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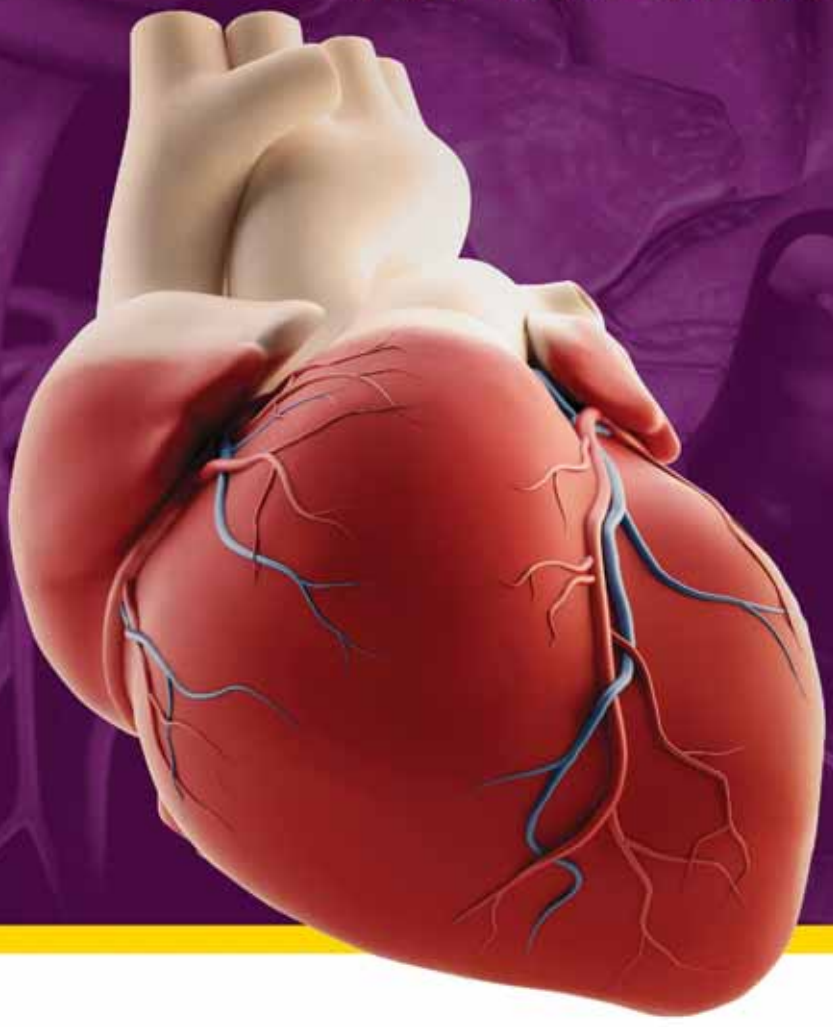
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CARDIOLOGY

An Illustrated Textbook



Barry London
Kanu Chatterjee
Donald Heistad
Richard E Kerber

Forewords
Barry London
William W Parmley

SECOND EDITION

JAYPEE

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CHAPTER

17

Stress Echocardiography

Ellen EI Gordon, Richard E Kerber

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INTRODUCTION

Coronary artery disease kills more adults in Western society than any other condition, and this alarming statistic has been true since the turn of the century. Given that coronary artery disease is the number one killer of adults today, identifying those at risk and preventing the sequelae of ischemic disease are major goals of current day practice. Stress echocardiography (SE) has been the main diagnostic tool for coronary artery disease for over a quarter of a century. Given the rapid escalation in use of SE,[1-3] and the large costs associated with the procedure, both cardiologists and noncardiologists alike should acquire an in-depth understanding of all clinical uses. This chapter will explore these clinical uses.

Over three-fourth of a century ago, Tennant and Wiggers[4] occluded a coronary artery and demonstrated the resulting wall motion abnormality. The stage was set for measurement of the functional significance of a coronary stenosis but it would take 40 more years before the resulting wall motion abnormality could be seen by ultrasound.

In 1975, Kerber et al.[5] reported the characteristic echo detectable wall motion abnormality following an experimental decrease in coronary blood flow.

In 1986, advances in computer technology allowed for ultrasound visualization of a functional myocardial blood flow mismatch. The resulting echo images, however, were viewed as little more than a "complement" to standard electrocardiogram (ECG) exercise testing.[6]

Today, SE is far more than a complement to exercise testing. Indications for stress testing have expanded far beyond the initial role in diagnosing ischemic disease. Exercise and pharmacologic stress protocols have been developed to estimate prognosis, and evaluate the hemodynamic effects of valvular heart disease.

In this chapter, we will focus on the clinical uses of echocardiographic stress testing. Sections will be organized by clinical questions. In the first section, we will review the pathophysiology involved in SE imaging. This will be followed by a review of the role of SE in diagnosing ischemic disease. Subsequent sections will focus on assessing prognosis in ischemic disease, and assessing myocardial viability. The final section will briefly list the use of SE in other disease states. Within each section, imaging protocols for the specific procedures will be provided, and pros and cons of the various SE modalities will be reviewed. Finally, speculation about what the future holds of SE imaging will be discussed.

USING STRESS ECHOCARDIOGRAPHY IN CLINICAL DECISION MAKING

Pathophysiology Involved in Stress Echocardiography

The major uses of SE have been in (1) diagnosing and (2) estimating risk in patients with suspected or known ischemic disease. An understanding of several factors involved in the disease pathophysiology and in the pathophysiology of the various forms of stress testing is critical to the appropriate use of SE. In order to establish a diagnosis of ischemic disease, SE must show a functional mismatch between myocardial oxygen supply and demand. The "gold standard" used for ischemic disease, however, is not a functional test, but rather an anatomic measurement of coronary stenosis. In addition, the decrease in blood flow necessary to produce ischemia and, hence, a wall motion abnormality has been variably defined in the literature. Both 50% and 70% stenoses of a major epicardial artery (as defined by coronary angiography) have been used to derive the sensitivity and specificity values for SE. These distinctions are important in understanding the limitations of SE and have resulted in some variation in the reported test characteristics.

Methods Used to Increase Oxygen Demand

The increase in myocardial oxygen demand achieved by stress testing can occur by various mechanisms. Three modalities are commonly used: (1) an exercise stress, which produces a dynamic increase in myocardial oxygen demand, (2) a pharmacologic stress (dobutamine), which increases myocardial oxygen demand and (3) a vasodilator stress, which produces a coronary 'steal.'

Exercise stress increases myocardial demand by increases in both chronotropy and inotropy. Because of the important prognostic implications associated with exercise tolerance, use of exercise as a stressor is almost always preferred.

In the United States, dobutamine is the predominant pharmacologic agent used to increase myocardial oxygen demand. It acts by both an increase in inotropy followed by an increase in chronotropy, both of which can be easily confirmed during the stress test. Atropine, added at the end of the protocol if heart rate response is inadequate, works via anticholinergic effects.

Dipyridamole (and adenosine) has been used more commonly in Europe in SE. The drug works as a vasodilator by setting up a coronary artery steal. An advantage of vasodilators includes the

extremely short half-life of these drugs. Disadvantages include the lack of a physiologic endpoint (i.e. wall motion abnormality).

Stress Echocardiography and the Diagnosis of Coronary Artery Disease

Exercise Stress Echocardiography

Assessment Prior to an Exercise Stress Echo

Clinical indications for exercise stress echocardiography (ESE): All stress testing begins with a review of the indication(s) for the stress test in particular, and contraindications for stress testing in general **(Table 1)**.

Indications for SE have been outlined by several professional societies. Initial appropriateness criteria for SE were published in 2008,[7] followed by an update in 2011.[8] In the area of diagnosis of ischemic disease, the most common appropriate indications include the following: (1) detection of coronary artery disease (CAD) in symptomatic patients with intermediate probability of disease and ability to exercise; and (2) detection of CAD in patients with low pretest probability and abnormal baseline ECG. For a more complete listing of appropriate indications from the 2011 guidelines, the reader is referred to the referenced article.

Inappropriate indications generally include patients in low-risk categories but can include both symptomatic and asymptomatic populations. *Inappropriate* conditions include (1) use of SE in *symptomatic* patient with a low pretest probability of disease with an interpretable ECG and the ability to exercise; and (2) use in *asymptomatic* patients with low or intermediate global risk with an interpretable ECG.[8]

Early literature suggested that there was room for improvement in the appropriate use of SE testing.[9] Using the 2008 appropriateness criteria, McCully reviewed 298 consecutive stress echocardiograms and classified them as appropriate, inappropriate, uncertain or not classifiable. Of the 298, 54% were classified as appropriate, 8% as uncertain, 19% were not classifiable, and 19% were inappropriate. The largest number of appropriate studies was in use of SE for diagnosis in symptomatic patients (94% appropriate). In contrast, the largest number of inappropriate studies involved use of SE in asymptomatic individuals (72% inappropriate and 26% uncertain).

Table 1: Checklist for patient assessment prior to exercise stress echo

Appropriate clinical indications
*No contraindications to exercise **(Table 2)***
*Ability to exercise—DASI score **(Table 3)***
- Exercise limitations
- Musculoskeletal limitations

Clinical symptom review
- Pretest probability **(Table 4)**
- Pretest score (Morise[27])

Baseline ECG Review
- Normal
- Baseline abnormalities

Current medications
- Beta-blocker (held for 48 hours?)
- Diltiazem or Verapamil
- Long-acting nitrates
- Digoxin

Similar findings were recently reported by Bhattacharyya et al. Out of 250 SE, 62% were felt to be appropriate and 28% inappropriate (9% were uncertain). Of the appropriate studies, more demonstrated inducible ischemia. The authors also concluded that better application of appropriateness criteria would reduce unnecessary testing.[10]

In an attempt to further promote optimal use of stress imaging, updated appropriate use guidelines were published in 2011.[8] Categories for SE were classified into the following categories:
- Detection in symptomatic or ischemic equivalent
- Detection in asymptomatic
- Detection in asymptomatic with defined comorbidities
- Following prior test results
- Perioperative evaluation for noncardiac surgery without active cardiac conditions
- Risk assessment within 3 months of an acute coronary syndrome (ACS)
- Risk assessment postrevascularization [percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG)]
- Assessment of viability/ischemia
- Hemodynamics.

In 2013, Willens et al. compared the effect of updated guidelines on physician ordering of stress echocardiograms. They found little change in ordering behavior from 2008 to 2011. In cohorts from both time periods, nearly 1/3 of stress echocardiograms were ordered for inappropriate indications. Even with a directed educational intervention, appropriate use did not improve. At their institution, the most common inappropriate use of SE in both 2008 and 2011 posteducation cohorts, was found to be evaluation of a low pretest probability patient with an ischemic equivalent, an interpretable ECG and ability to exercise. The second most common inappropriate echo request was in the re-evaluation in less than 2 years of asymptomatic or stable patients with known CAD, based on angiography or abnormal stress imaging.[11] They concluded that SE continued to be ordered inappropriately despite the guidelines and an educational intervention.

Despite publication of appropriate guidelines, use of echocardiography increased 54% between 2008 and 2011. In 2011, echocardiography services were delivered to 242 out of every 1,000 Medicare beneficiaries.[12] Continued efforts at optimizing use of medical resources continue to take place. For more information, the reader is referred to the Less is More Campaign by the Archives of Internal Medicine,[13] and the Choosing Wisely Campaign by the ABIM. As part of the Choosing Wisely Campaign, professional societies submit their top five recommendations that should be questioned by physicians and their patients. Out of the top five submitted by the ACC, three involve stress testing and are listed below:[14]

1. "Don't perform stress cardiac imaging or advanced noninvasive imaging in the initial evaluation of patients without cardiac symptoms unless high-risk markers are present."
2. "Don't perform annual stress cardiac imaging or advanced noninvasive imaging as part of routine follow-up in asymptomatic patients."
3. "Don't perform stress cardiac imaging or advanced noninvasive imaging as a preoperative assessment in patients scheduled to undergo low-risk noncardiac surgery."

Because a complete discussion of appropriate indications for SE is beyond the scope of this chapter, the reader is referred to the provided references for additional information.

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Table 2: Contraindications to exercise testing[16-18]

- Acute myocardial infarction, recent
- Unstable angina (not stabilized by medical therapy or recent pain at rest)
- Uncontrolled heart failure
- Uncontrolled symptomatic arrhythmias
- Symptomatic severe aortic stenosis
- Acute pulmonary embolus or pulmonary infarction
- Deep vein thrombosis
- Acute myocarditis or pericarditis
- Acute aortic dissection (or recent aortic surgery)
- Uncontrolled hypertension (> 220/120 mm Hg)
- Significant left main coronary stenosis
- Significant electrolyte abnormalities (particularly hyper- or hypokalemia)
- Severe hypertrophic cardiomyopathy
- High-degree atrioventricular block
- Inability to exercise adequately due to physical or mental limitation

Contraindications to exercise stress echocardiography: Contraindications to ESE are similar to those outlined for exercise testing in general and will not be detailed here. They are listed in **Table 2**.[15-18]

Clinical variables: If there are no absolute or relative contraindications to testing, assessing the patient's ability to exercise should be the next clinical question. Use of the Duke Activities Status Index (DASI) can be helpful in this regard. Initially developed in 1989 by Hlatky et al.[19] it has more recently been validated in women.[20,21] DASI consists of 12 questions about daily activity. The patient is instructed to circle all activities that they can do with "no difficulty". Answers such as "I don't do this" or "I can do this with some difficulty" do not count in the final assessment **(Table 3)**. Positive answers are summed using the scores listed in the far right column under metabolic equivalent of task (MET) value. The total sum has been correlated with MET level achieved on the Bruce protocol and is, therefore, also helpful in choosing the appropriate test protocol. Finally, musculoskeletal limitations that may influence the patient's ability to exercise should be reviewed by asking what typically limits exercise.

If it is established that the patient can exercise, an exercise protocol is almost always recommended because of the added information gained about prognosis (*See section on Prognosis and Exercise Tolerance*). If the patient cannot exercise or if exercise is limited, then a pharmacologic stress protocol should be considered (See *Use of Dobutamine Echo in Diagnosis of Ischemic Disease*).

Table 3: The Duke activity status index (in METs)[19,21]

Can you	*Score only for answers: "Yes, with no difficulty"*	*MET value*
• Take care or yourself, that is, Eating, dressing, bathing, and using the toilet?		0.8
• Walk indoors, such as around your house?		0.5
• Walk a block or two on level ground?		0.8
• Climb a flight of stairs or walk-up a hill?		1.6
• Run a short distance?		2.3
• Do light work around the house like dusting or washing dishes?		0.8
• Do moderate work around the house like vacuuming, sweeping floors, carrying in groceries?		1.0
• Do heavy work around the house like scrubbing floors, or lifting or moving heavy furniture?		2.3
• Do yard work like raking leaves, weeding or pushing a power mower?		1.3
• Have sexual relations?		1.5
• Participate in moderate recreational activities, like golf, bowling, dancing, doubles tennis, or throwing baseball or football?		1.7
• Participate in strenuous sports like swimming, singles, tennis, football, basketball or skiing?		2.1

Regardless of the type of study to be used, clinical symptoms should then be reviewed in order to assess pretest risk. Traditional definitions of angina outlined by the coronary artery surgery study (CASS) registry[22] and later validated by Diamond et al.[23] can provide a good start for estimating pretest probability. Probabilities are shown in **Table 4**. Similar tables used to estimate pretest probability could be found in the 2011 appropriateness criteria guidelines.[8]

An additional scoring system published by Morise has been validated in both men and women and can also be used to assess pretest probability.[24-27]

All of these measures provide an estimate of the pretest probability, necessary for correctly interpreting any exercise result.

The next clinical decision will be based on the patient's ECG. A normal ECG with no ST-segment abnormalities in a low-risk patient would not require the use of or added expense of imaging testing and is in keeping with current guidelines.[7,8] However, with

Table 4: Pretest probability of coronary artery disease (CAD) (defined as > 70% stenosis) in men and women according to chest pain description and age

	Nonanginas	*Atypical angina*	*Typical angina*			
Age (years)	*Men (Pretest probability of CAD, %)*	*Women (Pretest probability of CAD, %)*	*Men (Pretest probability of CAD, %)*	*Women (Pretest probability of CAD, %)*	*Men (Pretest probability of CAD, %)*	*Women (Pretest probability of CAD, %)*
30–39	5	1	22	4	70	26
40–49	14	3	46	13	87	55
50–59	22	8	59	32	92	79
60–69	28	19	67	54	94	91
Overall	21	5	70	40	90	62

Source: Adapted overall data from reference 120 and age data from reference 138.

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any baseline ST-segment abnormality, a stress imaging protocol using imaging should be considered in symptomatic patients.

The final clinical decision to be made before starting an exercise test is to review the medication list for medications, which may interfere with testing or with test interpretation. Concomitant use of beta-blockers may result in an inability to achieve 85% of maximum predicted heart rate, and as a result, has been reported to lower the sensitivity of testing. Therefore, if beta-blockers can be discontinued safely prior to testing, then it is recommended that they be discontinued for approximately 4–5 half-lives or 48 hours prior to testing. Similarly, other drugs, which slow heart rate (HR) response (diltiazem, verapamil) or alter the ischemic response (nitrates) should be reviewed and discontinued if clinically appropriate. If the question is not diagnostic in nature but rather one of adequacy of treatment, then beta-blockers may be continued in certain clinical circumstances. Use of digoxin, a known cause of baseline ST changes on ECG, is also another appropriate indication for the addition of imaging to exercise testing.[7]

Choosing an Exercise Protocol

The choice of the type of exercise is often made by what is available at one's own institution. In the United States, exercise treadmill is the most common form of stress exercise. Outside of the United States, exercise using a bicycle ergometer is performed more frequently. There are advantages and disadvantages to both. Exercise treadmill has the advantage in that walking is familiar to all, whereas patients may not be as familiar with use of a bike. From an SE standpoint, however, imaging must be performed after the completion of treadmill exercise and carries the risk that ischemic wall motion abnormalities will have resolved before imaging can be completed. In contrast, imaging is performed continuously during bicycle exercise, although image degradation due to motion artifact can be troublesome. It is therefore, not surprising that there is a lower sensitivity for SE performed with treadmill versus bike ergometry.[28-30] Most recently, Peteiro et al. have reported success with imaging during peak treadmill exercise. While technically more difficult, the technique appears promising with potentially higher sensitivities.[31]

The most common protocol used in exercise treadmill testing is the Bruce protocol. This protocol has the advantage of widespread use and literature validation. However, the large MET increase between stages is not optimal for all patients. For example, patients with musculoskeletal disorders may do better with a protocol such as the Naughton, with a 1 MET workload increase between each stage. This compares with the 4.7, 7, and 10 MET levels attained at the end of Bruce stages I, II, and III, respectively. Often a modification to the Bruce protocol is used, which involves starting exercise at a lower level. The workload at the end of the two additional stages = 2.9 and 3.7 METs, for stages 0 and 1/2, respectively. Finally, if an exercise prescription for rehabilitation is to be given based on the stress testing results, a protocol such as the Naughton, or Balke-Ware is recommended.[15,16]

Recently, Brenden et al.[32] and Nalawadi et al.[33] have reported the addition of atropine to exercise stress protocols and supine bike exercise, respectively. Brenden et al. studied 1,396 patients who underwent exercise stress study using a Bruce or modified Bruce protocol. They compared results to 7,319 historical controls. Atropine was given based on the clinical judgment of the supervising physician, often in patients who were on beta-blockers. The authors reported 78% achievement of target heart rate compared with 67% in historical controls. The authors are quick to point out that while the use of atropine appears to be safe and feasible; they have no data regarding outcome prediction.

Similarly, Nalawadi et al. have used atropine in 44 patients undergoing supine bike exercise SE testing and who did not achieve 85% of maximal predicted heart rate. With the use of atropine, 80% of the patients achieved target heart rate and rate pressure product. No significant complications were reported.

Overall, complication rates are low with ESE. Marwick has estimated a rate of approximately 3:1000 serious complications.[34] The risk of death or myocardial infarction with exercise testing has been reported to occur in approximately 1/2,500 patients.[15,16] Earlier data involving exercise testing alone suggested a serious complication rate (myocardial infarction, serious arrhythmia or death) of approximately 1/10,000.[35] In 2006, Varga et al. polled SE centers worldwide and reported on 26,295 exercise stress studies.[36] Using exercise stress protocols, life-threatening events were reported for only four patients for an event rate of 1 in 6,574 cases.

Conducting an Exercise Stress Echo

A detailed account of the technique required to conduct treadmill exercise testing is beyond the scope of this chapter. The reader is referred to the references provided on exercise testing[15,16] and to the chapter on Treadmill Exercise Testing. Comments about the protocol will be limited to the additional considerations associated with echo imaging.

Baseline echo images should be reviewed prior to the start of exercise. Secondary harmonic imaging should always be used. Images should be checked to ensure that they are centered within the chamber and not foreshortened. Segments within all coronary distributions should be visualized prior to starting exercise. If two or more segments cannot be visualized, then use of a contrast agent should be considered.[37] Originally, the FDA issued a black box warning, which restricted the use of perflutrens and required that all patients be monitored for 30 minutes following use **(Table 5)**. In 2008, Kusnetzky et al. reported a retrospective review of all deaths that occurred with 24 hours of an echo study.[38] No statistically significant difference was found in death rates between patients who received a contrast agent versus those who did not. Patients who did receive the contrast agent were found to have an increased number of comorbidities. The FDA black box warning has subsequently been revised and is shown in **Table 5**.

Platts et al. reported use of Perflutren contrast in 5,956 studies. Side effects were rare, self-limiting, and non-life-threatening.[39]

Table 5: FDA black box warning reuse of an ultrasound contrast agents

A. Original black box warning

- Unstable angina
- Acute heart attacks
- Unstable cardiopulmonary disease

ECG monitoring of all patients for 30 minutes after completion of the study

B. Revised black box warning

- Known or suspected right-to-left, bi-directional, or transient right-to-left cardiac shunts
- Hypersensitivity to perflutren

ECG monitoring in only patients with pulmonary hypertension or unstable cardiopulmonary conditions

Do not administer definite by intra-arterial injection

Abbreviation: FDA, US Food and Drug Administration

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Sixteen adverse events were detected in a retrospective review, the most common of which was back pain (10 patients). Five patients developed a rash or headache and one patient developed stuttering and speech difficulty. All side effects resolved within 30 minutes of administration.

Most recently, Weiss and colleagues[40] conducted a prospective, open-label, nonrandomized multicenter registry study involving 15 clinical sites in the United States. Out of 1,060 patients, 10.8% experienced some type of side effects from either contrast or the stress test itself. Thirty-seven events were felt to be attributable to the contrast agent (3.5%). Again, reported events were self-limited, and included headache, tremor, back pain and nausea.

In the majority of cases, a symptom-limited exercise study is recommended unless a study endpoint is reached. Exercise endpoints have been outlined by the American College of Cardiology (ACC) and American Heart Association (AHA) in guidelines published in 2002.[15,16] Exercise endpoints are listed in **Table 6**.

Interpretation of an Exercise Stress Echo

Final interpretation of the ESE should consider all components of the study: symptoms, ECG changes, BP response, echo imaging and exercise tolerance. Reports should contain all of the information that is standard in exercise treadmill studies. This would include information about limiting symptoms, BP response to exercise, ECG changes with exercise, HR achieved and percentage of maximum predicted HR, rate pressure product, and exercise tolerance as a percentage of predicted.

The most widely used method of echo interpretation is visual. Function in each myocardial segment is evaluated at rest and then compared at peak exercise. Contraction in each segment is graded as normal or hyperdynamic, hypokinetic, akinetic or dyskinetic. Both the timing of wall motion and thickening should be considered as ischemia results in both delayed contraction and relaxation. A wall motion scoring system can be used in a semiquantitative way to report the findings. The overall ventricular cavity size in systole should also be reviewed. Lack of a decrease in cavity size (or failure to develop hyperdynamic function) would be indicative of significant coronary artery disease.[41] For a review of the recommended LV segments see Chapter 16 on Transthoracic Echocardiography.

Final interpretation of the stress echocardiogram should include a review of factors known to reduce the sensitivity of exercise stress echocardiograms. Inadequate heart rate response (< 85%), concomitant antianginal treatment, poor image quality and delayed imaging postexercise. To avoid problems with the latter, HR for both maximal exercise and image acquisition should be reviewed.[34] Finally, mild coronary artery disease, particularly involving the left circumflex distribution can result in falsely negative studies. In contrast, false positive studies can be seen with pre-existing disease, in particular baseline abnormal septal motion [commonly seen following cardiothoracic surgery or in left bundle branch block (LBBB)], or with a hypertensive response to stress. Overinterpretation has been documented. Interobserver agreement is lowest for isolated basal inferior wall motion abnormalities and highest for basal anterior wall segments.[42]

Table 6: Endpoints for stress echocardiography[15]

- Achievement of target heart rate
- Symptom limitation
- Protocol completion (i.e. maximal dobutamine or dipyridamole dose)
- Significant wall motion abnormality (see text)
- Ischemic ECG response (i.e. ≥ 2 mm ST depression or ST elevation > 1 mm in non-Q wave lead)
- Severe ischemic symptoms (i.e. chest discomfort or exertional dyspnea)
- Severe hypertension (systolic BP > 220 mm Hg or diastolic BP > 120 mm Hg)
- Hypotension or fall in BP > 20 mm Hg with exercise
- Arrhythmias (SVT, VT, heart block, BBB)
- CNS symptoms

Pharmacologic Stress Echocardiography Assessment Prior to Pharmacologic Stress Testing

Clinical indications for dobutamine stress echocardiography (DSE): Similar to the ESE, pharmacologic SE starts with a review of the indication(s) for the stress test and contraindications for stress agent to be used **(Table 7)**. As with ESE, the reader is referred to the appropriateness criteria for SE for a review of the indications.[7] Appropriate indications for use of DSE for diagnosis are similar to those listed for use of ESE.

Contraindications for DSE and dipyridamole stress echo (DiSE): Contraindications to DSE differ considerably from ESE. Contraindications for both dobutamine use and atropine use should be reviewed.[28-30,42-44] A detailed list can be found in **Table 8**. Because beta-blockers are potent inhibitors of the increase in HR and contractility seen with dobutamine and may be frequently needed to reverse ischemic signs or symptoms, contraindications to their use should also be considered. In our laboratory, we use an intravenous dose of the rapidly acting beta-blocker, esmolol, to immediately slow the HR response and decrease contractility in the setting of any significant ischemic response. The required dose is calculated and ready prior to the start of all studies.

Table 7: Checklist and patient assessment prior to pharmacologic stress testing

Appropriate clinical indications

No contraindications to:

- Dobutamine
  - For contraindications **(Table 8)**
  - Precautions due to known side effects of dobutamine **(Table 8)**
  - Other considerations **(Table 8)**
- Atropine
  - Contraindications **(Table 8)**
  - Precautions due to known side effects of atropine **(Table 8)**
- Beta-blockers (If needed to reverse ischemic response)
- Dipyridamole

Clinical symptoms

- Pretest probability **(Table 4)**
- Clinically stable

Baseline ECG

- Baseline abnormalities
- Previous ECG available for comparison

Current medication use

- Beta-blocker held?
- Diltiazem or verapamil held? (particularly if high dose)
- Xanthine containing medications or caffeine (if using dipyridamole)

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Table 8: Contraindications and precautions with use of dobutamine and atropine[42-44]

Contraindications to dobutamine
• Symptomatic severe aortic stenosis
• Acute aortic dissection
• Recent or unstable coronary syndrome
• Obstructive hypertrophic cardiomyopathy
• Hypersensitivity
Conditions, which may worsen because of dobutamine side effects
• Uncontrolled atrial fibrillation or PSVT
• Uncontrolled hypertension
• Known ventricular arrhythmias
Precautions with other conditions
• Electrolyte abnormalities (particularly hypokalemia)
• Intraventricular thrombus
• Arterial aneurysms
• High-degree AV block
• Significant asthma and high-risk patients (Higher need for use of beta-blockers as reversal agent)
Contraindications to atropine
• Narrow angle glaucoma
• Obstructive GI disease
• Myasthenia gravis
• Hypersensitivity to atropine or anticholinergics
• Significant BPH or obstructive uropathy
Conditions, which may worsen because of atropine side effects
• Uncontrolled atrial fibrillation or PSVT
• Uncontrolled hypertension
• Known ventricular arrhythmias

Abbreviation: PSVT, paroxysmal supraventricular tachycardia

Contraindications for DiSE include severe conduction disease or advanced asthma. Vasodilator stress should be avoided in these patients, particularly given the other options for testing.[45]

Clinical variables important in DSE testing: Similar to ESE, clinical symptoms are next reviewed to assess pretest risk **(Table 4)**. As DSE is being performed in higher risk patients, it is incumbent that clinical stability of the patient be confirmed prior to initiating the study.

Baseline ECGs should be reviewed and compared with previous tracings whenever possible. When performed in the setting of acute chest pain, serial cardiac enzymes should also be documented to be normal before proceeding with the test.

The final clinical decision before starting a DSE is a review of the medications. Not only should medications that slow the HR response be considered, but review should include medications, which interact with either dobutamine or atropine. Beta-blockers are routinely stopped 48 hours (4–5 half-lives) before the study if the question is one of diagnosis. If dipyridamole stress is being considered, all xanthine-containing medications should be stopped for 72 hours or caffeine containing substances should be stopped 24 hours prior to testing.

Pharmacologic Stress Echo Protocols

Dobutamine stress protocol: In early studies, dobutamine protocols started with 5 μg/kg/min and increased every 3 minutes to a maximum dose of 40 μg/kg/min.[5,10,20,30,40] If the maximum heart rate (HR) was less than 85% of the target HR, atropine was then added in 0.5 mg doses up to a dose of 1–2 mg. Today, protocols have routinely become more aggressive. They begin at 10 μg/kg/min and now increase to a maximum dose of 50 μg/kg/min.[46] Atropine is added at the doses listed above. Use of atropine at the end of the protocol also allows additional time for dobutamine to reach steady state. If there is a vagal response to dobutamine with manifest bradycardia and relative hypotension, atropine may be added prior to the end of the dobutamine protocol. This is not uncommonly seen at dobutamine doses of 40 μg/kg/min or greater. In settings where atropine will not be used or is contraindicated, an additional 3 minutes may be added to protocol to ensure that dobutamine reaches steady state.

Dipyridamole stress protocol: Dipyridamole continues to be widely used in Europe.[47] Protocols vary but generally can be divided into two types. The first standard, longer protocol consists of dipyridamole intravenously at a total dose of 0.84 mg/kg over 10 minutes. The initial infusion rate is 0.56 mg/kg for 4 minute, followed by a 4 minute period of no infusion. A second infusion follows at a lower dose of 0.28 mg/kg. If no endpoint is reached, atropine can be added in doses of 0.25 mg up to a maximal dose of 1 mg. The second, shorter protocol consists of dipyridamole infusion at the 0.84 mg/kg over 6 minutes.

With the use of either protocol, aminophylline 240 mg IV should be readily available for immediate use with any adverse events and is often routinely infused at the end of the protocol (120 mg in 1 minute—up to a total of 240 mg in 2 minutes).

Other protocols have been described in the literature include infusion of adenosine, use of atrial pacing,[48] and hand grip exercise.[49] These protocols are less commonly used in the routine clinical setting. The reader is referred to the listed references for additional details.

Complications of Pharmacologic Stress Echo

Dobutamine stress echo complications: As familiarity with use of dobutamine has grown, sicker patients are now being referred for DSE testing. Given the increase in dosing and increased severity of illness, concern has been raised about the safety of the DSE. Geleijnse et al. have recently reviewed the complications associated with DSE testing.[46] In their review of over 55,000 patients in 26 studies, they report a complication rate of potentially life-threatening complications of approximately 1/475 cases. Marwick reports a serious complication rate of 3:1,000.[34] Varga et al. have reported an event rate of 1 in 557 with use of dobutamine, making it the riskiest of the three stress echo protocols.[36] A list of the complications and incidence reported by Geleijnse is provided in **Table 9**.

An additional complication of dobutamine infusion reported by Pelikka et al. is that of left ventricular outflow tract obstruction with associated hypotension.[50] Pellika described an average increase in velocity of 2.3 m/sec (21 mm Hg gradient) at peak dose. Peak dose velocities ranged from 2 m/sec to 5 m/sec. The associated change in BP ranged from a drop of 15 mm Hg to an increase of 4 mm Hg. In our experience, this complication is most often seen in patients with small LV cavities, hyperdynamic LV function at baseline, or significant LVH at baseline. In this setting, we routinely measure the left ventricular outflow tract (LVOT) Doppler at baseline and intermittently throughout the procedure. This complication can be rapidly reversed by saline infusion and reversal of the effects of dobutamine with beta-blocker.

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Table 9: Complications associated with use of dobutamine and atropine

Complications	*Incidence*
Mortality	< 0.01%
Cardiac rupture	< 0.01%
Myocardial infarction incidence	0.02%
Cardiovascular accident	< 0.01%
Cardiac asystole	< 0.01%
Sustained ventricular tachycardia	0.15%
Premature atrial complexes	7.9%
Supraventricular tachycardia	1.3%
A fib	0.9%
AV block	0.23%
Coronary spasm	0.14%
Hypotension	1.7%
Hypertension	1.3%
Atropine intoxication	0.03%
Dobutamine extravasation	One in two cases
Dobutamine hypersensitivity	1 patient

Dipyridamole stress echo complications: Varga et al. have recently reported complications associated with the use of dipyridamole as a stress agent in over 24,000 cases.[36] Serious, life-threatening complications were reported in 19 patients for an event rate of 1 in 1,294 cases. There was 1 reported death following dipyridamole stress testing. The authors concluded that exercise was the safest testing modality with dipyridamole stress second. However, they noted that selection bias could account for the latter. As outlined, most complications due to dipyridamole can be rapidly reversed with the use of IV aminophylline. For a more complete review, the reader is referred to the listed reference.

Conducting the Pharmacologic Stress Echo

As with ESE, baseline echo images should be reviewed prior to the start of the DSE. Secondary harmonic imaging should always be used. Images should be checked to ensure that they are centered within the chamber and not foreshortened. An off-center baseline image may result in a 'smaller' LV cavity. When compared to peak stress imaging, this may result in the false conclusion that there was no hypercontractile response.

Segments within all coronary distributions should be visualized prior to starting dobutamine infusion. If two or more segments cannot be visualized, then use of a contrast agent should be considered.[37] Contraindications to the use of contrast agents and a more extensive discussion of their use has been previously outlined[38-40] and can be found in **Table 5**,[38] and the section on Exercise Stress Echo and Diagnosis—Imaging considerations.

Throughout the DSE, the patient is monitored by 12 lead ECG. BP is checked at the end of every stage (every 3 minutes) and as clinically indicated. Echo images may be screened for all stages but are recorded at low dose (20 μg/kg/min) and at peak dose. Recovery images are also recorded at the end of the protocol when the HR has returned to baseline and clinical symptoms have resolved. Today's stress echo software allows additional image acquisition at any time during the study. For example, we routinely record additional echo images with any ischemic symptoms or ECG changes.

During infusion of dobutamine, a flow sheet listing the dobutamine dose, use of atropine, patient's symptoms, HR response and BP response is recommended. Unlike most exercise stress echocardiograms, the DSE protocol may be terminated due to imaging endpoints. This would include the development of a new wall motion abnormality or worsening of a baseline abnormality.

Interpreting the Pharmacologic Stress Echo

The most widely used method of echo imaging interpretation is visual. Like ESE, function in each myocardial segment is evaluated at baseline, and then compared at peak dobutamine or dipyridamole dose. With use of dobutamine, however, comparison with low dose must be considered. An *ischemic biphasic response* may occur in which an increase in contractility is seen at low dose, followed by no further change or a decrease at peak dose. As with ESE, contraction in each segment is graded as normal or hyperdynamic, hypokinetic, akinetic or dyskinetic. Both the timing of wall motion and thickening are evaluated. A wall motion scoring system such as the ASE 16-segment model or the 17-segment model can be used in a semiquantitative way to report the findings (see Chapter 16 on Transthoracic Echo). The overall change in ventricular cavity size in systole should also be reviewed. A progressive decrease in chamber size reflecting the progressive increase in contractility is expected. A lack of a decrease in cavity size in systole would be indicative of severe coronary artery disease.

The definition of an abnormal dobutamine stress echo has varied in the literature. In many studies, either stress-induced wall motion abnormalities or fixed wall motion abnormalities have been used as the definition of an ischemic response. In other studies, only stress-induced wall motion abnormalities are felt to represent ischemia. In studies which included patients with prior myocardial infarctions (and presumably an increase in resting wall motion abnormalities), sensitivities are generally reported higher with lower specificities. This has resulted in considerable variation in the reported test characteristics. Sensitivities have ranged from 54% to 96% and specificities have ranged from 62% to 93%.[51]

In a meta-analysis summarizing 45 studies, which included patients with prior myocardial infarction and 17 studies, which excluded prior myocardial infarction (MI), Geleijnse et al. have reported the test characteristics for DSE **(Table 10)**. The factor found to have the largest effect on test characteristics was the inclusion or exclusion of baseline wall motion abnormalities. Defining cases with resting wall motion abnormalities as positive raised sensitivity; specificity, however, was lower when referral bias was present.[51] Test characteristics for dipyridamole SE are similar and can be found in **Table 11**.

Other factors, which have been reported to affect sensitivity and specificity, include referral bias **(Table 12)**. The varying definition of the gold standard between 50% and 70% angiographic stenosis should theoretically affect test characteristics but was not found to be a significant factor in Geleijnse's review.[51] The authors theorized that few patients actually had stenoses between 50% and 70% as the reason for this finding. Surprisingly, neither use of beta-blockers nor use of atropine was found to affect outcome. Addition of atropine has been reported by others to affect test characteristics.[52]

In addition to interpretation of imaging results, a complete SE report should include information about symptoms, BP response to dobutamine, ECG changes or arrhythmias noted during infusion or in recovery, HR achieved in beats per minutes and as a percent of the maximum predicted HR and rate pressure product.

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Table 10: Summary test characteristics for DSE (A) Test characteristics for studies without resting wall motion abnormalities; (B) Test characteristics for studies with resting wall motion abnormalities; (C) Sensitivities for studies which allowed calculation of single versus multivessel disease

A. Studies without resting wall motion abnormalities (17 studies)	
Sensitivity (weighted mean)	Specificity (weighted mean)
74%	85%
LR (+)	LR (–)
2.84	0.35
B. Studies with resting wall motion abnormality (45 studies)	
Sensitivity (weighted mean)	Specificity (weighted mean)
83%	81%
LR (+)	LR (–)
4.37	0.21
C. Studies which allowed calculation of sensitivity for single versus multivessel disease (n-48)	
Degree of CAD	Sensitivity (%)
Overall	81
Single vessel CAD	73
Multivessel CAD	88%

Final interpretation of the pharmacologic stress echocardiogram (dobutamine or dipyridamole) should include a review of factors known to reduce the sensitivity of stress echocardiograms: Inadequate heart rate response (<85%), concomitant antianginal treatment, poor image quality. Finally, mild coronary artery disease, particularly involving the left circumflex distribution can result in falsely negative studies. In contrast, false positive studies can be seen with pre-existing disease, in particular baseline abnormal septal motion (commonly seen following cardiothoracic surgery or in LBBB), or with a hypertensive response to stress. As with ESE, interpretation has varied the most with wall motion changes involving the basal inferior wall.[42]

In summary, diagnosis of ischemic disease can be assessed with either exercise or pharmacologic SE. The choice of the testing modality should be based on the ability of the patient to exercise, the presence or absence of baseline ECG abnormalities and the experience of the echocardiography laboratory. A compilation of studies, which directly compare the various echo modalities, can be found in the Consensus Statement by the European Association of Echocardiography.[53] When used in patients with appropriate indications, both study types have been shown to identify patients at risk of ischemic disease with a high degree of accuracy.[42]

Stress Echocardiography and Estimating Risk or Prognosis in Coronary Artery Disease

Assessing Prognosis: Introduction

Stress echocardiography has been used to answer questions about diagnosis and can also be used to estimate ischemic risk and prognosis. For example, SE has been used to predict severity and risk of coronary disease and assess risk of mortality. This section will first review caveats regarding the design of studies about prognosis, and will be followed by a review of the use of ESE and pharmacologic SE in assessing prognosis of ischemic disease. A summary of prognostic implications of SE in special populations will be provided.

Table 11: Summary of test characteristics for dipyridamole stress echocardiography[53]

Overall sensitivity	*Sensitivity (single vessel CAD)*	*Sensitivity (multivessel CAD)*	*Specificity*
87%	81%	90%	90%

Table 12: Factors which alter test characteristics of stress echocardiography[51]

Factors associated with increased sensitivity of stress echocardiography

- Clinical spectrum of coronary disease in study population
- Inclusion of resting wall motion abnormality in definition of abnormal response

Factors associated with decreased specificity of stress echocardiography

- Referral bias

Prognostic Studies: Design and Limitations

In a perfect world, testing for ischemic disease would identify those patients who not only have obstructive coronary artery disease but also those who have an unstable plaque (diagnosis). Prognostic studies would then tell us which unstable plaque is likely to rupture or cause thrombosis (prognosis). The reader is reminded that because stress testing is often correlated with an anatomic diagnosis (coronary angiography), SE is best used in the setting of obstructive disease. Our ability to predict the future ischemic events that often result from nonflow limiting atherosclerotic plaque is, therefore, limited.

Study design represents another limitation of prognostic studies. *Study populations* are rarely randomized to various workups with measurements of patient outcome, although the need for such studies has recently been outlined.[54-56] In the worst case, studies are designed based on retrospective reviews of cases and controls with their inherent selection bias. In better studies, nonrandomized cohorts of consecutive patients are followed prospectively. The study population should consist of a well-defined population who are at a similar point in the course of disease.[57] Because of this, prognostic studies are, therefore, highly dependent on the make-up of the selected patient population and have a high potential for both selection bias and referral filter bias.

The definition of *outcome* is another important factor in determining quality of a prognostic study. Because of the expense of conducting long-term studies, investigators often use a combination of events (*composite outcome*) as their primary endpoint. This can result in a decrease in time of study design but can introduce significant problems in clinical application.

By definition, a composite endpoint represents a combination of multiple endpoints. Montori et al. have developed three questions designed to help interpret composite endpoints:[58]

1. "Are the component outcomes of similar importance to patients?"
2. "Did the more and less important outcomes occur with similar frequency?"
3. "Are the component outcomes likely to have similar RRRs (Relative Risk Reductions)?"

To illustrate further, assume that a statistically significant decrease in a composite endpoint of angina and cardiac death

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Table 13: Exercise stress echo—summary of prognostic variables

Variable	*Poor prognostic indicators*
Summary	*Effort-induced or limiting angina*
ECG	• ST segment depression or elevation • Arrhythmias
Hemodynamics—BP	• No rise in BP with exercise • Fall in BP with exercise
Hemodynamics—HR	< 85% of maximum predicted heart rate
Echo imaging	• New or worsening regional wall motion abnormality • Lack of decrease in LV systolic dimension with exercise
Workload	< 5 METs in women < 7 METs in men
Combination variables	• Duke treadmill score (≤ –11 points) • Exercise score (Men > 60; women > 57)

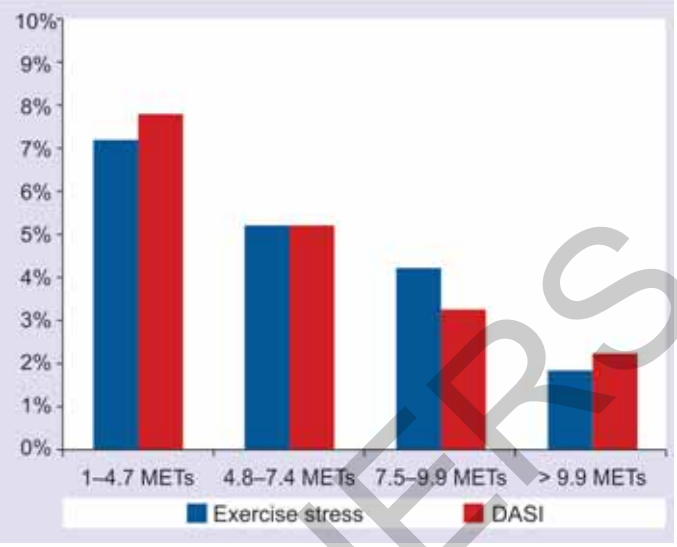


Fig. 1: Mortality and exercise capacity in the WISE study.[14] Annual mortality is predicted by exercise treadmill stage (blue bars) or estimated exercise capacity using the Duke activity status index (DASI) (brown bars)
Source: Shaw LJ, Olson MB, Kip K, et al. The value of estimated functional capacity in estimating outcome: results from the NHBLIsponsored Women's Ischemia Syndrome Evaluation (WISE) Study. J Am Coll Cardiol. 2006;47:S36-43.

is reported. This may not mean that a significant decrease in both events has occurred. By applying Montori's questions, an appropriate interpretation can be made. For example, in answering the first question, it becomes obvious that the importance of angina and cardiac death may differ. The second question reveals that the outcomes will likely occur at differing frequencies. Finally, by quickly looking at the RRR and confidence intervals for the individual events, a final interpretation can be made. In the example provided, it is conceivable that a statistically significant composite outcome could be based predominantly on the change in frequency of angina.

Exercise Stress Echo and Prognosis in Coronary Artery Disease
Prognostic Variables in Exercise Stress Echo

Exercise stress echo has been used to assess prognosis in ischemic disease for many years. The advantages of ESE include the additional clinical information found from the exercise portion of the study. In reviewing ESE studies and prognosis, both exercise and imaging, and combination variables have been shown to be helpful in predicting prognosis and will be subsequently reviewed. ESE variables, which have been used to predict prognosis, are listed in **Table 13**.

Exercise variables: Despite years of technical progress, one of the most powerful predictors of outcomes remains exercise tolerance. Arruda-Olson et al. confirmed this with exercise echo in 2002.[59] The authors followed 5,798 consecutive patients who had an exercise echo for known or suspected coronary artery disease for an average of 3.5 years. Outcomes were defined as noncardiac death and nonfatal MI. Of all of the exercise ECG predictors, workload was the only one predicted by multivariate analysis. Other authors have reported similar findings.[60] Additional predictive variables have included a fall (or lack of rise) in systolic BP with exercise which has also correlated with a poorer prognosis.[61] Exercise-induced angina was originally found to predict a poorer prognosis[62] but has been shown to be less predictive when exercise tolerance is included.[22,61]

The importance of exercise tolerance as a predictor of mortality is not new as it has been shown to be important in nonimaging stress testing. In the WISE study, exercise tolerance in women, whether measured by treadmill stage or estimated by DASI score correlated inversely with mortality and was shown to be one of the strongest predictors of mortality **(Fig. 1)**.[21]

Nomograms for predicted exercise capacity have been published for both men and women. Myers et al. followed 6,213 men with cardiovascular risk factors who had undergone exercise testing. They found that exercise tolerance was the most powerful predictor of death. For every 1 MET increase in exercise tolerance, there was a 12% decrease in mortality.[63] Gulati et al. found that the risk of death in women with exercise tolerance less than 85% of that predicted for age was twice that of women whose exercise tolerance was greater than 85% of predicted. This was found in both symptomatic and asymptomatic women.[64]

Achievement of greater than 85% of maximal predicted heart rate has been a standard component of exercise testing. Failure to achieve this threshold has been reported as a poor prognostic indicator even after adjustment for echo indicators of myocardial ischemia.[65]

In 2013, Fine et al. reported the outcomes of 862 patients who achieved more than 10 METs with ESE testing. In this group, additional exercise echo variables did not provide incremental prognostic information as both those with ischemic response and normal responses had good prognoses.[66] Bourque et al. also studied the 10 METs threshold in exercise perfusion imaging and have gone so far to say that perfusion imaging could be eliminated in intermediate probability patients who could achieve a 10-MET workload given the zero prevalence of ischemic events.[67]

This was again confirmed when Yao et al. studied patients with high exercise capacity greater than or equal to 10 METs (n = 970) and patients with chronotropic incompetence, i.e. those who did not achieve more than 85% of their maximal predicted heart (MPHR) (n = 970).[68] These 1,781 patients were followed for up to 5 years for endpoints of nonfatal myocardial infarction and death. The presence of a new exercise-induced wall motion abnormality was found to be the most powerful predictor in both groups. Risk, however, varied by group. In the patients who did not achieve more than 85% MPHR, a new wall motion abnormality conferred a risk of 4.4%/year compared with a normal echo response (1.3%/year).

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In the high exercise capacity group, a similar abnormal echo finding conferred a 1.5%/year risk compared with 0.2%/year in those with normal wall motion.

Imaging variables: Echo imaging abnormalities have been found to be highly predictive and have been reported to add incremental value to the exercise variables. Abnormal responses have variably been defined:

1. New or worsening regional wall motion abnormality
2. No decrease in LV end-systolic size with exercise
3. Abnormal resting LV wall motion.

The most commonly agreed upon definitions include the first two. The reader is again cautioned as inclusion of resting LV wall motion abnormalities as part of the abnormal response can have significant effects on reported test characteristics. Numerous authors have reported that the severity and extent of wall motion abnormalities was predictive of cardiac death and major adverse cardiac events (MACE), most often defined as cardiac death, nonfatal myocardial infarction and unstable angina.[31,59,69-71]

Combining ESE and clinical variables: Adding clinical information to the data obtained from an ESE has been reported to show further increases in predictive accuracy. In 2001, Marwick et al. reported that the use of the Duke Treadmill Score added to the prognostic ability of exercise stress echo, particularly when applied to intermediate risk patients.[72] Previously shown to improve clinical prediction in men, the Duke treadmill score[19] has recently been validated in women.[20,73] The scoring system outlined in **Table 14** can be quickly calculated following any exercise test using the Bruce protocol.

Morise et al. have also combined clinical factors with ESE results and published an exercise score for both men **(Table 15A)** and women **(Table 15B)**. In patients undergoing exercise testing for suspicion of coronary artery disease, clinical factors and ESE results are scored as outlined. The total exercise score correlates with probability of outcome and has shown an improved prediction of all-cause mortality when compared with the Duke treadmill score.[25]

Both scores can be used to complement ESE interpretation as they provide a way to incorporate clinical factors, which have been shown to independently predict risk in ESE studies.

Exercise Stress Echo and Prognosis in Ischemic Disease

Exercise SE has been used in many populations. Most commonly, it has been used to assess chest pain in patients with known or suspected coronary artery disease. Because the interpretation of any study is highly dependent on the extent and severity of ischemic disease in the study population, studies will be reviewed according to clinical presentation. This section will review early prognostic studies, followed by a review of studies in patients with chest pain, with known CAD, and in patients undergoing coronary interventions.

Table 14: Duke treadmill score[141]

Duke treadmill score:

- *Low risk:* ≥ +5 points,
- *Intermediate risk:* –10 to +4 points,
- *High risk:* ≤ –11 points (9).

Duke treadmill score equation:

Duration of exercise in minutes —(5 × the maximal ST-segment deviation during or after exercise, in millimeters) — (4 × the treadmill angina index)

Early studies of ESE and prognosis: Early studies confirmed the increased prognostic ability of exercise stress echo over exercise treadmill testing.[74] In 1998, McCully et al.[60] reviewed the outcome of 1,325 patients who had a normal exercise echocardiogram. Regardless of pretest risk, patients with negative ESE were shown to be free of cardiac death, MI, or revascularization over the ensuing year. At 1 year, 2 years and 3 years, event-free survival was reported as 99.2%, 97.8% and 97.4%, respectively. Predictors of increased risk included low exercise tolerance, angina during exercise, echocardiographic LVH and increased age. In their

Table 15A: Exercise score—men[25]

Variable	*Choose response*	*Sum*
Maximal heart rate	Less than 100 bpm	= 30
	100–129 bpm	= 24
	!30–159 bpm	= 18
	160–189 bpm	= 12
	190–220 bpm	= 6
Exercise ST depression	1–2 mm	= 15
	> 2 mm	= 25
Age	> 55 years	= 20
	40–55 years	= 12
Angina history	Definite/typical	= 5
	Probable/atypical	= 3
	Noncardiac pain	= 1
Hypercholesterolemia?	Yes	= 5
Diabetes?	Yes	= 5
Exercise test induced angina	Occurred	= 3
	Reason for stopping	= 5
	Total Score	

Source: Morise AP, Olson MB, Merz CN, et al. Validation of the accuracy of pretest and exercise test scores in women with a low prevalence of coronary disease: the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. Am Heart J. 2004;147: 1085-92.

Table 15B: Exercise Score—women[27]

Variable	*Choose response*	*Sum*	
Maximal heart rate	Less than 100 bpm	= 20	Exercise test score **Women** choose only one per group 40 = low probability 40–60 = intermediate probability > 60 = high probability
	100–129 bpm	= 16	
	!30–159 bpm	= 12	
	160–189 bpm	= 8	
	190–220 bpm	= 4	
Exercise ST depression	1–2 mm	= 6	
	> 2 mm	= 10	
Age	> 65 years	= 25	
	50–65 years	= 15	
Angina history	Definite/typical	= 10	
	Probable/atypical	= 6	
	Non-cardiac pain	= 2	
Smoking?	Yes	= 10	
Diabetes?	Yes	= 10	
Exercise test induced angina	Occurred	= 9	
	Reason for stopping	= 15	
Estrogen status	Positive = –5, Negative	= 5	
	Total score		

Source: Morise AP, Olson MB, Merz CN, et al. Validation of the accuracy of pretest and exercise test scores in women with a low prevalence of coronary disease: the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. Am Heart J. 2004;147:1085-92.

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