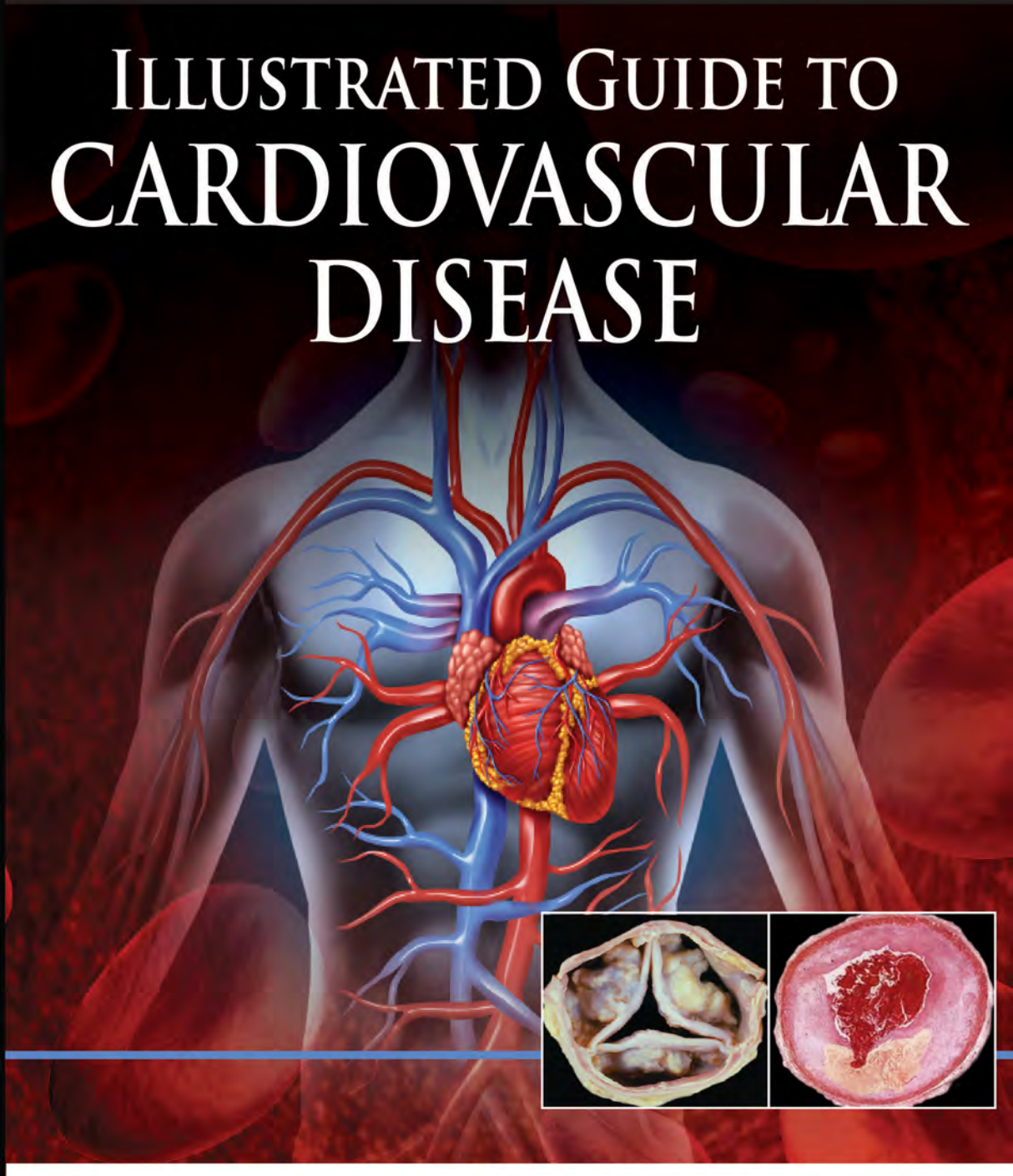
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ILLUSTRATED GUIDE TO CARDIOVASCULAR DISEASE



Glenn N Levine

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CHAPTER

3 Cardiac Stress Tests

Jo Mahenthiran

Snapshot

- Stress Modalities
- Stress Echocardiography
- Radionuclide Myocardial Perfusion Imaging Stress
- Cardiac MRI Stress

INTRODUCTION

Cardiac stress testing is an important non-invasive tool for the diagnosis and prognostic risk assessment of patients with suspected or known coronary artery disease (CAD). Stress tests elicit the physiological significance of a high grade (≥70%) lumen stenosis by highlighting the mismatch between coronary blood flow (supply) and myocardial oxygen consumption (demand) as the cause of myocardial ischemia (Fig. 3.1). Since the pioneering work Robert Arthur Bruce (Fig. 3.2), there have been a dramatic evolution in cardiac stress testing.

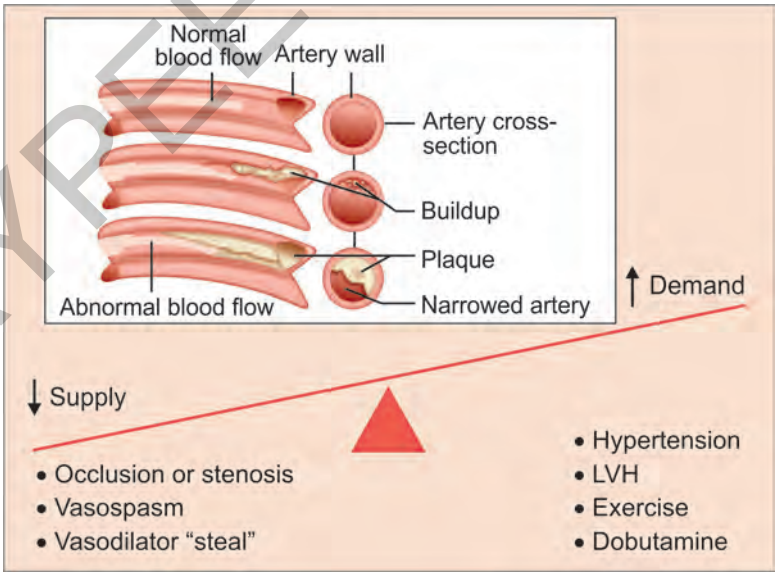


Fig. 3.1: Schematic diagram outlining the principle of stress testing and common causes of imbalance between decreased blood supply and increased myocardial oxygen demand. (LVH: Left ventricular hypertrophy).

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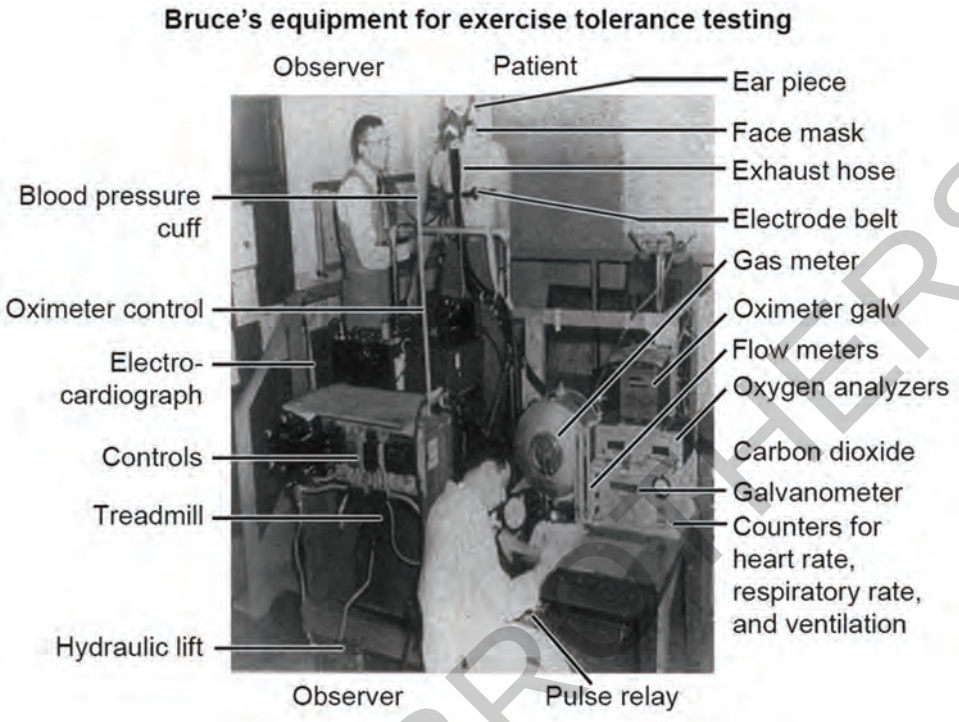


Fig. 3.2: Historic photograph of the arrangement of equipment for Bruce's method of exercise tolerance testing. While one observer remains on the treadmill platform with the patient, records blood pressure, electrocardiogram, symptoms and signs, the other observer seated at the continuous analyzer records the heart rate respiratory rate, ventilation volume, gas concentrations, and oxymeter at 1 minute intervals. [Image and figure legend from Upadhyayula S and Kapur KK. History of stress echocardiography. In: Chopra HK and Nanda NC (Eds). Textbook of cardiology (a clinical & historical perspective). Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, India].

Common indications for stress testing are listed on Table 3.1. Cardiac stress testing is generally not indicated as part of screening asymptomatic patients except for a few select sub-groups, such as high risk occupations (airline pilots) and CAD risk equivalent clinical status (diabetes, high coronary calcium score). Stress testing should be avoided in acutely symptomatic patients, such as those with clear rest (unstable) angina.

Figure 3.3 summarizes the ischemic cascade in patient who develop myocardial ischemia. It is of note that other than frank myocardial necrosis, chest pain is the last manifestation of myocardial ischemia.

STRESS MODALITIES

Cardiac stress testing is generally performed with exercise in most patients able to attain adequate cardiac work load. Pharmacological agents are used as an alternate in those who cannot or unable to exercise adequately. Low level exercise can be combined with some pharmacological agents to reduce side effects. Common types of cardiac stress modalities include: symptom-limited exercise electrocardiographic (ECG) stress; symptom-limited exercise ECG combined with imaging using either echocardiography (stress echo) or radionuclide myocardial perfusion imaging (stress

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MPI); pharmacological stress test using vasodilator stress agents (adenosine, dipyridamole or A2A receptor agonists such as regadenoson) or inotropic and or chronotropic agents (dobutamine, dopamine) combined with stress echo or stress MPI or cardiac magnetic resonance imaging (CMRI); and alternate rare forms of stress includes rapid pacing, emotional stress and cold pressor.

The choice of stress tests depends on many factors such as but not limited to: the patient's ability and willingness to exercise; resting electrocardiogram (ECG) abnormalities; body habitus; clinical indication(s) for stress

Table 3.1: Indications for cardiac stress testing.

Adult patients with chest pain suspected of angina or angina equivalent symptoms, or abnormal EKG suspicious for coronary artery disease with intermediate or high pre-test probability for atherosclerotic vascular diseases based on gender, age and medical co-morbidities.
Low risk patients with unstable angina symptoms, 8–12 hours after presentation without active ischemic or heart failure signs
Patients following myocardial infarction after > 48 hours of presentation without active ischemic symptoms or signs for active prescription, prognostic risk stratification or evaluation of medical treatment.
Patients with known CAD or prior coronary revascularization with new or worsening symptoms suggestive of coronary ischemia or heart failure.
Patients with certain valve disease for assessment of functional status, symptoms and/or hemodynamic response with exercise.
Patients with cardiomyopathy or heart failure for exclusion of ischemia, to assess functional capacity and for being considered for heart transplant (with ventilatory gas analysis).
Prior to selected non-cardiac surgeries as part of further CAD risk stratification.
Patients with selected heart rhythm disorders, congenital heart block, exercise-induced arrhythmia and to evaluate response to therapy.

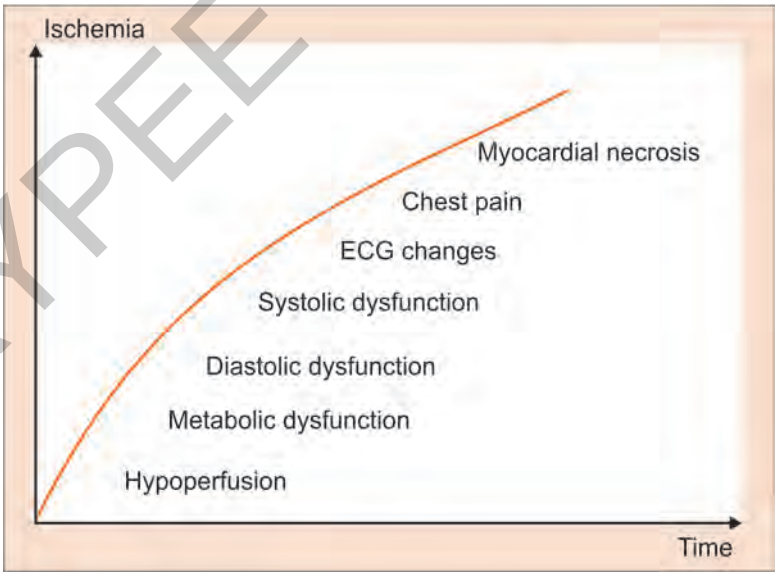


Fig. 3.3: The ischemic cascade. (Image from Lonnebakken MT and Gerdts E. Contrast echocardiography in coronary artery disease. In: Baskot B. Coronary angiography—advances in noninvasive imaging approach for evaluation of coronary artery disease. Intechweb.org.).

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testing; the need for obtaining a conclusive test (specificity, sensitivity, positive and negative predictive values); and whether there is a clinical reason to compare a current stress test result with a similar prior stress test result.

Exercise Stress Tests

Symptom-limited exercise on a treadmill would be the preferred stress modality in most patients who are able to exercise and have a normal resting ECG. Exercise provides additional information on symptoms, hemodynamic response, rhythm abnormalities and additional incremental prognostic risk assessment. Other modes of exercise include bicycle (supine and upright) and 6-minute walk test. A cardiopulmonary stress testing combines exercise with ventilatory gas exchange analysis (Fig. 3.4). Although numerous exercise protocols have been developed and utilized over time (Fig. 3.5), the most common exercise treadmill test (ETT) protocol currently utilized is the Bruce protocol, in which treadmill elevation grade and speed increase every 3 minutes.



Fig. 3.4: Historic photograph of the original bicycle ergometer used in Benedict's experiments to assess exercise energy metabolism in 1919. [Image and figure legend from Upadhyayula S and Kapur KK. History of stress echocardiography. In: Chopra HK and Nanda NC (Eds). Textbook of cardiology (a clinical & historical perspective). Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, India].

Functional class	Clinical status	O_2 cost mL/kg/min	METs	Bicycle ergometer	Treadmill protocols					METs
					Bruce	Bulke-wate	Ellestad	McHonry	Naughton	
				1 watt-6 kpds	3 min stages	% GT at 3.3 mph 1-min stages	3/2/3 min stagess		2-min stages 3.0 mph % GR	
					mph % GR					
				For 70 kg body weight, kpds	5.5 2.0		mph % GR			
Normal and I	Healthy dependent on age, activity	56.0	16		5.0 1.8	26	6 15		32.5	16
		52.5	15			25			30.0	15
		49.0	14	1500		24	5 15	mph % GR	27.5	14
		45.0	13		4.2 16	23		3.3 21	25.0	13
		42.0	12	1350		22		3.3 18	22.5	12
		38.5	11	1200		21	5 10	3.3 15	20.0	11
		35.0	10	1050		20			17.5	10
		31.5	9	900	3.4 14	19			15.0	9
		28.0	8	750		18	4 10	3.3 12	12.5	8
		24.5	7		2.5 12	17			10.0	7
II	Sedentary healthy	21.0	6	600		16	3 10	3.3 9	7.5	6
		17.5	5	450	1.7 10	15			5.0	5
III	Limited	14.0	4	300	1.7 5	14	1.7 10	3.3 6	2.5	4
		10.5	3	150		13			0.0	3
IV	Symptomatic	7.0	2		1.7 0	12		2.0 3		2
		3.5	1			11				1
						10				
						9				
						8				
						7				
						6				
						5				
						4				
						3				
						2				
						1				

Fig. 3.5: Exercise treadmill testing protocols and their associated metabolic equivalents (METS) at different test stages. [Image from Uveroi A and Froelicher. In: Chatterjee K, et al. Cardiology—an illustrated textbook. Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, India].

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Table 3.2: Contraindication to cardiac stress testing.

Acute myocardial infarction of < 2 days duration
High risk unstable angina
Decompensated clinical heart failure or arrhythmia
Advanced atrioventricular heart block
Symptomatic severe valve disease
Acute myocarditis or pericarditis
Uncontrolled accelerated hypertension (> 220 /110 mm Hg).
Acute systemic illness (Pulmonary embolism, Aortic dissection)

Maximum predicted heart rate during treadmill testing is predicted by the formula:

Maximum heart rate (HR) estimate = 220–Age (in years) ± 10–12 beats/minute

Estimated 85% of this maximum HR is considered diagnostic with exercise stress testing.

Metabolic Equivalent (MET) as a measure of exercise capacity refers to a unit of oxygen uptake in a resting person. 1 MET is equivalent to 3.5 mL O_2/Kg/min of the body weight. Measured respiratory oxygen uptake (VO_2) in ml O_2/Kg/min divided by 3.5 mL O_2/Kg/min determines the number of METs. This helps to standardize exercise protocols, quantify exercise capacity, and assess prognosis.

Patients with ECG abnormalities such as complete left bundle branch block (LBBB), preexcitation (Wolff-White Parkinson syndrome, WPW), left ventricular hypertrophy (LVH) with ST segment changes greater than 1 mm (0.1 mV), ST-segment depression on resting ECG, current digoxin use, and paced ventricular rhythms are considered to have conditions that preclude diagnostic interpretation of changes in the ST segment, and should undergo a pharmacological stress exam combined with an imaging modality. A summary of the common contraindications and indications for terminating an exercise stress is listed in Tables 3.2 and 3.3, respectively.

Table 3.3: Indications for terminating exercise testing.

ST-segment elevation (≥ 1.0 mm) in two contiguous leads without pathological Q waves other than leads V1 or aVR
Systolic blood pressure drop > 20 mm Hg from baseline despite an increase in workload, especially with other evidence of coronary ischemia
Patient's desire to stop or increasing nervous system symptoms such as ataxia or near syncope
Exercise limiting symptoms of severe angina, fatigue or shortness of breath.
Sustained or symptomatic ventricular tachycardia, uncontrolled arrhythmia.
Technical difficulties in monitoring EKG or blood pressure.
Marked ST-segment (> 2.5 mm horizontal ST depression) or marked QRS axis shift.
Accelerated hypertensive response (systolic pressure > 240 mm Hg and/or diastolic pressure > 115 mm Hg)

Exercise Stress ECG

The standard configuration of ECG leads during exercise stress testing is shown in Figure 3.6. Peak exercise stress ECG with the development of 1 mm (0.1 mV) or greater junctional point (J-point) depression, as compared to PQ segment as the isoelectric reference, with relatively flat ST segment slope or 1.0 mm or more horizontal or downsloping ST depression 60-80 msec after the J-point, on three consecutive beats with a stable baseline, is considered abnormal (Figs. 3.7 to 10). The J-point depression with a rapid upsloping ST segment shift of more than 1 mm (0.1 m) but less than 1.5 mm is considered a normal variant exercise ECG response (Fig. 3.11).

Greater ST-segment depression (> 1.5 mm), early onset, greater number of leads (especially involving leads V4-V6) with ST-segment depression have the greatest diagnostic yield for myocardial ischemia. About 10% of patients would have ST-segment depression seen only during the recovery stages of exercise (Fig. 3.12). This finding has comparable diagnostic accuracy compared to ST depression occurring

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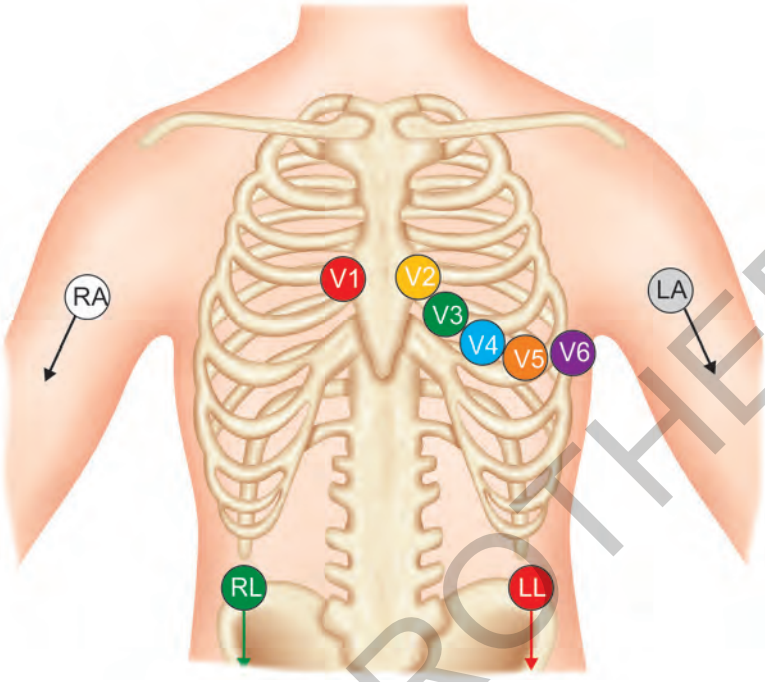


Fig. 3.6: Standard configuration of ECG lead placement during exercise treadmill testing.



Fig. 3.7: Interpretation of ST segment changes during treadmill stress testing. ST-segment depression is assessed 0.08 msec after the J-point (0.06 msec during tachycardia). The PQ segment is used as a reference isoelectric point to assess the degree of ST-segment depression.

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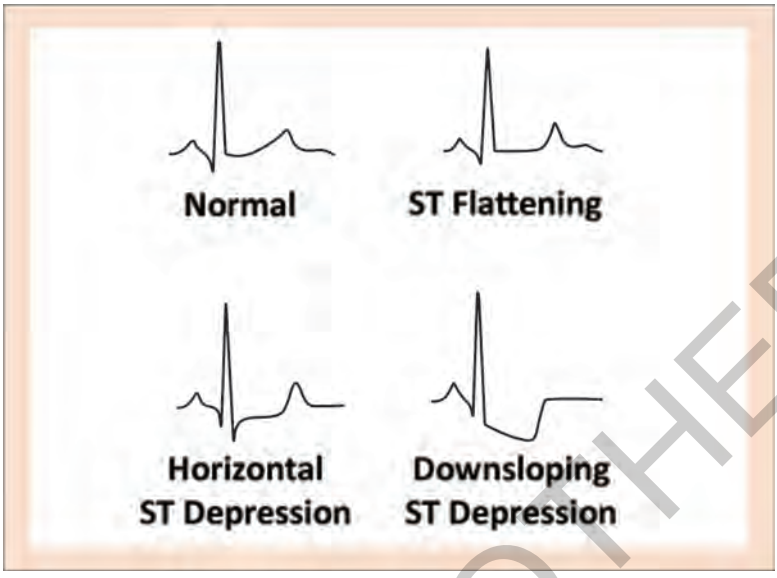


Fig. 3.8: Normal and abnormal ST segment responses to exercise.

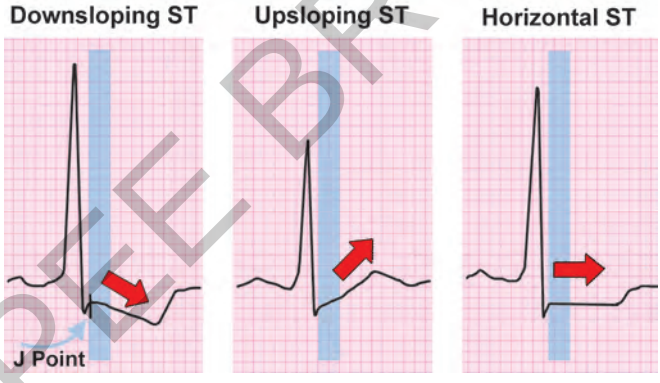


Fig. 3.9: The types of ST-segment depression during exercise stress testing. A downsloping ST segment is considered more specific for ischemia than an upsloping ST segment.

during exercise. Exercise induced new persistent ST-segment elevation of ≥1.0 mm at 60-80 msec after J-point in three consecutive beats with a stable baseline and in the absence of corresponding Q-waves (Fig. 3.13) is a specific marker of transmural ischemia due to high grade coronary luminal stenosis or coronary spasm. ST-segment elevation in lead aVR during exercise stress testing, particularly if there is also diffuse ST-segment depression in other leads (Fig. 3.14), has been correlated with a greater incidence of significant left main and/or 3 vessel coronary artery disease.

Exercise-induced ST-segment depression is a poor localizer and ST-elevation is more specific for the territory of coronary ischemia. Anemia, hyperventilation, left ventricular hypertrophy, cardiomyopathy, valve disease,

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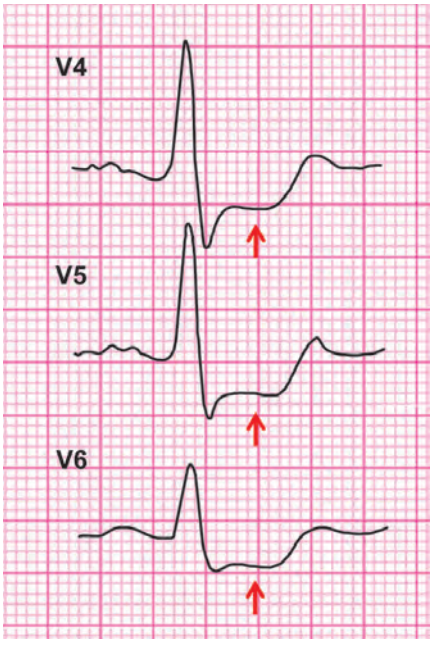


Fig. 3.10: Example of horizontal ST segment during exercise treadmill testing. There is 2-3 mm horizontal ST-segment depression in leads V4-V6. [Image adapted from Bhalerao JC. Exercise electrocardiographic testing. In Bhalerao JC. Essentials of Clinical Cardiology. Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, India].

hyperglycemia and hypokalemia are some common non-CAD related causes of abnormal ST-segment depression with exercise.

Pharmacologic Stress Tests

Adenosine receptor agonists (adenosine), A2A receptor agonists (regadenoson), and dipyridamole (Persantine) induce coronary arteriolar vasodilation and may induce relative or absolute reduction in blood flow and ischemia in areas of the myocardium subtended by significant coronary stenoses by coronary steal phenomenon. These agents are contraindicated in patients with hypersensitivity to the agents, severe bronchospasm-related airway disease, sick sinus syndrome, second degree or higher degree atrioventricular block in the absence of a pacemaker, severe hypotension (systolic < 90 mm Hg), and in acute clinical syndromes as listed in Table 3.2. Several transient systemic side effects such as headache, nausea, flushing, dizziness, abdominal discomfort, dysgeusia and shortness of breath are commonly reported with these agents. Development of chest discomfort is non-specific for ischemia

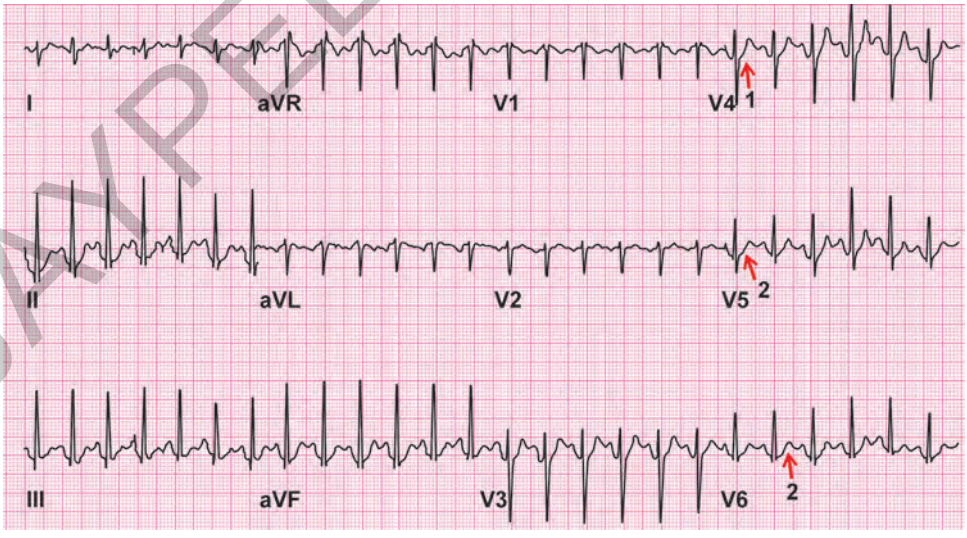


Fig. 3.11: Peak exercise 12-lead EKG with upsloping J-point depression (arrow 1) and <1.5 mm early upsloping ST-segment depression (arrow 2) is a normal response with exercise.

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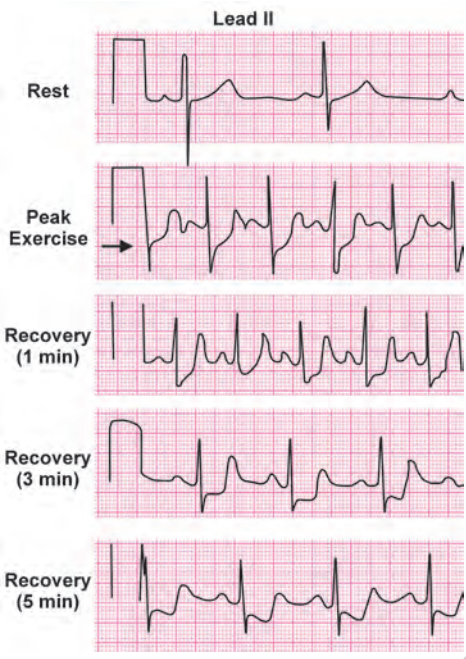


Fig. 3.12: ST-segment depression occurring predominantly during the recovery phase of an exercise treadmill test. This finding has comparable diagnostic accuracy compared to ST depression occurring during exercise. [Image from Chugh SN. Stress Electrocardiography. In: Chugh SN (Ed). Textbook of Clinical Electrocardiography (2nd edition). Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, India].

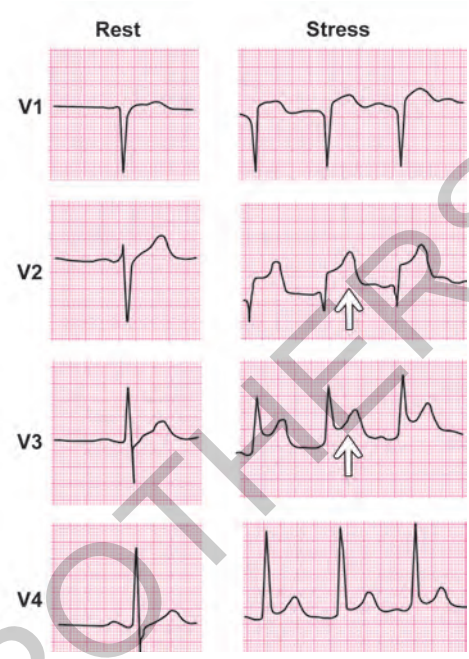


Fig. 3.13: ST-segment elevation, most prominently in leads V2 and V3 (arrows), occurring during an exercise treadmill test. Exercise induced new persistent ST-segment elevation of ≥1.0 mm at 60-80 msec after the J-point occurring in three consecutive beats with a stable baseline and in the absence of corresponding baseline Q-waves is a specific marker of transmural ischemia due to high grade coronary luminal stenosis or coronary spasm. [Image from Chugh SN. Stress Electrocardiography. In: Chugh SN (Ed). Textbook of Clinical Electrocardiography (2nd edition). Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, India].

with these agents. Recent exposure to caffeine, aminophylline or theobromine block the effect of adenosine, and anti-ischemic medications may decrease the diagnostic accuracy of such pharmacologic stress testing, and thus it is recommended that patients refrain from ingestion of caffeine-containing products, and hold aminophylline- or theobromine-containing drugs and anti-ischemic medications prior to such testing. Some patients who experience significant chest pain with dipyridamole stress testing may be treated with aminophylline administration to reverse the vasodilating effects of dipyridamole.

The sensitivity of ECG changes with pharmacological agents is low, but rare abnormal ST-segment depression in response to administration of vasodilator agents may be a specific marker of high grade CAD (Fig. 3.15).

An alternative to vasodilator agents in the performance of stress testing is the use instead of dobutamine. Dobutamine is a synthetic catecholamine that causes ischemia by increased heart rate and increased myocardial contractility via beta-adrenergic receptor stimulation that results in increased myocardial work load and wall stress. Hypotension, hypertension and rhythm complications are more common with

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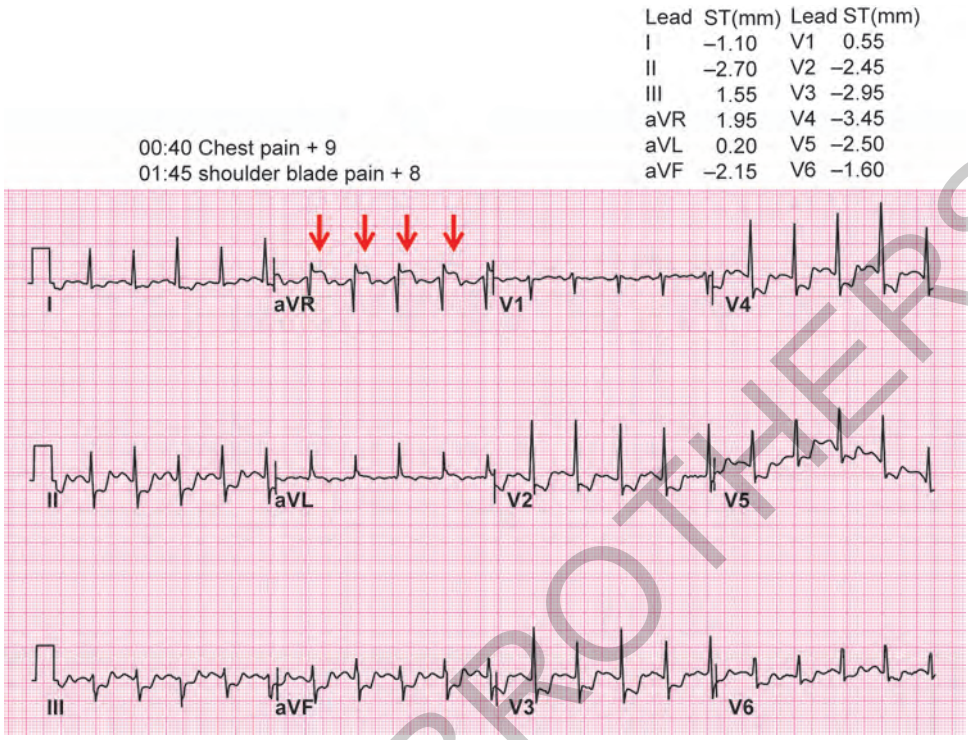


Fig. 3.14: ST-segment elevation in lead aVR (arrows), as well as diffuse marked ST-segment depression in numerous other leads during exercise treadmill testing. These findings are suggestive of the presence of left main or 3 vessel coronary artery disease.

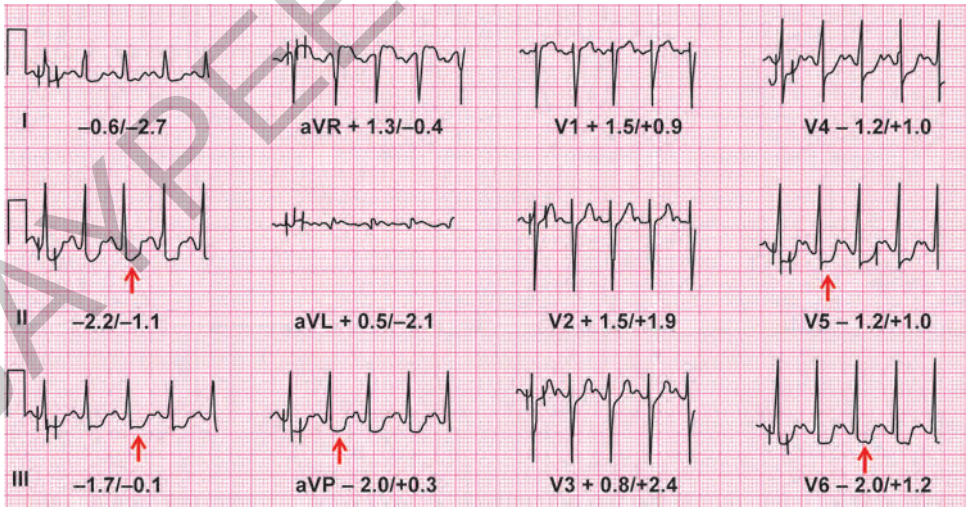


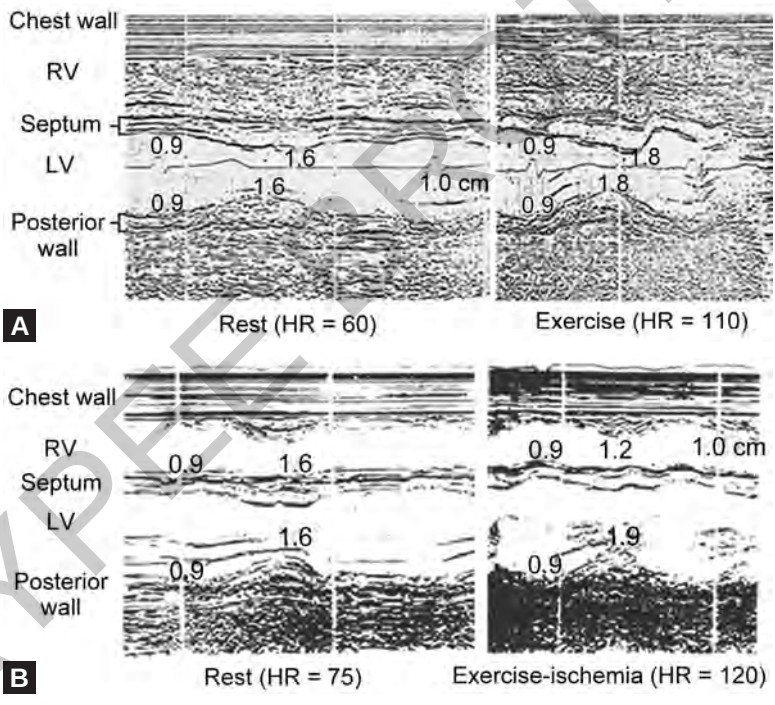
Fig. 3.15: Rare ST depression (arrows) occurring with dipyridamole administration during a chemical nuclear stress test, suggestive of high grade obstructive CAD. [Image from Mahapa GN. History of nuclear cardiology. In: Chopra HK and Nanda NC (Eds). Textbook of cardiology (a clinical and historical perspective). Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, India].

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high-dose dobutamine stress testing. Achieving adequate stress peak heart rate (HR) and double product (HR × systolic BP) improves CAD diagnosis. If an adequate HR response is not achieved with dobutamine infusion alone, atropine may be additionally administered in some cases.

STRESS ECHOCARDIOGRAPHY

In stress echocardiography, ventricular wall thickening and ventricular contraction is compared between basal conditions and during stress. Both treadmill stress testing and pharmacological-induced stress testing are utilized in clinical practice. Treadmill stress testing has the advantage of being a more "physiological" stress test, though obtaining good quality images immediately after exercise performance can be challenging. The agent most commonly utilized during stress echocardiography is dobutamine. Although the earliest forms of stress testing imaged the heart using M-mode echocardiography (Figs. 3.16A and B), current practice is to image the heart using 2D images obtained in multiple views (usually including apical 4 chamber, apical 2 chamber, and short axis views). 3D imaging is also being used at some centers.



Figs. 3.16A and B: Historical images of M-mode echocardiography during stress testing. (A) M-mode echocardiograms at rest (left) and exercise (right) in a person without any significant coronary artery disease. Systolic thickening of the septal and posterior (inferolateral) walls is the same at rest and increases in both territories with exercise. (B) M-mode echocardiograms at rest (left) and peak exercise (right) from a patient with near total occlusion of the left anterior descending (LAD) artery and normal left circumflex and right coronary arteries. Both septal and posterior wall thickening are the same at rest. In exercise, at the time of ischemia, posterior wall systolic thickening has increased, while septal thickening has decreased, indicative of ischemia. [Image and figure legend from Upadhyayula S and Kapur KK. History of stress echocardiography. In: Chopra HK and Nanda NC (Eds). Textbook of cardiology (a clinical & historical perspective). Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, India].

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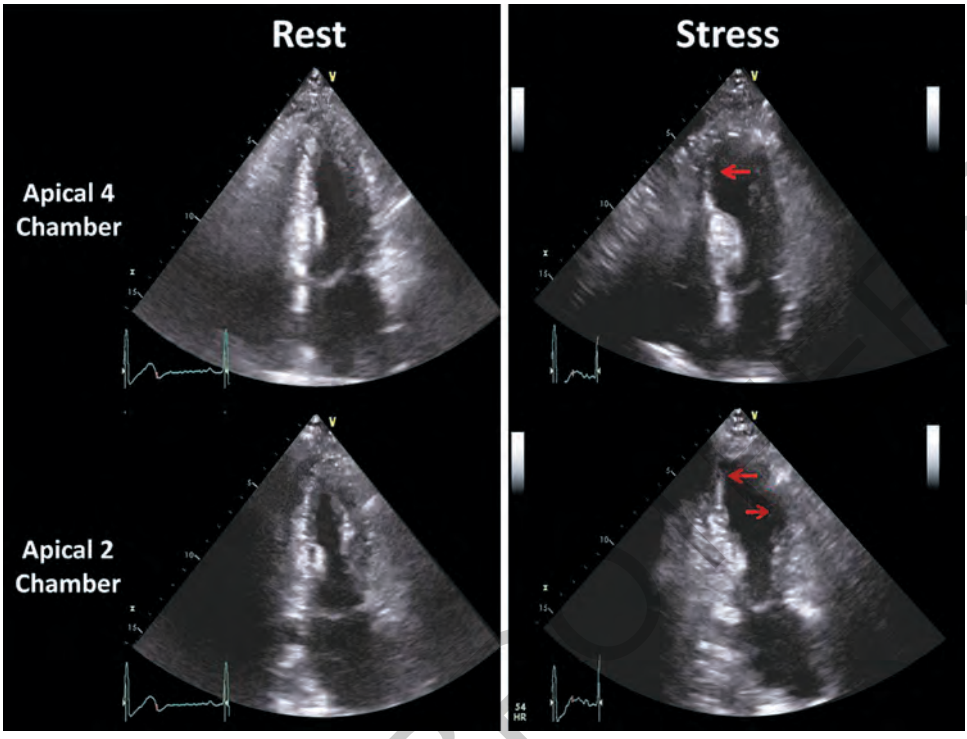


Fig. 3.17: Exercise stress echo test images. Apical four and two chamber stress echo images demonstrate normal systolic wall thickening at rest and reduced systolic thickening, motion and increased cavity size (arrows) in the mid and distal anterior walls, apex, and distal inferoseptal wall immediately post-exercise, suggestive of left anterior descending coronary artery (LAD) stenosis (large wrap-around LAD). (Image courtesy of Glenn N Levine).

The current standard for analysis of a normal stress echo is the visual assessment of uniform increase in systolic wall motion, systolic wall thickening and reduction in left ventricular cavity size from rest to stress. Reduction or worsening regional wall motion and or reduced thickening with increase in corresponding cavity size in systole following stress is indicative of myocardial ischemia (Figs. 3.17 to 3.19).

With exercise (treadmill) stress echocardiography, images are obtained before and after exercise (Fig. 3.17). With dobutamine stress echo, images are obtained during test, low dose dobutamine infusion, high dose dobutamine infusion, and during recovery (Fig. 3.18).

Administration of an echo contrast agent is often used during dobutamine stress echo to improve image quality (Figs. 3.19A and B). Myocardial contrast echocardiography with administration of a contrast agent may also allow for detection of delayed contrast enhancement in areas of the left ventricle, suggestive of significant coronary stenosis or occlusion in the artery subtending that segment or segments (Fig. 3.20).

Regional wall motion abnormalities are interpreted with respect to the usual coronary artery which subtends the abnormal myocardial segment or segments, with the recognition that there is some variability and overlap in the coronary supply of some segments (Fig. 3.21).

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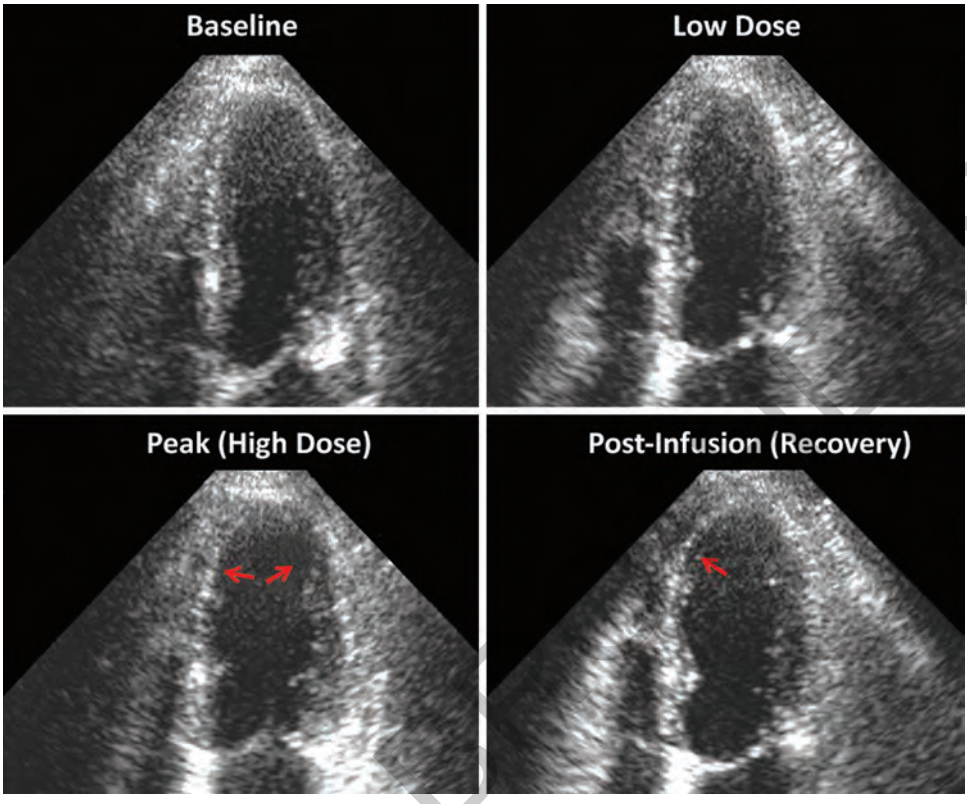


Fig. 3.18: End-systolic images obtained during dobutamine stress echocardiography. Images displayed are the apical four chamber view at baseline, at low dose dobutamine infusion, at peak dobutamine infusion, and post-infusion (recovery). There is reduced wall thickening (arrows) and an increase in cavity size at peak and post-infusion images, consistent with stress—induced ischemia in multiple coronary artery territories, suggestive of the presence of multivessel coronary artery disease. (Image courtesy of Glenn N Levine).

Stress echocardiography has a number of advantages as compared to other imaging techniques, including great versatility and providing ancillary information of global left and right ventricular systolic function, diastolic function, valvular function, and hemodynamics, with reliable accuracy and at a low cost. However, several factors, , suboptimal image quality (such as in patients of very large body habitus or with severe COPD), inadequate achievement of peak stress (such as poor chronotropic response), and subjectivity and variability of image interpretation, may reduce the overall sensitivity of stress echocardiography, especially in patients with less severe CAD. Although some false positive studies may result from challenges in wall motion assessment, a significant proportion of false positive studies are due to myocardial ischemia in the absence of obstructive CAD as seen with left ventricular hypertrophy, cardiomyopathy, or microvascular disease. False positive studies may result from tethering of myocardial segments from prior myocardial infarction or to less mobile structures such as the mitral annulus, or from dyssynchronous contraction

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Illustrated Guide to CARDIOVASCULAR DISEASE

The success of the hardcover textbook Color Atlas of Cardiovascular Disease served as the impetus for this handbook *Illustrated Guide to Cardiovascular Disease*. Illustrated Guide is an endeavor in handbook form to illustrate the spectrum of normal cardiovascular anatomy and function, cardiovascular disease, and cardiovascular therapies. Diseases and conditions included in this guide include coronary artery disease, acute coronary syndromes, heart failure and cardiomyopathies, valvular heart disease, congenital heart disease, peripheral arterial disease, renovascular disease, diseases of the aorta, arrhythmias, cardiac tumors, venous thromboembolism, and other cardiovascular conditions. Normal and abnormal cardiovascular anatomy, function, and pathology are described and illustrated. Dozens of well established and emerging device-based therapies are illustrated and discussed, including PCI, CABG, ablation therapy, stent grafts, peripheral bypass, endarterectomy, arrhythmia ablation, septal closure devices, atrial appendage occluders, and TAVR. Both American and European practice guidelines for the management of specific cardiovascular diseases are summarized and discussed.

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Over one hundred and fifty national and international cardiovascular experts, representing almost every continent and part of the world, contributed to this project. Hundreds of other investigators, academicians, and practitioners shared images that were used in this project.



Glenn N Levine MD FAHA FACC is Professor of Medicine at Baylor College of Medicine and Director of the Cardiac Care Unit at the Michael E DeBakey VA Medical Center in Houston, Texas, USA, and an internationally recognized author and expert on cardiovascular disease. He has authored or edited 12 books on cardiovascular disease and pharmacotherapy. Dr Levine lectures extensively throughout the United States, as well as internationally, on antiplatelet and antithrombotic therapies, acute coronary syndromes, coronary revascularization, and guideline-directed cardiovascular therapies. Dr Levine is the recipient of 5 Fulbright & Jaworski educational and teaching awards. Dr Levine has been and continues to be very involving in formulating cardiovascular practice guidelines and statements. He has been writing as Group Chairman for 5 American Heart Association (AHA) Scientific Statements and AHA-sponsored scientific manuscripts. He served as Chair of the writing group of the 2011 ACCF/AHA/SCAI Guideline on Percutaneous Coronary Intervention, and as a writing group member of the 2014 ACCF/AHA Guideline for the Management of Patients with Non-ST-Segment Elevation Acute Coronary Syndrome and the 2014 ACCF/AHA Guideline Focused Update on the Management of Patients with Stable Ischemic Heart Disease. Dr Levine is co-chair of the 2015 ACC/AHA Focused Update on Primary PCI and Chair of the 2015 ACC/AHA Focused Update on Duration of Dual Antiplatelet Therapy. Dr Levine has been designated as Chair-elect of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.

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