VALUE OF ADDING CONTINUOUS ECG MONITORING TO STRESS ECHOCARDIOGRAPHY TEST IN MYOCARDIAL ISCHEMIA

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Abstract:
Dobutamine stress echocardiography (DSE) continues to be widely and successfully applied to determine whether patients with and without known cardiac disease have ischemia. Dobutamine stress echocardiography (DSE) has bitfalls in intermediate patients for CAD which are poor echo windows with low specificity and sensitivity. Also, Exercise ECG has bitfalls including limitations of use and artifacts. So, we hypothesize that adding ECG recorded during dobutamine stress echo will improve specificity and sensitivity for diagnosis of stress induced ischemia in intermediate probability for CAD and will overcome bitfalls of exercise ECG (limitations and artifacts) and bitfalls of dobutamine stress echo (poor echo window).

Keywords: ECG, Stress Echocardiography Myocardial Ischemia.

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Introduction:

Coronary artery disease (CAD) is the largest cause of disease burden globally, both in terms of mortality and morbidity **(1)**.

Myocardial ischemia results in a typical 'cascade' of events in which the various markers are hierarchically ranked in a well-defined time sequence **(2)**. Flow heterogeneity, especially between the subendocardial and subepicardial perfusion, is the forerunner of ischemia, followed by metabolic changes, alteration in regional mechanical function, and only at a later stage by electrocardiographic changes, and pain **(3)**.

The pathophysiological concept of the ischemic cascade is translated clinically into a gradient of sensitivity of different available clinical markers of ischemia, with chest pain being the least and regional malperfusion the most sensitive **(4)**.

Timely diagnosis via exercise testing may enable efficient use of health resources when compared with interventions such as coronary angiography which are more expensive and more invasive. Exercise stress testing offers a non-invasive, less expensive way of risk stratification prior to coronary angiography, and a negative stress test may actually avoid angiography. Exercise stress testing has been used to assess risk of CAD for over 60 years **(5)**.

There have been successive guidelines regarding the value of exercise testing and how it should be administered, but concern and confusion exist **(6)**. For instance, a recent guideline from the National Institute for Health and Clinical Excellence (NICE) states, ''Do not use exercise ECG to diagnose or exclude stable angina for people without known CAD'', and yet exercise ECG testing is still commonly used in this clinical setting **(7)**.

Stress echocardiography has emerged as a sophisticated and sensitive noninvasive method for the detection of coronary artery disease and a cost-effective alternative to myocardial scintigraphy **(8)**. However, it is known that exercise ECG has only a limited sensitivity, especially in patients with 1-vessel disease. Temporary disturbance of wall motion is an earlier and more sensitive marker of myocardial ischemia than chest pain and ST-T changes **(9)**.

Individually, both physical and pharmacological stress echocardiography have shown high diagnostic accuracy for the diagnosis of CAD **(10)**.

Furthermore, dobutamine stress echocardiography (DSE) have been proposed as alternatives to exercise testing in patients who are unable to exercise. DSE is a well-established imaging modality in the detection of CAD on the basis of regional wall motion abnormalities induced by myocardial ischemia. Numerous studies have shown the high accuracy and prognostic value of DSE for obstructive CAD **(11, 12)**.

The diagnosis of CAD in women remains a challenge for clinicians. The high specificity and positive predictive value of stress echocardiography have raised the question whether dobutamine test could solve the gender limitations of noninvasive techniques. It has been demonstrated to be a safe and useful method for detecting CAD **(13, 14)**. However, results were obtained in studies in which patient populations were predominantly men, who have a higher prevalence of CAD than women; in addition, scant information is available in women **(15, 16)**.

Studies have reported on heterogeneous populations since patients with previous myocardial infarction or known CAD had been included **(17, 18)**. The value of adding ECG recorded during dobutamine stress echo in diagnosis of stress induced ischemia in intermediate probability CAD was assessed for the first time in **Rollán et al.** study **(19)**.

Interpretation of ECG changes during stress test:

Electrocardiographic data: Although not the only data that should be examined, electrocardiographic changes garner the most attention in test interpretation. The portion of the electrocardiogram (ECG) most sensitive to ischemia is the ST-segment. The pathophysiologic mechanism of the ST-change is net depression caused by a current of ischemia from the affected myocardial cells. The TP-segment may be useful at rest and should be used when possible; however, it shortens or disappears with exercise. Baseline electrocardiographic abnormalities that can obscure the correct diagnosis of ST-changes are listed in Table below **(20).**

Table (1): Baseline ECG abnormalities that may obscure ECG changes during stress test

Left bundle branch block
Left ventricular hypertrophy with repolarization abnormality
Digitalis therapy
Ventricular paced rhythm
Wolff–Parkinson–White syndrome
ST abnormality associated with supraventricular tachycardia or atrial fibrillation
ST-abnormalities with mitral valve prolapse and severe anemia

ST segment depressions during exercise stress test:

The myocardial ischemia that can be provoked by exercise is located to the subendocardium of the left ventricle. As discussed previously (refer to ST segment depression in ischemia), subendocardial ischemia redirects the ST vector such that it becomes directed from the epicardium to the endocardium, which means that the ST vector will be directed towards the back. Hence, the ST vector is directed away from all chest leads (V1, V2, V3, V4, V5, V6). Chest leads that detect this ST vector will display ST segment depressions (because the ST vector heads away from these leads). However, leads with ST segment depressions do not necessarily reflect the ischemic area; e.g. ST segment depressions in leads V3 and V4 do not necessarily imply that the ischemia is located anteriorly.

The T-wave vector may similarly be directed towards the back which yields a negative T-wave (T-wave inversion). However, the primary ECG manifestation of myocardial ischemia (during exercise) is the ST segment depression and not the T-wave inversion. Myocardial ischemia does not manifest only with T-wave inversions during exercise; if there are T-wave inversions during ischemia, there will always be ST segment depressions as well. The ST segment, on the other hand, may be depressed (during ischemia) without simultaneous T-wave inversion. In summary:

- ST segment depression is the hallmark of myocardial ischemia (during exercise) on the ECG.
- ST segment depression may be isolated or accompanied by T-wave inversions (negative T-waves).
- T-wave inversion (negative T-waves) never appear without simultaneous ST depression in patients with myocardial ischemia. **(21)**

Figure 1 illustrates how subendocardial ischemia generates ST vectors that lead to ST depression and inverted T-waves.

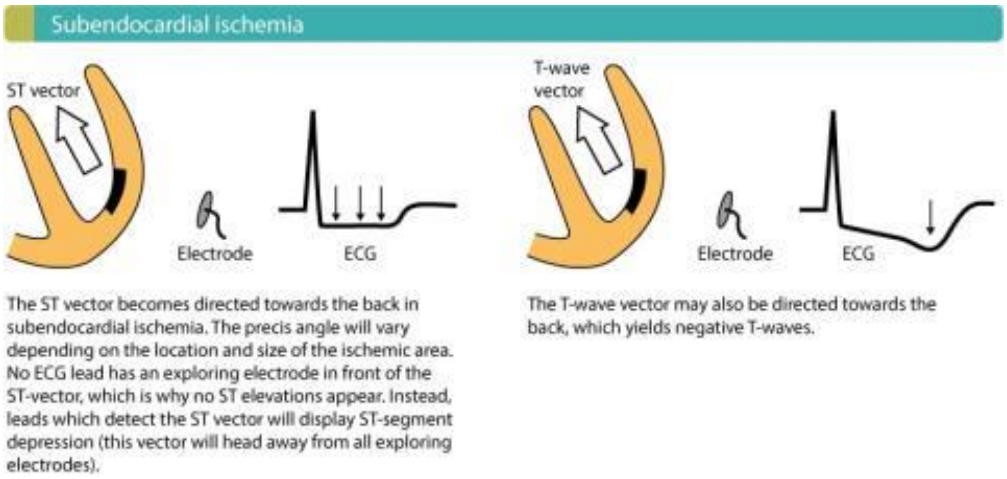

Figure (1): Exercise causes subendocardial ischemia and thus ST segment depression on the ECG.

Measuring ST depression: J point, J 60 point & J 80 point

ST segment depression is measured anywhere between the J-60 point and J-80 point. The J-60 point and J-80 point are located 60 ms and 80 ms, respectively, after the J point. As usual, the PR segment is the reference (baseline) level. The magnitude of the ST depression is simply the difference (in millimeters) between the PR segment and the J-60/J-80 point.

Study **Figure 2** (below) carefully, as it illustrates the J point, J 60 point, J 80 point and the baseline to which these points are compared.

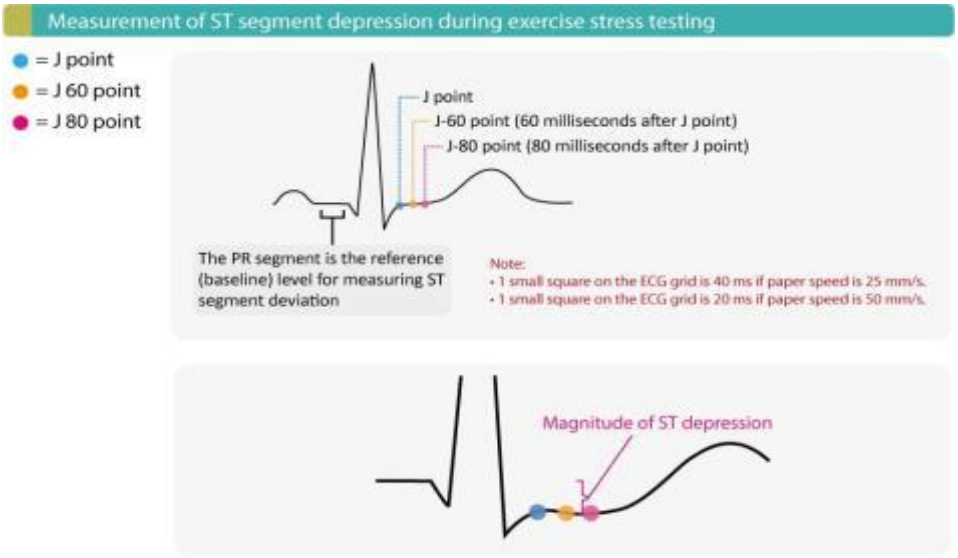

Figure (2**):** Measurement of ST segment depression during exercise stress testing (**20**)

Types of ST segment depressions:

ST segment depressions may be characterized as (1) J point depressions, (2) ups loping ST depressions, (3) horizontal ST depressions or (4) down sloping ST depressions. Myocardial ischemia causes ST segment depressions with horizontal or down sloping ST segment. The depression should be 1 mm or more in the J-60 point or J-80 point (or anywhere between). 1 mm ST depression provides a sensitivity of 70% and specificity of 80% for coronary artery disease. The deeper the ST depression, the greater sensitivity and specificity.

- **Myocardial ischemia is diagnosed if there is ≥1 mm horizontal or down sloping ST depression in J-60/J-80 point (or between J-60 and J-80).**

The typical ischemic ST depression is illustrated in **Figure 3**, below.

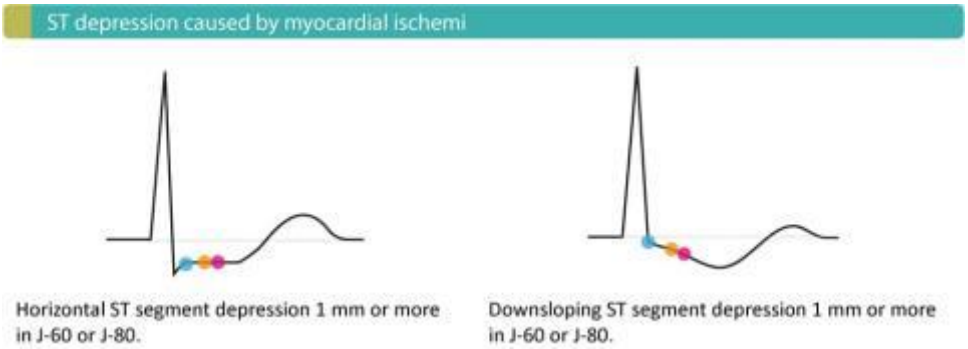

Figure (3): ST segment depressions that are typical of ongoing myocardial ischemia.

Non-ischemic ST segment depressions

Approximately 20% of healthy individuals exhibit upsloping ST depressions during exercise stress testing. Upsloping ST depressions are thus very common during exercise and they are not typical of myocardial ischemia. If only the J point is depressed (**Figure 3**, left panel), then it is referred to as **J point depression**. J point depression is normal during exercise and it is not a diagnostic problem because there is no actual ST depression. In summary, J point depression is not caused by ischemia.

The right panel of shows an upsloping ST depression with depressed J-60 point and J-80 point. Such ST depressions are also common during exercise and situations with tachycardia. These ST depression do, however, cause differential diagnostic problems, because in a minority of cases they are caused by ischemia. The following characteristics suggest that upsloping ST depressions may be of ischemic origin:

- If the ST depression is very pronounced (≥1.5 mm)
- The smaller the inclination of the slope, the more likely is ischemia.
  - The steeper the slope the less likely is ischemia.
  - The more horizontal the slope the more likely is ischemia.
- If the ST depression appears at low workload then ischemia should be considered.

Nevertheless, in the majority of cases, the upsloping ST depressions are not caused by ischemia. Non-ischemic ST depressions are illustrated in Figure 4, below.

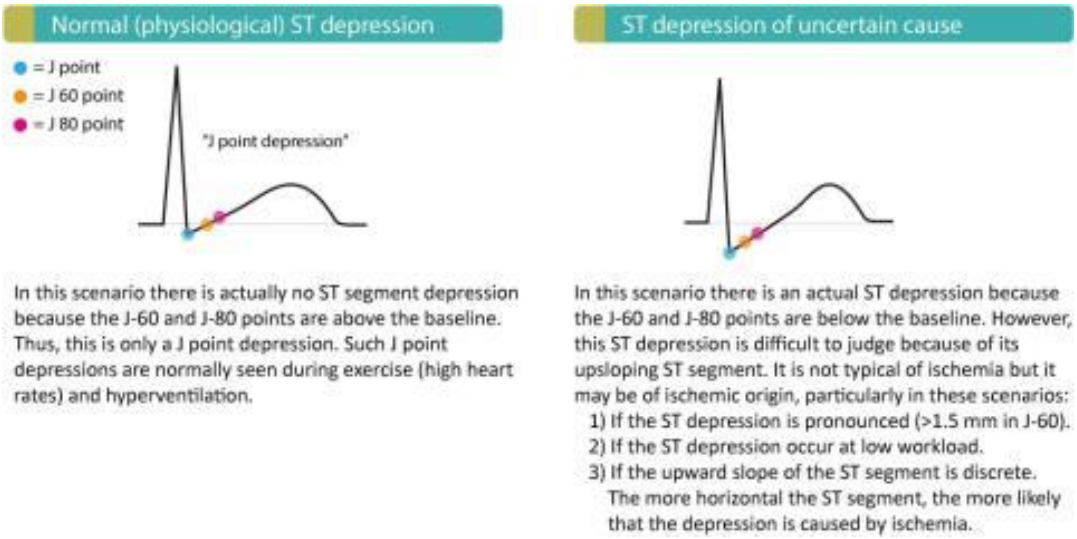

Figure (4): ST segment depressions not typical of myocardial ischemia. **(22)**

ECG leads to detect ischemia:

ECG leads V4, V5 and V6 are the best leads to detect ischemia during exercise. These leads have the highest sensitivity for myocardial ischemia, which means that the probability of detecting ischemia is highest in these leads. The limb leads are less sensitive in terms of detecting ischemia. However, ST segment depressions in lead -aVR suggest severe myocardial ischemia (multivessel disease or left main disease).

If ST segment depressions occur early in the test, or if ST depressions are pronounced, or if ST depressions occur in many ECG leads, then there is probably extensive myocardial ischemia. The probability of multivessel disease increases with the number of leads showing ST segment depressions. Moreover, ST depressions with long duration during the recovery period also suggest more severe coronary artery disease.

Note that some patients only display ST depressions during the recovery period. This is explained by the fact that myocardial workload increases once the patient is placed in supine position (the preload of the heart increases because of increased venous return in supine position).

Figure 5 (below) illustrates the ECG reaction of a male with coronary artery disease.

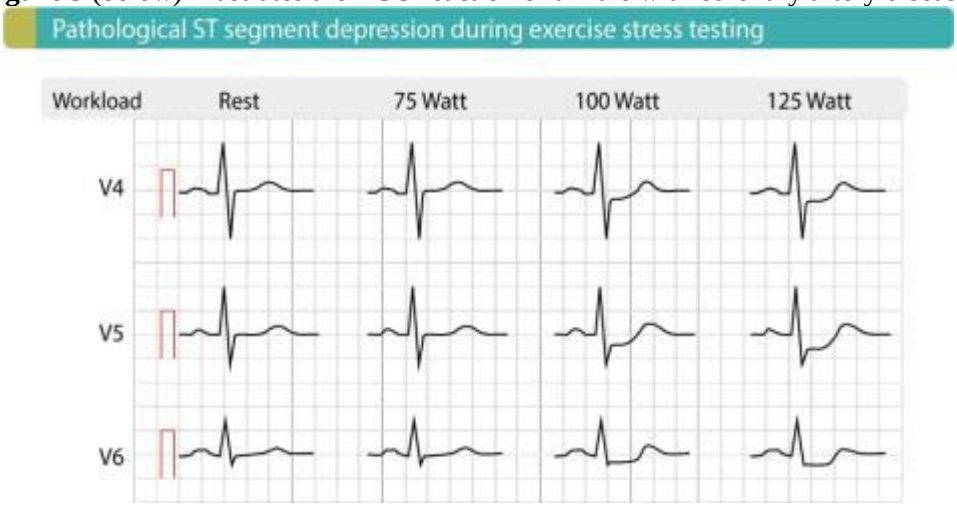

Figure (5**):** Exercise ECG in patient with coronary artery disease shows significant ST depressions in J-60 point, J-80 point. These depressions become more pronounced as workload increases. This test was performed on bicycle**(20).**

To distinguish normal (physiological) ST depressions from ischemic ST depressions, the following rules are suggested:

1. Normal (physiological) upsloping ST depressions only occur at high heart rates. Upsloping ST depressions due to ischemia occur already at low heart rates.
2. Normal (physiological) upsloping ST depressions are rapidly normalized during the recovery period. Upsloping ST depressions due to ischemia are slow to normalize during the recovery period.
3. Normal (physiological) upsloping ST depressions have a steeper slope than ischemic ST depressions.
4. Normal (physiological) upsloping ST depressions rarely exceed 1.5 mm.

Patients with ST depressions on resting ECG:

In patients with ST segment depressions on resting ECG (e.g., due to left ventricular hypertrophy), the ST depression is measured from the initial level (at rest) of the J-60/J-80 point (and not from the level of the PR segment). Moreover, if there are ST depressions at rest, additional ST depression induced by exercise will not be as specific to ischemia as is otherwise the case (unless the depressions are very pronounced).

Atrial repolarization may mimic ST depressions:

Atrial repolarization occurs simultaneously with ventricular depolarization (QRS complex), which generates stronger electrical potentials and therefore conceals atrial repolarization. Occasionally during exercise, atrial repolarization may become visible and create a negative wave just after the QRS complex. This may imitate an ST segment depression, particularly in the inferior leads.

Judging ST depression in relation to heart rate: frequency adjusted ST depressions:

Some experts emphasize that heart rate must be taken into consideration when judging ST segment depressions. Taking heart rate into account may actually facilitate differentiating normal (physiological) ST segment depressions from ischemic ST segment depressions. The rationale for this is as follows:

1. Healthy individuals often achieve high heart rates which may induce normal (physiological) ST depressions (typically with an upsloping ST segment) that are not caused by ischemia. Approximately 20% of healthy subjects display ST depressions during exercise testing.

2. Patients with coronary artery disease frequently fail to achieve sufficient workload (heart rate) to provoke myocardial ischemia. The ST depressions may not reach the criteria of 1 mm because of insufficient workload. **(21)**

Thus, adjusting the magnitude of the ST depression to the heart rate may be a reasonable approach. ST depressions occurring at high heart rates are given less significance, while ST depressions occurring at low heart rates are given more significance. The adjustment can be made by either the **ST/HR index** or **ST-HR slope**.

The ST/HR index:

The magnitude of the ST depression (in mV, where 0.1 mV=1mm) is divided by the heart rate increase during the test. An example follows:

- Maximal ST depression during the test is 2 mm, which equals 0.2 mV.
- The heart rate increased from 70/min (at rest) to 170/min (at maximal workload), which equals an increase of 100/min.
- HR index = 0.2 / 100 = 0.002 mV/beat/minute
- An HR index above 0.0016 mV/beat/minute suggest myocardial ischemia.

ST-HR slope

This parameter is calculated automatically in most ECG machines. It is the slope of the linear association between the heart rate and the amplitude of the ST depression. An ST-HR slope greater than 2.4 mV/beat/minute is significant.

ST segment elevation during exercise stress test

ST segment elevation during exercise stress testing is measured in the J-60 point (whereas ST elevation is measured in the J-point on the resting ECG). In patients with ST elevations on the resting ECG (e.g. male pattern, early repolarization, left ventricular hypertrophy etc…), any additional ST elevation induced by exercise is measured from the initial level of the J-60 point (and not the level of the PR segment).

The implication of ST elevations during exercise depends on whether they occur in leads with or without pathological Q-waves.

ST elevation in leads without pathological Q-waves

ST elevations in leads without pathological Q-waves are rare during exercise stress testing. Such ST elevations indicate transmural ischemia, i.e., ischemia that affects the entire thickness (from endocardium to epicardium) of a myocardial region. This type of ischemia requires a (more or

less) complete obstruction of blood flow, which may be explained by the following:

- Acute coronary syndrome (rupture of an atherosclerotic plaque) emerging during the test. The thrombosis caused by plaque rupture may occlude the artery completely.
- Presence of a severe and proximal stenosis (>90% luminal obstruction).
- Coronary artery vasospasm.

Importantly, the stress test must be terminated if ST segment elevations occur in leads without pathological Q-waves.

ST elevations in leads with pathological Q-waves (previous myocardial infarction)

ST elevations may occur in leads with pathological (infarction) Q-waves. Such ST elevations may be caused by the following conditions:

- Residual ischemia in the infarct area
- Left ventricular aneurysm
- Wall motion abnormalities

Reciprocal ST depression may be evident in each of these cases. If transmural ischemia cannot be ruled out, then the test must be terminated.

Psuedonormalization of ST-T changes

ST depressions and T-wave inversions that are present during rest but disappear during exercise indicate an abnormal reaction. If the patient has a high pre-test probability, this should lead to suspicion of myocardial ischemia.

Other morphological ECG changes:

- The PR interval and QRS duration are shortened during exercise (normal reaction).
- Septal q-waves in leads I, aVL, V5, V6 may be accentuated during exercise (normal reaction).
- The R-wave amplitude may decrease during exercise (normal reaction).
- T-wave amplitude may decrease or increase (during heavy workload) during exercise, both of which are normal reactions.
- QT duration is shortened by exercise (normal reaction).
- If U-waves are evident on resting ECG and become inverted during exercise, it suggests myocardial ischemia **(22).**

Arrhythmias occurring during exercise stress testing:

Supraventricular and ventricular arrhythmias may occur during exercise. This is more common in persons taking digoxin (digitalis) and those with coffee or alcohol in their blood. The subendocardial ischemia induced by exercise rarely induces any serious arrhythmias. In fact, exercise may actually suppress arrhythmias that are present at rest. For example, ectopic atrial arrhythmias may be suppressed when the sinoatrial node accelerates its discharge frequency; ventricular extrasystoles (premature beats) may also be suppressed during exercise. This has no prognostic implication.

Sinus arrhythmia and sinus bradycardia may occur during or after exercise. Atrial fibrillation and atrial flutter occur in 0.1% of all tests.

The only exercise-induced arrhythmia that is related to coronary artery disease is ventricular tachycardia (VT). Ventricular extrasystoles are common during exercise and they have no prognostic implication (ventricular extrasystoles are harmless unless there is electrical instability in the ventricles).

Conduction defects (disturbances) during exercise stress testing:

Bundle branch block and fascicular block may occur during exercise. Left bundle branch block (LBBB) indicates underlying heart disease, particularly ischemic heart disease. Right bundle branch block (RBBB) may also occur, even in healthy individuals and it is not considered a sign of heart disease.

Atrioventricular (AV) block is uncommon during exercise, with the exception of first-degree AV block which is frequently seen during the recovery period (return of Vagal activity). Any degree of AV block during exercise and high-degree AV block (second-degree AV block or third-degree AV block) in the recovery period suggest ischemic heart disease.

The recovery period

Occasionally, ST segment depressions are only seen during the recovery period (the preload of the heart increases in supine position). The duration of the recovery period is 6 to 8 minutes, during which the patient must be monitored. The test is completed when all parameters have returned to their baseline values. **(23)**

Overview of Stress Echocardiography

Introduction:

Stress echocardiography combines two-dimensional echocardiography with a physical, pharmacological, or less commonly, electrical stress with atrial pacing **(24).**

Stress-induced ischemia generates new or worsening wall motion abnormalities in the

segment supplied by the stenosed coronary artery **(25).**

Stress echocardiography plays an important role in identifying these wall motion abnormalities in the assessment of ischemic heart disease, and also plays a vital role in the evaluation of systolic or diastolic heart failure, valvular pathologies, non-ischemic cardiomyopathy, pulmonary hypertension, and congenital heart disease**(10).**

In this chapter we discuss only stress echocardiography in ischemic cardiac diseases as its use in non-ischemic cardiac diseases is out of this study scope. Also we will not discuss exercise protocols as our study focuses on dobutamine stress echocardiography.

Pathophysiology

A. Exercise stress testing:

Myocardial ischemia results from a mismatch between oxygen supply and demand. Echocardiography detects ischemia by identifying new or worsening WMAs earlier in the cascade than is detected by the electrocardiogram (ECG) or the onset of symptoms but usually after the onset of worsening diastolic function. Exercise can be performed with a treadmill or a bicycle**(26).**

B. Pharmacologic stress testing:

In patients who cannot exercise, pharmacologic stressors can be used. These drugs are sympathomimetic agents or vasodilators.

1. Sympathomimetic agents: Myocardial oxygen demand is determined by contractility (inotropy), heart rate (chronotropy), and wall stress (preload + afterload). Sympathomimetic agents produce stress by causing an increase in myocardial oxygen demand through increased inotropy, chronotropy, and blood pressure (BP) (afterload). Although a number of agents have been evaluated in combination with echocardiography, dobutamine is most widely used. Low-dose dobutamine has positive inotropic effects mediated through cardiac α1- and β1-receptors. At higher doses, it has positive chronotropic effects mediated through β2-receptors. The plasma half-life of dobutamine is 2 to 3 minutes. The normal response to dobutamine is an increase in heart rate and hyperdynamic wall motion, with only minimal effect on end-diastolic LV volume. It can be combined with atropine to achieve the usual target of at least 85% of age-predicted maximum heart rate (APMHR).
2. A vasodilator stress test is performed with dipyridamole or adenosine infusion. These agents result in perfusion abnormalities by causing blood to be preferentially shunted away from myocardial segments supplied by stenotic coronary arteries (i.e., coronary steal) and into more normal coronary vessels. This may lead to WMA in the perfusion territory of the stenotic coronary artery that is seen on echocardiography. These agents are less commonly used for SE. Adenosine has fewer side effects than dipyridamole, owing to a shorter half-life. However, because of the shorter duration of action of adenosine, the echocardiographic findings tend to be less pronounced and of shorter duration, resulting in a lower sensitivity **(27).**

C. Atrial pacing:

Tachycardia induced by atrial pacing is an alternative to pharmacologic testing in patients that cannot exercise and in whom pharmacologic agents are contraindicated. In patients with a permanent pacemaker, stress is achieved by increasing the pacing rate until the target heart rate is reached. Transvenous and transesophageal pacing are options for patients without a permanent pacemaker but are rarely used in practice**(28).**

Indications:

The following list presents the main indications of SEC **(29):**

1) CAD: diagnostic and prognostic (i.e. including preoperative risk assessment, search for ischemia location, myocardial viability)
2) Evaluation of prognosis and severity of valvular heart disease
3) Diastolic stress echocardiography
4) Diagnosis of microvascular CAD
5) Evaluation of non-ischemic dilated cardiomyopathy and hypertrophic cardiomyopathy
6) Evaluation of pulmonary hypertension
7) Evaluation for some patients with suspicious cardiac etiology of exertional dyspnea
8) Evaluation of some patients with congenital heart disease
9) Evaluation of some patients after heart transplantation
10) Evaluation of athletes and subjects submitted to extreme physiology (e.g. diving, high altitude).

Contraindications:
Contraindications to exercise/ pharmacologic stress echocardiography **(30):**

Absolute:
• Acute myocardial infarction within 48 hours
• Acute pericarditis/Myocarditis
• Symptomatic severe aortic stenosis
• Uncontrolled Arrhythmias causing symptoms or instability
• Acute aortic dissection
• High-risk Unstable Angina
• Decompensated or unstable heart failure with left ventricle ejection fraction (LVEF) less than 35%
• Acute pulmonary embolism or pulmonary infarction

Relative:
• Left main coronary artery stenosis
• High degree atrioventricular (AV) block
• Severe hypertension (greater than 180/100mm Hg)
• Electrolyte abnormalities
• Mental or physical disability
• Tachycardia or bradyarrhythmia
• Moderate stenotic valvular heart disease

Specific contraindications to dipyridamole (or adenosine) and dobutamine stress echocardiography include severe conduction abnormalities (high-degree AV block without pacemaker), active bronchospasm, Sick sinus syndrome without a pacemaker, systolic blood pressure less than 90 mmHg, and tachyarrhythmias such as atrial fibrillation.

Methodology:
A. Patient preparation
1. Patients should avoid heavy food intake for several hours before the test.
2. Rate-slowing agents (particularly β-blockers) blunt the normal heart rate response to exercise and may limit the ability of the patient to achieve at least 85% of the APMHR. This may reduce the sensitivity of the test results. If possible, these agents should be withheld before the stress test, unless the aim of the test is to evaluate their effectiveness in preventing exercise-induced ischemia.
3. The standard connections for a 12-lead ECG may be used with minor modifications to allow imaging in the parasternal and apical windows without affecting the accuracy of the exercise electrocardiographic testing results. **(31)**

B. Equipment: All SE studies are conducted with exercise electrocardiographic testing and standard hemodynamic monitoring equipment. An SE software package on the echocardiographic machine is necessary to acquire digital images and to allow side-by-side comparison of prestress images with peak stress or post–peak stress images.
Resuscitation equipment and a defibrillator should be readily available. **(32)**

C. Performing the test
1. Exercise SE: Regardless of the exercise modality, a complete baseline echocardiographic scan is obtained for all patients. Resting images areobtained in the parasternal long- and short-axis and apical two- and four-chamber views and stored digitally. An apical long-axis view may be substituted for a parasternal long-axis view if the parasternal images are suboptimal. If endocardial definition is suboptimal, intravenous ultrasound contrast should be given to optimize the images.
a. Treadmill exercise is performed with standard protocols according to the functional status of the patient. Exercise is continued until at least 85% of the APMHR is reached, but it is preferably continued to the level of maximum exertion to maximize test sensitivity. APMHR equals 220 minus the patient's age. Post–peak stress images are obtained as quickly as possible (in the left lateral decubitus position) after the patient transfers from the treadmill to the imaging table. Stress images in the same views as the baseline study are stored digitally and recorded on videotape. All post–peak stress images should be obtained within 90 seconds of completing exercise to maximize test sensitivity.
b. During upright bicycle echocardiography, baseline images are obtained in the standard left lateral position and are repeated with the patient in the upright position on the cycle ergometer. Adequate parasternal images may be recorded by having the patient lean forward. These images are recorded and digitized to allow comparable windows for the rest and peak stress images. Cycle ergometry is started at a workload of 25 W and increased by 25 to 50 W every 2 to 3 minutes until the patient reaches his or her level of perceived maximal effort. During upright bicycle echocardiography, images are obtained and digitized at rest, before peak, at peak, and after peak exercise.
c. With supine bicycle exercise, the entire study is performed while the patient is tilted 30° in the left lateral decubitus position, and images are

obtained and digitized at rest, before peak, at peak, and after exercise. This exercise modality is not widely used.

d. Study end points for exercise SE include target heart rate (85% APMHR), severe electrocardiographic ischemia (ST-segment depression > 5 mm), intolerable symptoms (chest pain and dyspnea), severe hypertension (systolic BP > 220 mm Hg or diastolic BP > 110 mm Hg), hypotension (systolic BP < 90 mm Hg or a fall in systolic BP > 20 mm Hg from baseline), ventricular tachycardia or sustained supraventricular tachycardia, and the development of new WMAs in at least two contiguous segments.

2. Pharmacologic SE:

a. Dobutamine SE

1. Dobutamine infusion is started at 10 μg/kg/min and increased every 3 minutes to 20, 30, and 40μg/kg/min. If the patient has not reached 85% of APMHR by the end of the 40 μg/kg/min dose, a 3-minute dosage of 50 μg/kg/min may be used. Infusion is begun at lower doses (5 μg/kg/min) if baseline LV function is abnormal and myocardial viability is being sought or if assessment of valvular lesions is being pursued. Images are digitized at rest and at low dosage (5 to 10μg/kg/min), pre–peak dosage (30 μg/kg/min), and peak dosage.
2. Atropine is used as needed to reach target heart rate >85% of APMHR if dobutamine alone is not effective. Atropine (0.25 to 0.5 mg) is given intravenously every minute, starting at the 40μg/kg/min dobutamine dose level and continuing until an end point is reached or a total dose of 2 mg is given. Atropine should be used with caution in patients that have glaucoma or benign prostatic hypertrophy. Isometric handgrip may be performed at the peak infusion rate to help achieve target heart rate, as well.
3. Study end points for dobutamine SE are the same as those used for exercise SE. If 85% APMHR has been achieved without any other end points, it is preferable to complete the protocol to the end of the 40 μg/kg/min infusion to increase the sensitivity of the test.
4. Side effects. The most serious potential side effect of dobutamine is arrhythmia provocation. However, serious complications (e.g., arrhythmia, MI, and cardiac arrest) are rare, occurring in about 0.3% of studies in a large series of >5,000 patients. Less serious side effects include tremor, nervousness, and marked hypertensive and hypotensive responses. The most common minor complication is hypotension, which usually responds to supportive therapy including intravenous fluids. A hypotensive response with dobutamine may be caused by ischemia and dynamic outflow tract obstruction or may result from the vasodilatory effect of dobutamine in combination with a small hyperdynamic LV and a low stroke volume.
5. If angina or severe side effects develop, the effects of dobutamine may be reversed with intravenous β-blockade (0.5 to 1 mg/kg esmolol given over 1 minute or 2 to 5 mg/kg metoprolol given every 2 to 5 minutes). Like dobutamine, esmolol has a very short half-life and, therefore, may be the preferred agent.

b. Dipyridamole or adenosine SE

1. Patients with hypotension, AV block, or a history of severe bronchospasm should not undergo testing with these agents.
2. Different protocols of dipyridamole infusion have been studied. The protocol recommended by the ASE is a low-dose, two-stage infusion. The first stage begins at 0.56 mg/kg dipyridamole over 4 minutes; if no adverse effect or clinical end points are reached, an additional 0.28 mg/kg is infused over 2 minutes. A high-dose regimen of 0.84 mg/kg given over 10 minutes has been developed to improve the sensitivity of the test relative to low-dose protocols.
3. Adenosine is given as a continuous infusion because of its very short half-life. A typical protocol starts at a low dose of 80 μg/kg/min and is increased every 3 minutes by 30 μg/kg/min to a peak dose of 170 to 200 μg/kg/min.
4. Regadenoson is an adenosine receptor agonist with a 2- to 3-minute half-life, as compared with adenosine's 30-second half-life. Regadenoson is administered as one 0.4-mg dose over 10 seconds.
5. Study end points for dipyridamole or adenosine SE are similar to those used for exercise SE. A notable exception is that patients are not stressed until the APMHR is achieved. Additional end points include third-degree AV block, severe hypotension, and intolerable side effects (e.g., bronchospasm). Symptoms usually start to resolve within 60 seconds after medication administration.
6. If hypotension, bradycardia, or bronchospasm occurs, the effects of dipyridamole, adenosine, and regadenoson can be reversed with

intravenous aminophylline 50 mg over 60 seconds **(28)**

Imaging techniques:

Modern technology allows digital image acquisition of multiple cardiac cycles and side-by-side comparison in a split screen display, enabling easy comparison of regional wall motion at rest and peak stress or after stress. Detailed frame by-frame evaluation of wall thickening or excursion is possible, which helps in the evaluation of regional myocardial function. Obesity and lung disease remain the primary reasons for poor-quality images. Harmonic imaging has improved endocardial definition, which can be further optimized with microbubble contrast agents.

1. Contrast echocardiography: Microbubble contrast agents provide improved echocardiographic resolution and allow real-time assessment of intracardiac blood flow. These agents are helpful when baseline SE images are suboptimal.

a. Intravenous agitated saline improves visualization of the right atrium and ventricle and enables visualization of intracardiac shunts. However, intravenous agitated saline is not able to cross the pulmonary circulation and opacify the left ventricle.
b. Second-generation microbubble contrast agents, such as Optison and Definity incorporate perfluoropropane gas encased in an albumin-based or phospholipid shell, are more durable and are able to cross the pulmonary circulation and opacify the left ventricle.
c. These agents are well tolerated and have a low complication rate. Absolute contraindications to administration include previous hypersensitivity reaction and fixed right-to-left, bidirectional, or transient right-to-left cardiac shunts. Intraarterial injection is contraindicated. Administration is relatively contraindicated in patients who are pregnant or nursing, although data are limited in these populations, and guidelines indicate that contrast should be given if needed. **(22)**

2. Real-time three-dimensional (3D) echocardiography. Significant advances have been made in 3D data acquisition without the need for off-line reconstruction. 3D imaging may shorten the acquisition period of post exercise images or peak exercise images, allowing improved sensitivity and minimizing the technical strains imposed on the technologist obtaining the images. Limitations include lower spatial resolution and lower frame rates; at this time, 3D SE is not routine in clinical use and remains under investigation.

Image Interpretation

A. Qualitative versus quantitative approach

1. Interpretation of SE findings is predominantly qualitative. Visual assessment of LV wall thickening and motion remains the standard method of interpretation of SE but is subject to interobserver and interinstitutional variability. Each myocardial segment is visually assessed for wall thickening, rather than just wall motion, which may be influenced by myocardial tethering and translation. LV wall motion normally becomes hyperdynamic with stress. Worsening of WMAs or the development of new ones is the hallmark of stress induced myocardial ischemia. SE responses and interpretation are summarized in Table below **(32).**

Table (2): Stress echocardiography responses and interpretation **(33)**

Interpretation	Resting or Baseline Function	Response to Low-Dose Pharmacologic Stress	Peak and Poststress Function
Normal	Normal	Normal	Hyperdynamic
Ischemic	Normal	Normal; decreased in severe ischemia (new wall motion abnormality)	Decreased (new wall motion abnormality); LV dilatation (severe ischemia)
Scar	Decreased	Decreased	Decreased
Viable and ischemic (hibernating)	Decreased	Improved	Decreased (biphasic response)
Viable and not ischemic (stunned)	Decreased	Improved	Improved
Nonspecific	Decreased	Decreased	Improved

2. Quantitative methods of analysis improve the reproducibility of interpretation and enhance the detection of CAD, particularly by less experienced physicians. However, at this time, the ASE recommends further validation and simplification of quantitative analysis methods before they can be recommended for routine use. Examples of quantitative analysis methods include Doppler assessment of global systolic and diastolic function; automated endocardial border detection

using integrated backscatter; and tissue Doppler assessment of myocardial displacement, velocity, strain, and strain rate.

a. Tissue Doppler assessment along the long axis using apical views allows quantification of regional longitudinal myocardial function. Tissue Doppler is thought to be a potentially sensitive marker of subendocardial ischemia because abnormalities in regional contraction occur earlier in longitudinal than radial segments.

b. Strain rate is a measure of the speed or velocity of regional myocardial contraction (time from QRS to the onset of regional myocardial relaxation). During dobutamine SE, strain rate increases (interval of time from QRS to myocardial relaxation decreases) in normal hearts and is reduced in areas of myocardial ischemia. The optimal cutoff for strain rate that gives the best sensitivity and specificity has been reported to be an increment of <0.6 per second. Strain rate imaging is a reliable predictor of coronary stenosis, is more specific than visually assessed wall motion scoring, and may allow readers to detect intermediate severity coronary stenosis that produces only subtle WMAs. It may be difficult to acquire technically adequate images at rest and especially at higher heart rates following stress, which limits its applicability. **(26)**

B. 17-Segment model. Regional wall motion is assessed using a 17-segment model, with results geographically represented on a circumferential polar plot.

1.The individual myocardial segments can be assigned to coronary artery territories. Of note, this approach is not always correct because of the anatomic variability. For instance, the left anterior descending coronary artery does not always supply the entire apex and the posterior wall is not always supplied by the left circumflex coronary artery. The system may also be problematic if multivessel disease is present, in which case the territory with the most ischemia is identified and less severe lesions may not be apparent. **(27).**

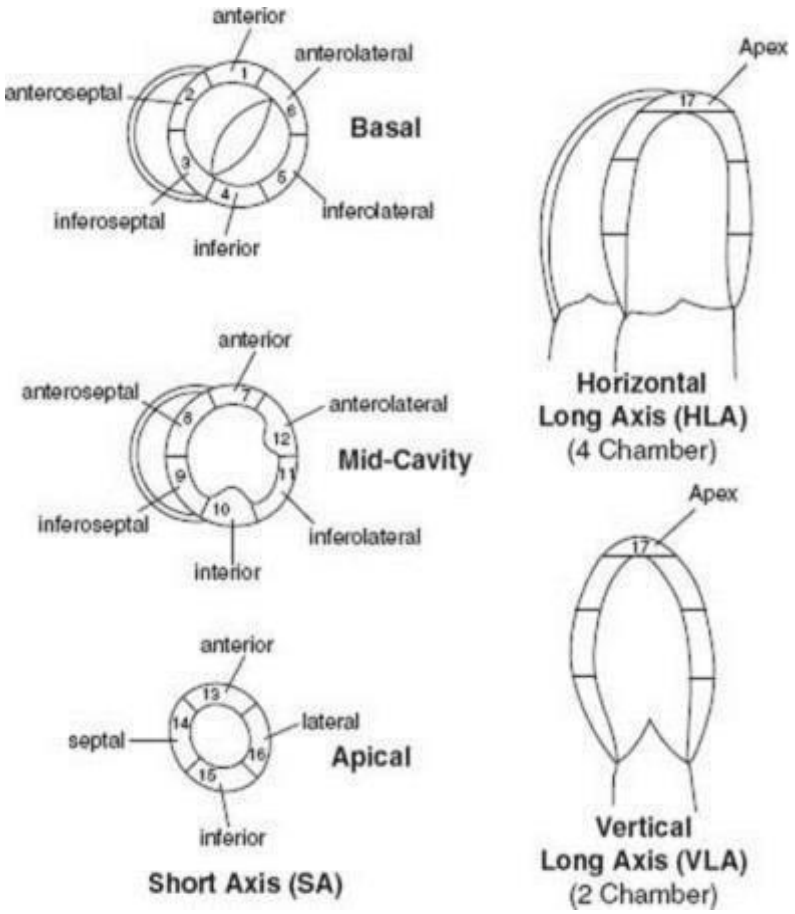

Figure (6): Regional wall segments. This diagram demonstrates how the left ventricle can be divided into standardized segments for cardiac imaging. Short-axis, horizontal long-axis, and vertical long- axis views are depicted **(34).**

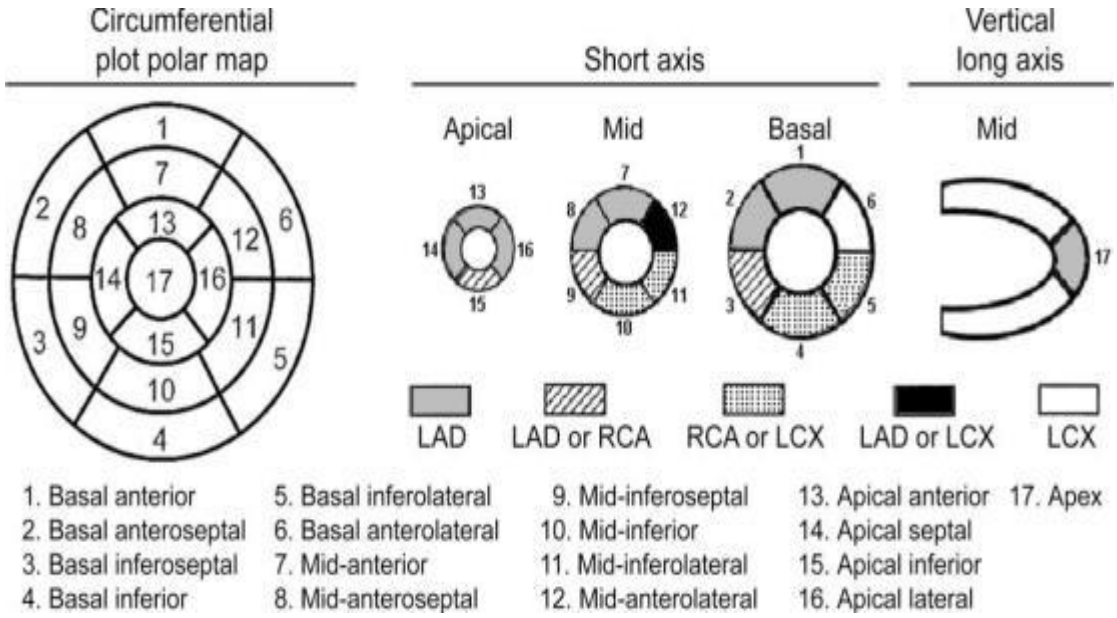

Figure (7): Display on a circumferential polar plot of the 17 myocardial segments and the recommended nomenclature for tomographic imaging of the heart. And assignment of the 17 myocardial segments to coronary artery territories.

2. Wall motion is subjectively graded as normal, mildly hypokinetic, severely hypokinetic, akinetic, or dyskinetic and may be assigned a wall motion score of 1 to 4 (normal, hypokinetic, akinetic, or dyskinetic, respectively). Each myocardial segment in the rest and stress images is graded in this manner.

C. Exercise SE

1. A normal response to exercise stress includes a global increase in contractility, the development of hyperdynamic wall motion, and a gradual rise in the heart rate. This is manifested by increased wall thickness and increased endocardial excursion with stress.
2. Resting WMAs usually indicate prior MI, although regional variability may be seen in diffuse myopathic processes. Resting WMAs may be defined as hypokinetic, akinetic, or dyskinetic. Akinesia and dyskinesia usually indicate transmural infarction, whereas hypokinetic segments may be partially infarcted or viable.
3. An abnormal response to exercise is defined by the development or worsening of regional myocardial function. Regional myocardial dysfunction, as manifested by decreased endocardial excursion and wall thickening, is specific for myocardial ischemia. Decreased excursion alone is less specific and can occur with conduction abnormalities, with paced rhythms, and in the normal basal inferior myocardial segments.
4. Adjunctive diagnostic criteria for a positive SE examination include LV cavity dilation, a decrease in global systolic function, worsening diastolic function, and new or worsening mitral regurgitation (MR). However, these adjunctive diagnostic criteria are more specific for detecting severe CAD and may not be sensitive for detecting the presence of mild or moderate CAD.
5. False-positive findings may occur with left bundle branch block (septal WMA) and right ventricular (RV) pacing (apical WMA). A pathologic hypertensive response to exercise may also cause LV dilation and systolic dysfunction as can afterload mismatch in the setting of severe valvular lesions such as, MR, or aortic regurgitation.
6. False-negative findings may occur with a delay in capturing postexercise images, low workload, or inadequate heart rate response (i.e., with inadequate stress or the presence of β-blockers). Additional causes of false-positive and false-negative findings are outlined in Table below. **(31)**

Table (3): Causes of false-positive and false- negative stress echocardiography test results **(31)**

Causes of False Stress Echocardiographic Results	Factors Reducing Specificity or Sensitivity
False-Positive Results	
Abnormal septal motion (LBBB, after cardiac surgery)	Reduced or abnormal septal excursion with normal septal thickness
Nonischemic cardiomyopathy	May develop RWMAs (exact cause unknown)
Hypertensive response to exercise (SBP > 230 mm Hg, DBP > 120 mm Hg)	Nonischemic WMAs or LV dilatation
Poor image quality	
Overinterpretation	Observer bias may result in a lower threshold for calling a positive study; important to be blinded
Basal inferior or septal wall segments	Areas most likely to be overcalled; reduced excursion due to annular tethering effects
False-Negative Results	
Single-vessel disease	More likely to have subtle, rapidly resolving WMA than multivessel disease
Inadequate level of stress (more likely with beta-blockers)	Important to stress maximally; reach at least 85% of age-predicted maximum heart rate
LV cavity obliteration (more likely to occur with dobutamine)	Makes segmental wall motion analysis difficult
Poor image quality	
Left circumflex disease	Lateral wall drop-out; more likely to miss ischemia

DBP; diastolic blood pressure, LBBB; left bundle branch block, LV; left ventricle, SBP; systolic blood pressure, WMA; wall motion abnormality

D. Pharmacologic SE. With only a few exceptions, the principles of interpretation of pharmacologic SE findings are similar to those used for exercise echocardiography.

1. The typical ischemic response to dobutamine is characterized by normal resting wall motion and an initial hyperdynamic response at low doses followed by a decline in function at higher doses. Ischemia may also be identified on the basis of deterioration of normal wall motion without any transient hyperdynamic response.
2. LV cavity dilation and a decrease in global systolic function are not considered adjunctive diagnostic criteria in dobutamine SE. The LV cavity may not dilate, and global systolic function may improve with dobutamine despite new WMAs because of severe CAD.
3. Interpretation of results obtained from dipyridamole or adenosine SE requires detection of a new or worsening regional WMA during the infusion. There is only a mild increase in cardiac contractility during vasodilator stress. **(28)**

Reproducibility:
The person who interprets the images must be well trained in order to develop an acceptable level of accuracy and must interpret an adequate number of studies on a regular basis to maintain accuracy. Concordance within centers is generally good; however, concordance between different centers may be <80%, particularly with technically difficult studies and studies of patients with mild CAD.

Limitations:
The ability to interpret stress echocardiograms is mitigated by image quality, the presence of arrhythmias, conduction abnormalities, respiratory interference from hyperventilation, and difficulty in reproducing the translational and rotational motion of the heart.

Complications:
Dobutamine stress echocardiography: The most common cardiovascular side effects associated with dobutamine are angina, hypotension, and cardiac arrhythmias **(35).** Atrial fibrillation and non sustained ventricular arrhythmias occur in about 3% of patients **(36).**

Sustained ventricular tachycardia is not common. Dobutamine can also induce left ventricular mid-cavity and outflow tract obstruction. Frequent premature atrial or ventricular contractions occur in about 10% **(37).**

Vasodilator stress echocardiography: Major adverse reactions include myocardial infarction, asystole, and ventricular tachycardia **(38).** Hypotension and bradycardia may occur but can be treated with aminophylline.
Pacing stress echocardiography: Wenckebach's second-degree heart block may occur, requiring atropine administration **(39).**

Diagnostic accuracy:
The diagnostic accuracy of SE is superior to exercise electrocardiographic testing alone and similar to radionuclide perfusion techniques. Reported sensitivities and specificities (using coronary arteriography as the gold standard) vary between studies, depending on the prevalence of disease in the study population, the angiographic definition of significant disease, and the criteria used for a positive test. Clinical factors such as age, cardiac risk factors, and symptoms that influence the pretest likelihood of CAD also influence sensitivity and specificity. For the overall detection of patients with CAD, sensitivity ranges from 75% to 92%, depending on lesion severity, and specificity ranges from 64% to 100%. As with other imaging methods, the sensitivity is less for the detection of single-vessel disease and greater for the detection of multivessel disease **(22).**

A. Exercise SE:
1. Comparison with exercise electrocardiographic testing. Exercise electrocardiographic testing remains the first-line diagnostic test for CAD. However, SE has greater diagnostic sensitivity and specificity, which is predictable on the basis of the earlier occurrence of a systolic WMA before electrocardiographic changes or symptoms in the ischemic cascade. Many factors limit the sensitivity of electrocardiographic testing alone to detect CAD, and these subgroups should be considered for exercise electrocardiographic testing with an imaging modality.

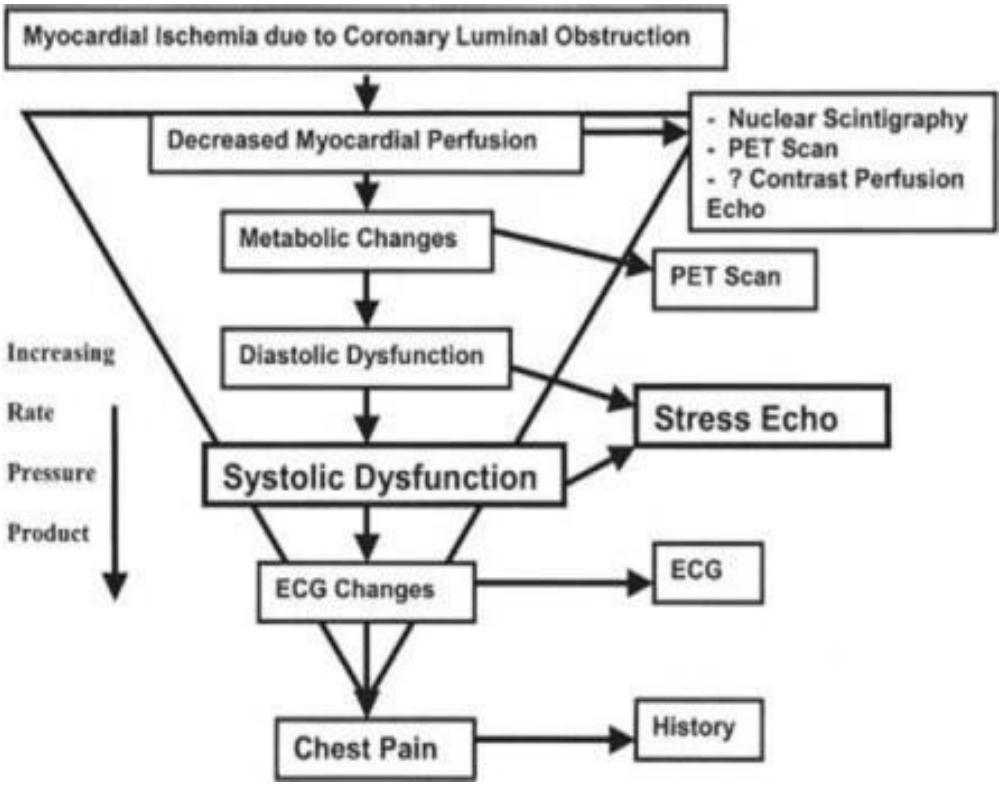

Figure (8): Ischemic cascade. ECG; electrocardiogram, PET; positron emission tomography **(33)**

Table (4): Factors limiting the sensitivity of stress ECG to detect CAD **(32)**

TABLE 47.1 Factors Limiting the Sensitivity of Stress Electrocardiography to Detect Coronary
Abnormal ST-segments at baseline:
Digitalis effect
Electrical left ventricular hypertrophy
Previous evidence of myocardial infarction
Nonspecific, abnormal ST-segment changes
Women (higher rate of false-positive ST-segment changes)
Left ventricular hypertrophy (even with normal-appearing electrocardiogram)

2. Comparison with myocardial perfusion scintigraphy

a. Myocardial perfusion scintigraphy is based on the detection of a perfusion defect during maximal hyperemia, with reduced perfusion of areas subtended by significant coronary artery stenosis (>50% stenosis). Perfusion abnormalities occur at an earlier stage in the ischemic cascade than do systolic WMAs, and nuclear scintigraphy should, theoretically, have a higher sensitivity than SE for CAD.
b. Studies using single-photon emission computed tomography (SPECT) myocardial perfusion scintigraphy have demonstrated a sensitivity of >90%, slightly higher than that for SE. However, the specificity of SE is superior to that of SPECT, especially in patients with LV hypertrophy or left bundle branch block. The overall accuracy of SPECT and SE has been found to be similar in meta-analyses; the superior sensitivity of SPECT is balanced by the superior specificity of SE. The exception may be in women, where SE may be more accurate than SPECT, owing to less artifact from breast attenuation.
c. SE is convenient and provides information on cardiac structure and function, and the results can be interpreted immediately, with rapid feedback to the patient and referring physician. SE also avoids exposure to radioactive tracers and is substantially less expensive than SPECT.
d. SPECT allows for more objective interpretation, with quantification of perfusion abnormalities. It may also be slightly superior for patients on antianginal therapy when it is necessary to induce ischemia. SPECT appears to be more sensitive in the detection of single-vessel disease and may be superior in the detection of ischemia in the setting of resting WMAs, in which the recognition of worsening wall motion may be difficult. SPECT may also be superior in patients that have poor acoustic windows, for example, those with chronic obstructive pulmonary disease. Local expertise, cost, exposure to radiation, and patient selection are all important factors in determining which imaging modality to use. **(28)**

B. Pharmacologic SE

1. Dobutamine SE has a sensitivity ranging from 68% to 96% and a specificity of 80% to 85%, similar to the values for exercise SE. Vasodilator SE has a sensitivity of 52% to 92% and a specificity of 80% to 100%. In general, the specificity of vasodilator SE is superior to that of other echocardiographic stress techniques. However, single-vessel disease is more difficult to detect with this technique.
2. Myocardial perfusion scintigraphy. Compared with dipyridamole SPECT, dipyridamole SE is believed to be less sensitive but more specific; however, few studies have compared the two tests in the same patients. As with exercise SE, dobutamine SE appears to be slightly less sensitive but more specific than SPECT. **(22).**

Adding Continuous ECG Monitoring to Stress Echocardiography Test

Continuous 12-lead ECG monitoring may be performed during SE but the positions of the chest leads often need to be lower than usual to avoid interfering with the acoustic window. Moreover, whether using exercise or dobutamine, the ECG data do not add to the prognostic value of the SE result and there are no consistent data to indicate this improves accuracy **(40).** Although the performance of 12-lead ECG monitoring during SE is not mandated, ECG monitoring for arrhythmia is necessary. The ECG leads attached to the echo machine must achieve a very clear tracing of the QRS complexes because well-demarcated imaging loops are critical at high heart rates, specifically for acquisition of correctly timed systolic images **(41).**

Positive stress echocardiography is associated with a threefold increased incidence of a cardiac event and a fourfold increased incidence of myocardial infarction within 12 months of follow-up when compared with negative stress echocardiography **(42).** During stress echocardiography, the echocardiologist routinely collects both echocardiographic images and stress electrocardiogram (ECG) concurrently. The managing physician faces a dilemma when the stress ECG and stress echocardiography results are discordant (e.g. when a patient has negative stress echocardiography but positive stress ECG). A positive stress ECG could indicate a high risk of imminent cardiac event, whereas negative stress echocardiography would indicate the contrary **(43).**

Many studies were conducted to help answer this dilemma, **Kobal et al. (44)** and **Mahenthiran et al. (40)** have demonstrated, in their studies, that a normal finding on stress echocardiography confers a benign prognosis independent of the type of stress ECG response during stress studies). Siang Chew Chai et al, who also studied Prognostic impact of stress echocardiography with discordant stress electrocardiography in patients with suspected coronary artery disease resulted that discordant results (negative stress

echocardiography but positive stress ECG) do not portend a higher risk of MACE when compared to concordant results (i.e. both stress echocardiography and stress ECG are negative) **(45).**

Hwang et al. (46) who compared diagnostic and prognostic values according with exercise ECG and Echo findings during treadmill exercise echocardiography in patients with chest pain and no history of CAD. Concluded that, exercise Echo findings may be a better predictor for clinical outcomes than exercise ECG findings. However, in patients with positive exercise Echo results, exercise ECG findings should be considered together with Echo findings for improved decision-making associated with coronary intervention and prediction of prognosis.

On other hand **Daubert et al., (47**), study showed that the presence of +ECG results with normal stress Echo imaging may identify a population of patients who are at slightly increased risk for adverse cardiac events, which was not previously recognized. Further study is needed to determine whether these patients will benefit from intensification of medical management.

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