  $>6$  mm with any improvement on LDDE gives optimum sensitivity (88%) and specificity (77%).<sup>[91]</sup> Further, the combination of EDWT  $>5$  mm and either dobutamine echocardiography or thallium-201 scintigraphy results in similar high positive predictive value as a combination of dobutamine echocardiography and thallium-201 scintigraphy.<sup>[81]</sup>

Contrast LVO permits accurate estimation of EDWT and may be helpful in viability assessment [Figure 21]. Additionally, perfusion imaging with myocardial contrast echocardiography (MCE) can also be performed. MCE may be especially useful in the evaluation of myocardial viability in dobutamine nonresponsive segments. The ten MCE studies in the literature evaluating viability have shown sensitivity ranging from 62% to 92% and specificity ranging from 67% to 87% for identifying myocardial viability.<sup>[81]</sup>

Compared with nuclear or MRI techniques, LDDE is more specific but less sensitive for prediction of viability. Therefore, in case of negative DSE results, especially in myocardial segments with  $>5$  mm EDWT, it may be prudent to take the help of MRI or nuclear method.<sup>[92]</sup> A meta-analysis of LDDE trials involving 1090 patients showed sensitivity of 81% and specificity of 80% for the prediction of myocardial viability. Similar meta-analysis of thallium scintigraphy trials involving 858 patients showed sensitivity of 86%–88% and specificity of 50%–60% whereas a meta-analysis of fluorodeoxyglucose-positron emission tomography (FDG-PET) trials involving 598 patients showed sensitivity of 93% and specificity of 58%. Similarly, 13 MRI



**Figure 21:** Use of ultrasound contrast for left ventricular cavity opacification improves accuracy of end-diastolic wall thickness measurement



studies involving 420 patients showed sensitivity of 80%–82% and specificity of 68%–70% for prediction of myocardial viability.<sup>[92]</sup>

### **Role of strain imaging as adjunct to wall motion analysis during low-dose dobutamine echocardiography**

Compared with assessment of inducible ischemia, viability assessment is more suited for incorporation of strain imaging as tachycardia is not a limitation here. Doppler-based measurement of segmental longitudinal strain and strain rate has been shown to be useful in enhancing the diagnostic accuracy of LDDE for the detection of myocardial viability. In a study involving 55 patients undergoing revascularization, a longitudinal strain-rate increment of  $>0.25/s$  at low-dose dobutamine predicted functional recovery after revascularization with sensitivity of 80% and specificity of 75%.<sup>[93]</sup> This diagnostic accuracy was superior to that of wall motion analysis alone. In another study, an increase in systolic strain rate value  $>0.23/s$  or increase in early diastolic strain rate  $>0.8/s$  predicted viability in akinetic segments with a sensitivity of 83% and specificity of 84%.<sup>[94-96]</sup> STE-based strain analysis has also been evaluated for the assessment of viability but it had sufficient accuracy only in anterior circulation and not in the posterior circulation.<sup>[97]</sup>

### **Clinical algorithm for myocardial viability assessment**

Using multiple imaging modalities to assess viability in a single patient is not a cost-effective approach. Such a practice invariably leads to more confusion in clinical decision-making due to discordant results. Therefore, in patients with ischemic dilated cardiomyopathy, myocardial viability assessment should follow a systematic algorithm.<sup>[81]</sup> The first step is to accurately measure EDWT of the akinetic segment on echocardiography. Contrast LVO may help in improving the accuracy of EDWT measurement. In case of poor acoustic window, cardiac MRI may also be used. A preserved segment with EDWT  $>5$ – $6$  mm suggests  $>50\%$  probability of recovery while a thinned out segment with EDWT  $<5$  mm indicates  $<5\%$  probability of recovery.<sup>[81]</sup> In the presence of preserved wall thickness ( $>5$ – $6$  mm), either LDDE or thallium scintigraphy is sufficient to establish viability. However, in the presence of EDWT of  $<5$  mm, more downstream investigations are required. If LDDE results are negative or equivocal in segments with EDWT  $<6$  mm, a combination of LDDE and late gadolinium enhancement on MRI or LDDE with FDG-PET is required for further assessment.

### **Clinical relevance of myocardial viability assessment**

The role of myocardial viability assessment in clinical practice is currently quite controversial. A large number of studies, mostly single center and small, have demonstrated clear benefit of revascularization in patients with evidence of viable myocardium. However, most of these studies were limited by retrospective and nonrandomized nature and wide heterogeneity in the patient populations studied and the modalities used for viability testing. In contrast, the large STICH (Surgical Treatment of IsChemic Heart Failure) trial failed to demonstrate any significant interaction between myocardial viability and medical versus surgical treatment outcome, whether assessed according to treatment assigned

(intention-to-treat) or to the treatment actually received.<sup>[98]</sup> Unfortunately, this trial itself had several limitations because of which no definite conclusions can be drawn about the value of viability assessment in clinical decision-making.

However, what is well understood now is that the traditional practice of defining myocardial viability in a dichotomous manner as presence or absence of functional recovery after revascularization is too simplistic, considering the complex pathophysiology of chronic ischemic myocardium. Myocardial segments with viable myocytes but with no contractile reserve may still benefit after revascularization through prevention of re-infarction, reduced risk of arrhythmias, LV remodeling because of intact epicardial layer, and improvement in LV diastolic function.

In these circumstances, the practical role of myocardial viability assessment may be envisaged in the following clinical situations: (1) Decision about the need to perform PCI of infarct-related artery in stable acute MI patients presenting more than 24 h after of symptom onset, (2) deciding about CABG in patients with severe triple-vessel CAD and severe heart failure who are at high risk of perioperative mortality due to comorbidities, (3) to choose PCI over CABG in a patient with multivessel CAD when the left anterior descending artery territory is infarcted and surgical risk appears to be high, and (4) for identifying culprit vessel responsible for angina, for partial revascularization by PCI, in patients of multivessel CAD with multiple myocardial infarcts.

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Nil.

### **Conflicts of interest**

There are no conflicts of interest.

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## APPENDICES

### Appendix 1a: Template for consent form for stress echocardiography

#### NON-INVASIVE CARDIOLOGY LABORATORY

#### CONSENT FORM

Patient name: \_\_\_\_\_ MR/IP No.:

I, \_\_\_\_\_ resident of \_\_\_\_\_

(A) Do hereby consent to undergo or (B) Subject my son / daughter / husband /wife / mother /father named \_\_\_\_\_

to undergo \_\_\_\_\_ procedure / investigation advised by Dr. \_\_\_\_\_ and performed by Dr. \_\_\_\_\_.

In order to evaluate the ability of my heart to respond to exercise/ pharmacological stress, I voluntarily agree to undergo an exercise stress test/ pharmacological stress e/ contrast Echo/ contrast stress echo.

I understand that the test, like all other procedure in a hospital, may involve an extremely remote possibility of cardiac arrest and also that the test may in very rare cases cause symptoms such as abnormal heart rhythm, fainting, heart attack, chest pain or headache, flushing, nausea, asthma attack, IV site bleeding, contrast adverse reaction, orthopedic injury.

However, this test will be conducted by trained expert(s) in a careful manner and will be discontinued well in advance if any significant abnormality is observed.

I have been explained all the risks and benefits involved in this investigation / procedure in a language that is understood by me.

I have read the above and give my consent to proceed with the test and will not hold the hospital or personnel involved responsible if untoward events or injury result.

Patient Details		Relative Detail		Witness Detail	
Name		Name		Name	
Sign		Sign		Sign	
Date Time		Date Time		Date Time	
NA	NA	Relation		NA	NA

Consultant Name and signature: \_\_\_\_\_

## Appendix 1b: Template for reporting findings form stress echocardiography

### EXERCISE STRESS ECHOCARDIOGRAPHY REPORT

**NAME:**

**AGE:**

**SEX:**

**LAB NO:**

**ID NO:**

**DATE:**

**INDICATION:**

**Max Predicted Heart Rate (MPHR):**

**85% MPHR (Target HR):**

#### PROCEDURE:

**Protocol:**

**Duration:**

**End point:**

**Heart Rate Achieved:** \_\_\_\_\_ bpm (\_\_\_\_% of MPHR) **METs achieved:**

Stage	Time (min)	Heart rate (bpm)	B.P (mmHg)	Symptoms
Supine	0.00			Nil
Standing	0.00			Nil
Stage I				Nil
Stage II				Nil
Stage III				Nil
Stage IV				Nil
Stage V				Nil
Recovery				Nil

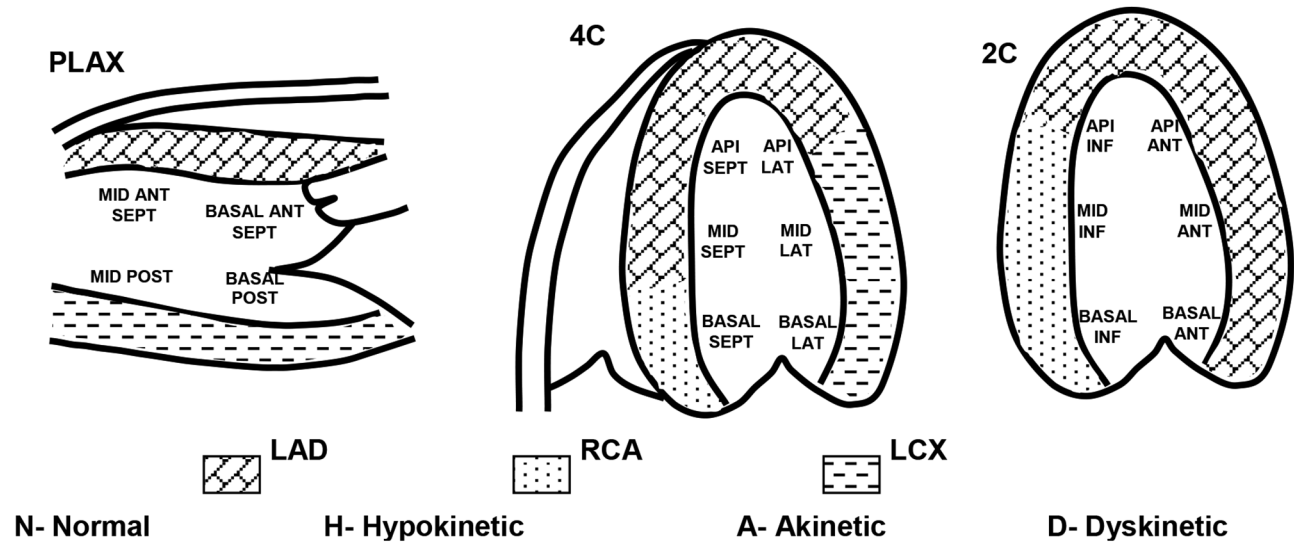
#### ECG FINDINGS:

Stage	ST-T Changes	Arrhythmia
Baseline	No significant ST-T Changes	
Standing	No significant ST-T Changes	Nil
Exercise	No significant ST-T Changes	Nil
Recovery	No significant ST-T Changes	Nil



ECHOCARDIOGRAPHIC FINDINGS:

Wall motion analysis:



LV segment	Rest	Immediate post-exercise	Interpretation
<b>PLAX</b>			
Basal ant septum	N	N	Normal
Mid ant septum	N	N	Normal
Basal posterior	N	N	Normal
Mid posterior	N	N	Normal
<b>Apical 4-chamber</b>			
Basal septum	N	A	Normal
Mid septum	N	N	Normal
Apical septum	N	N	Normal
Basal lateral	N	N	Normal
Mid lateral	N	N	Normal
Apical lateral	N	N	Normal
<b>Apical 2-chamber</b>			
Basal inferior	N	A	Normal
Mid inferior	N	A	Normal
Apical inferior	N	N	Normal
Basal anterior	N	N	Normal
Mid anterior	N	N	Normal
Apical anterior	N	N	Normal

### Other findings:

Parameter	Rest	Immediate post-exercise
LV end-diastolic volume (ml)		
LV end-systolic volume (ml)		
LV ejection fraction (%)		
Mitral inflow E/A vel (cm/s)		
Mitral annular E' vel (cm/s)		
Estimated LVEDP (mmHg)		
Mitral regurgitation		
Tricuspid regurgitation		
Estimated RVSP (mmHg)		

### **SUMMARY & INTERPRETATION:**

1. Normal exercise capacity.
2. No chest pain or ECG changes during the stress test.
3. Normal heart rate and blood pressure response.
4. Normal LV systolic function at rest. No inducible wall motion abnormality.

### **FINAL IMPRESSION:**

Stress echocardiography is negative for inducible myocardial ischemia.



**DOBUTAMINE STRESS ECHOCARDIOGRAPHY REPORT****NAME:****AGE:****SEX:****LAB NO:****ID NO:****DATE:****INDICATION:****Max Predicted Heart Rate (MPHR):****85% MPHR (Target HR):****PROCEDURE:**

Dobutamine infusion was administered intravenously at a starting dose of 5 µg/kg/min and incremental doses of 5, 10, 20, 30 and 40 µg/kg/min were administered at 3 min intervals. Atropine injection (\_\_\_\_mg) was given intravenously in 0.3 mg boluses to achieve the desired heart rate.

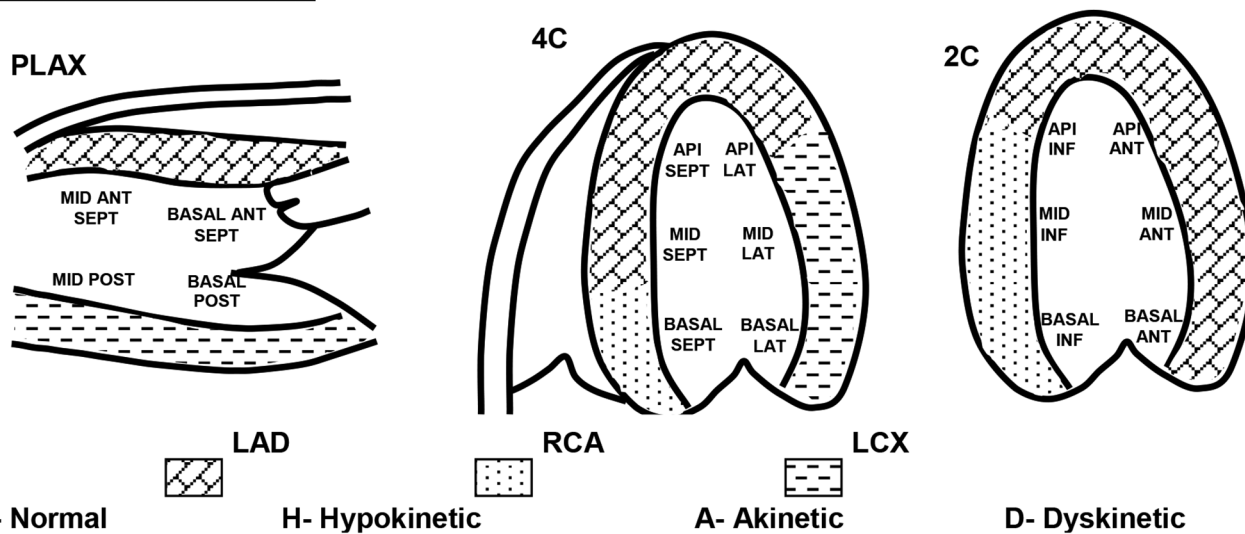
	<b>Time (min)</b>	<b>Heart Rate (BPM)</b>	<b>B.P (mmHg)</b>	<b>Symptoms</b>
Baseline	0.00			Nil
Stage I (5µg/kg/min)	3.00			Nil
Stage II (10µg/kg/min)	3.00			Nil
Stage III (20µg/kg/min)	3.00			Nil
Stage IV (30µg/kg/min)	3.00			Nil
Stage V (40µg/kg/min)	3.00			Nil
Recovery				Nil

**End point:** \_\_\_\_\_**Heart Rate Achieved:** \_\_\_\_\_ bpm ( \_\_\_\_\_ % of MPHR)**ECG FINDINGS:**

	<b>ST-T Changes</b>	<b>Arrhythmia</b>
Baseline	No significant ST-T Changes	Nil
Dobutamine infusion	No significant ST-T Changes	Nil
Recovery	No significant ST-T Changes	Nil

## **ECHOCARDIOGRAPHIC FINDINGS:**

### **Wall motion analysis:**



LV segment	Rest	Low-dose	Peak-dose	Interpretation
<b>PLAX</b>				
Basal ant septum	N	N	N	Normal
Mid ant septum	A	H	A	Viable, ischemic
Basal posterior	N	N	N	Normal
Mid posterior	N	N	N	Normal
<b>Apical 4-chamber</b>				
Basal septum	N	N	N	Normal
Mid septum	A	H	A	Viable, ischemic
Apical septum	A	A	A	Non-viable
Basal lateral	N	N	N	Normal
Mid lateral	N	N	N	Normal
Apical lateral	A	A	A	Non-viable
<b>Apical 2-chamber</b>				
Basal inferior	N	N	N	Normal
Mid inferior	N	N	N	Normal
Apical inferior	A	A	A	Non-viable
Basal anterior	N	N	N	Normal
Mid anterior	A	H	Mild H	Viable, non-ischemic
Apical anterior	A	A	A	Non-viable

### Other findings:

Parameter	Rest	Peak-dose
LV end-diastolic volume (ml)		
LV end-systolic volume (ml)		
LV ejection fraction (%)		
Mitral inflow E/A vel (cm/s)		
Mitral annular E' vel (cm/s)		
Estimated LVEDP (mmHg)		
Mitral regurgitation		
Tricuspid regurgitation		
Estimated RVSP (mmHg)		

### **SUMMARY & INTERPRETATION:**

1. No chest pain or ECG changes during the stress test.
2. Normal hemodynamics.
3. Akinetic apex at baseline, low-dose and peak-dose dobutamine.
4. Akinetic mid anterior septum and mid inferoseptum that improve at low-dose but worsen at peak dose dobutamine.
5. Akinetic mid anterior wall but shows sustained improvement at low- and peak-dose dobutamine.

### **FINAL IMPRESSION:**

Dobutamine stress echocardiogram shows evidence of LAD territory infarct with non-viable apex and areas of viability with or without ischemia in adjacent segments.