Ischemic Heart Disease

Chapter 284 | Harrison's 22e | Part 6 – Cardiovascular Disorders | DETAILED EDITION

KEY CLINICAL POINTS

1. See source text for full details

FIGURES IN THIS CHAPTER

RAW CONTENT

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PART

6

Disorders

of

the

Cardiovascular

System

the general context of population growth and as a result of the increase

Section 5 Coronary and Peripheral

in the average age of the world’s population. With urbanization in

Vascular Disease countries with emerging economies and a growing middle class, ele-

ments of the energy-rich Western diet are being adopted. As a result,

the prevalence of risk factors for IHD and the prevalence of IHD itself

are both increasing rapidly, so that in analyses of the global burden

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of disease, there is a shift from communicable to noncommunicable

diseases, and it is estimated that globally over 200 million people live

Robert P. Giugliano, Elliott M. Antman, with IHD. Population subgroups that appear to be particularly affected

Joseph Loscalzo are men in South Asian countries, especially India and the Middle East.

IHD is a major contributor to the number of disability-adjusted life-

years (DALYs) experienced globally.

Ischemic heart disease (IHD) is a condition in which there is an inad-

PATHOPHYSIOLOGY

equate supply of blood and oxygen to a portion of the myocardium;

it typically occurs when there is an imbalance between myocardial Central to an understanding of the pathophysiology of myocardial

oxygen supply and demand. The most common cause of myocardial ischemia is the concept of myocardial supply and demand. In normal

ischemia is atherosclerotic disease of an epicardial coronary artery conditions, for any given level of a demand for oxygen, the myocar-

(or arteries) sufficient to cause a regional reduction in myocardial dium will control the supply of oxygen-rich blood to prevent under-

blood flow and inadequate perfusion of the myocardium supplied perfusion of myocytes and the subsequent development of ischemia

by the involved coronary artery. This chapter focuses on the chronic and infarction. The major determinants of myocardial oxygen demand

manifestations and treatment of IHD (sometimes referred to as chronic (MVO) are heart rate, myocardial contractility, and myocardial wall

2

coronary disease or chronic coronary syndrome), while the subsequent tension (stress). An adequate supply of oxygen to the myocardium

chapters address the acute phases of IHD. requires a satisfactory level of oxygen-carrying capacity of the blood

(determined by the inspired level of oxygen, pulmonary function,

EPIDEMIOLOGY AND GLOBAL TRENDS and hemoglobin concentration and function) and an adequate level

IHD causes more deaths and disability and incurs greater economic of coronary blood flow. Blood flows through the coronary arteries in

costs than any other illness in the developed world. IHD is the most a phasic fashion, with the majority occurring during diastole. About

common, serious, chronic, life-threatening illness in the United States, 75% of the total coronary resistance to flow occurs across three sets

where 20.5 million persons have IHD. Although there is regional of arteries: (1) large epicardial arteries (Resistance 1 = R), (2) prear-

1

variation, ~3–4% of the population has sustained a myocardial infarc- teriolar vessels (R), and (3) arteriolar and intramyocardial capillary

2

tion. Genetic factors, a high-fat and energy-rich diet, smoking, and a vessels (R). In the absence of significant flow-limiting atheroscle-

3

sedentary lifestyle are associated with the emergence of IHD. In the rotic obstructions, R is trivial; the major determinant of coronary

1

United States and Western Europe, IHD is growing among low-income resistance is found in R and R (Fig. 284-1). The normal coronary

2 3

groups, but primary prevention has delayed the disease to later in life circulation is dominated and controlled by the heart's requirements

across socioeconomic groups. Despite these sobering statistics, it is for oxygen. This need is met by the ability of the coronary vascular

worth noting that epidemiologic data show a decline in the rate of bed to vary its resistance (and, therefore, blood flow) considerably

deaths due to IHD, about half of which is attributable to treatments and while the myocardium extracts a high and relatively fixed percentage

half to prevention by risk factor modification. of oxygen. Normally, intramyocardial resistance vessels demonstrate a

Obesity, insulin resistance, and type 2 diabetes mellitus are increas- great capacity for dilation (R and R decrease). The changing oxygen

2 3

ing and are powerful risk factors for IHD. These trends are occurring in needs of the heart with exercise and emotional stress affect coronary

Macrocirculation Microcirculation

Segment Epicardial arteries >400 µm Small arteries <400 µm Arterioles <100 µm Capillaries <10 µm

and size

Main stimulus

Flow Pressure Metabolites

for vasomotion

Main

Transport Regulation Exchange

function

Percentage of

total resistance

to flow

FIGURE 284-1 Macrocirculation and microcirculation across segments and sizes of the arteries. The location and size of the arteries supplying blood to the heart is shown

at the top. Vasomotion of the arterial segments occurs in response to the stimuli shown. The main function of each of the arterial segments is shown next, followed by a

depiction of the relative resistance to antegrade flow. (Adapted from J Knuuti et al: 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes.

Eur Heart J 41:407, 2020/.)

[TABLE]

Macrocirculation | Microcirculation

Epicardial arteries >400 µm | Small arteries <400 µm Arterioles <100 µm Capillaries <10 µm

Pressure Metabolites

Regulation Exchange

Flow

Transport |

|

[/TABLE]

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CHAPTER

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vascular resistance and, in this manner, regulate the supply of oxygen the bloodstream. Upon exposure of the plaque contents to blood, two

and substrate to the myocardium (metabolic regulation). The coronary important and interrelated processes are set in motion: (1) platelets

resistance vessels also adapt to physiologic alterations in blood pres- are activated and aggregate, and (2) the coagulation cascade is acti-

sure to maintain coronary blood flow at levels appropriate to myocar- vated, leading to deposition of fibrin strands. A thrombus composed

dial needs (autoregulation). of platelet aggregates and fibrin strands traps red blood cells and can

By reducing the lumen of the coronary arteries, atherosclerosis reduce coronary blood flow, leading to the clinical manifestations of

limits appropriate increases in perfusion when the demand for more myocardial ischemia.

coronary flow occurs. When the luminal reduction is severe, myocar- The location of the obstruction influences the quantity of myo-

dial perfusion in the basal state is reduced. Coronary blood flow also cardium rendered ischemic and determines the severity of the clini-

can be limited by spasm (see vasospastic angina in Chap. 285), arterial cal manifestations. Thus, critical obstructions in vessels, such as the

thrombi, and, rarely, coronary emboli as well as by ostial narrowing left main coronary artery and the proximal left anterior descending

due to aortitis. Congenital abnormalities such as the origin of the left coronary artery, are particularly hazardous. Chronic severe coronary

anterior descending coronary artery from the pulmonary artery may narrowing and myocardial ischemia frequently are accompanied by the

cause myocardial ischemia and infarction in infancy, but this cause is development of collateral vessels, especially when the narrowing devel-

very rare in adults. ops gradually. When well developed, such vessels can by themselves

Myocardial ischemia also can occur if myocardial oxygen demands provide sufficient blood flow to sustain the viability of the myocardium

are markedly increased and particularly when coronary blood flow at rest but not during conditions of increased demand.

may be limited, as occurs in severe left ventricular hypertrophy (LVH) With progressive worsening of a stenosis in a proximal epicardial

due t

FLOWCHARTS & ALGORITHMS — FROM HARRISON'S

intraglomerular hypertension and hyperfiltration. Evidence exists that they are helpful in patients with and without diabetes who have a reduced LV ejection fraction.

Colchicine exhibits a number of broad cellular effects (interferes with chemotaxis and phagocytosis of inflammatory cells, reduces the expression of adhesion molecules, modifies cytokine production) that result in an anti-inflammatory effect and may favorably affect the progression of atherosclerosis. In placebo-controlled randomized trials after myocardial infarction, low-dose colchicine (0.5 mg daily) prevented future cardiovascular events; however because it has a narrow therapeutic window, has a long half-life dependent upon renal clearance, is metabolized by CYP3A4, and is a substrate for P-glycoprotein (both of which that may result in drug-drug interactions), additional monitoring is required.

In contrast, nonsteroidal anti-inflammatory drug (NSAID) use in patients with IHD may be associated with a small but finite increased risk of myocardial infarction and mortality. For this reason, they generally should be avoided in IHD patients. If they are required for symptom relief, it is advisable to coadminister aspirin and strive to use an NSAID associated with the lowest risk of cardiovascular events, in the lowest dose required, and for the shortest period of time.

Nicorandil opens ATP-sensitive potassium channels in myocytes, leading to a reduction of free intracellular calcium ions. It is typically administered orally in a dose of 20 mg twice daily for prevention of angina. Nicorandil is not available for use in the United States but is used in several other countries and is recommended as second-line treatment in the European chronic coronary disease (CCD) guidelines. Similarly, trimetazidine, which improves mitochondrial metabolism through inhibition of myocardial fatty acid uptake and oxidation and consequent stimulation of glucose oxidation, is recommended as a second-line antianginal in CCD and is available in many countries outside the United States.

Ivabradine (2.5–7.5 mg orally twice daily) is a specific sinus node inhibiting agent that may be helpful for preventing cardiovascular events in patients with IHD who have a resting heart rate ≥70 beats/min (alone or in combination with a beta blocker) *and* LV systolic dysfunction. However, the data are mixed regarding its clinical benefit, with the most recent U.S. CCD guideline recommending against its use in patients with normal LV function due to an increased risk of death or myocardial infarction).

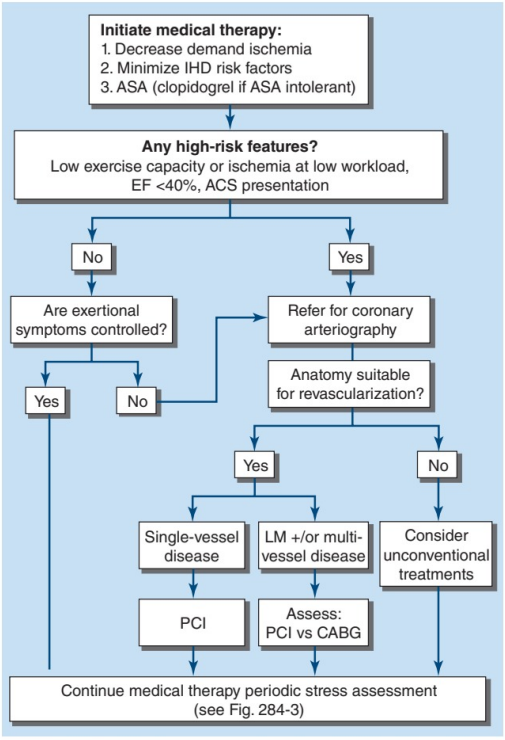


FIGURE 284-4 Algorithm for management of a patient with ischemic heart disease. All patients should receive the core elements of medical therapy as shown at the top of the algorithm. If high-risk features are present, as established by the clinical history, exercise test data, and imaging studies, the patient should be referred for coronary arteriography. Based on the number and location of the diseased vessels and their suitability for revascularization, the patient is treated with a percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery or should

Harrison's 22e · Flowchart 1

FIGURE 284-4 Algorithm for management of a patient with ischemic heart disease. All patients should receive the core elements of medical therapy as shown at the top of the algorithm. If high-risk features are present, as established by the clinical history, exercise test data, and imaging studies, the patient should be referred for coronary arteriography. Based on the number and location of the diseased vessels and their suitability for revascularization, the patient is treated with a percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery or should be considered for unconventional treatments. See text for further discussion. ACS, acute coronary syndrome; ASA, aspirin; EF, ejection fraction; IHD, ischemic heart disease; LM, left main.

They can be detected by using radionuclide scans of myocardial perfusion and metabolism, PET, cardiac MRI, or delayed scanning with thallium-201 or by improvement of regional functional impairment provoked by low-dose dobutamine. In such patients, revascularization improves myocardial blood flow, can return function, and can improve survival.

The Choice Between PCI and CABG All the clinical characteristics of each individual patient must be used to decide on the method of revascularization (e.g., LV function, diabetes, lesion complexity). A number of randomized clinical trials have compared PCI and CABG in patients with multivessel CAD who were suitable technically for both procedures. The redevelopment of angina requiring repeat coronary angiography and repeat revascularization is higher with PCI. This is a result of restenosis in the stented segment (a problem largely solved with drug-eluting stents) and the development of new stenoses in unstented portions of the coronary vasculature. It has been argued that PCI with stenting focuses on culprit lesions, whereas a bypass graft to the target vessel also provides a conduit around future culprit lesions proximal to the anastomosis of the graft to the native vessel (Fig. 284-5). By contrast, stroke rates are lower with PCI.

Based on available evidence, it is now recommended that patients with lifestyle-limiting angina despite guideline-directed medical management and therapy be considered for coronary revascularization. Patients with single- or two-vessel disease with normal LV function and anatomically suitable lesions ordinarily are advised to undergo PCI (Chap. 287). For patients who are poor candidates for surgery, it is reasonable to choose PCI over CABG to improve symptoms and reduce major adverse

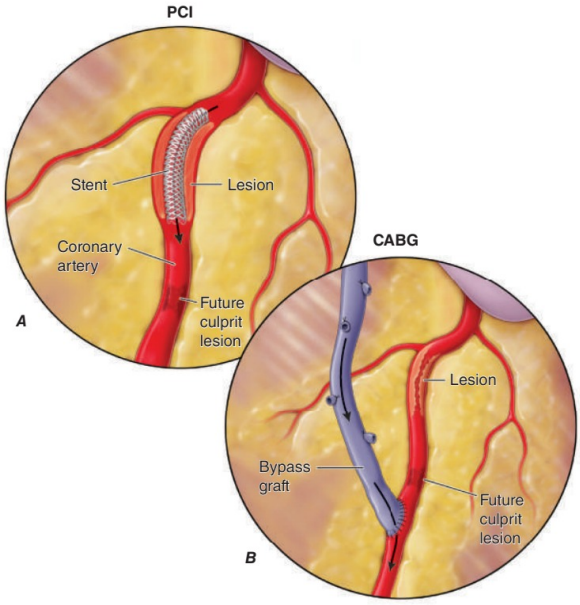


FIGURE 284-5 Difference in the approach to the lesion with percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). PCI is targeted at the "culprit" lesion or lesions, whereas CABG is directed at the epicardial vessel, including the culprit lesion or lesions and future culprits, proximal to the insertion of the vein graft, a difference that may account for the superiority of CABG, at least in the intermediate term, in patients with multivessel disease. (*From The*

Harrison's 22e · Flowchart 2

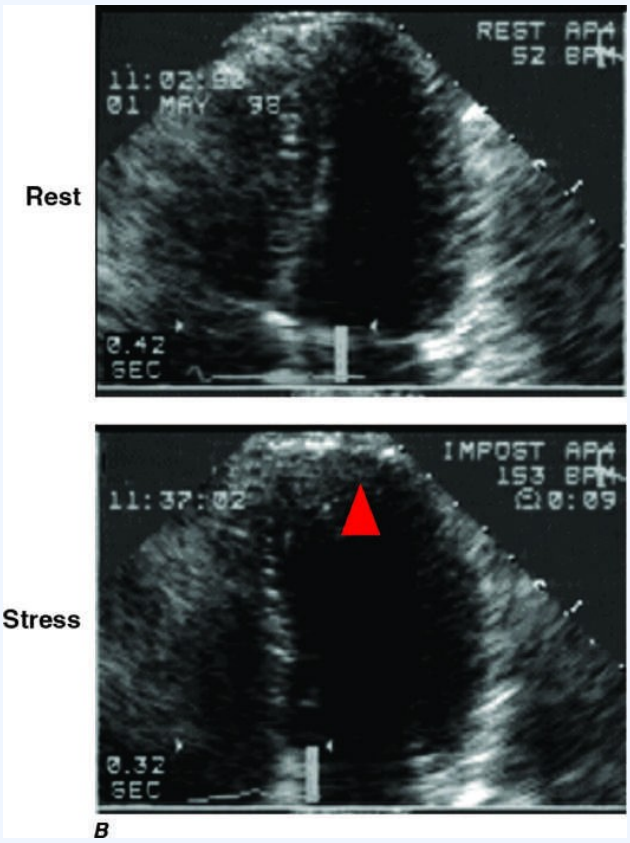
FIGURE 284-5 Difference in the approach to the lesion with percutaneous coronary (PCI) and coronary artery bypass grafting (CABG). PCI is targeted at the "culprit" lesion whereas CABG is directed at the epicardial vessel, including the culprit lesion or lesions culprits, proximal to the insertion of the vein graft, a difference that may account for the of CABG, at least in the intermediate term, in patients with multivessel disease. New England Journal of Medicine, Quantitative Determinants of the Outcome of Mitral Regurgitation, M Enriquez-Sarano et al. 352, 2235. Copyright © 2005. Society. Reprinted with permission from Massachusetts Medical Society.)

FIGURES & ILLUSTRATIONS — FROM HARRISON'S

FIGURE 284-3 Selecting appropriate testing patients with angina and suspected coronary artery disease (CAD). On the left of the figure is an algorithm for selecting from among testing options. In patients who are at low risk, in whom prior testing was equivocal, or in whom the diagnosis of is CAD uncertain, noninvasive functional stress testing with imaging for myocardial ischemia or computed tomography angiography (CTA) is reasonable to establish the diagnosis of CAD prior to initiation of treatment. Patients with a high clinical likelihood of CAD, patients with symptoms despite antianginal therapy or with low-level activities, and patients with high-risk features based on the initial clinical evaluation may proceed directly to invasive coronary angiography without further diagnostic testing. *(Adapted from J Knuuti et al: 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 41:407, 2020.)* Panels ***A–F*** are examples of the data obtained with electrocardiogram (ECG) monitoring and specialized imaging procedures. CMR, cardiac magnetic resonance; EBCT, electron beam computed tomography; ECHO, echocardiography; FFR, fractional flow reserve; IHD, ischemic heart disease; iwFR, instantaneous wave-free ratio; MIBI, methoxyisobutyl isonitrite; MR, magnetic resonance; PET, positron

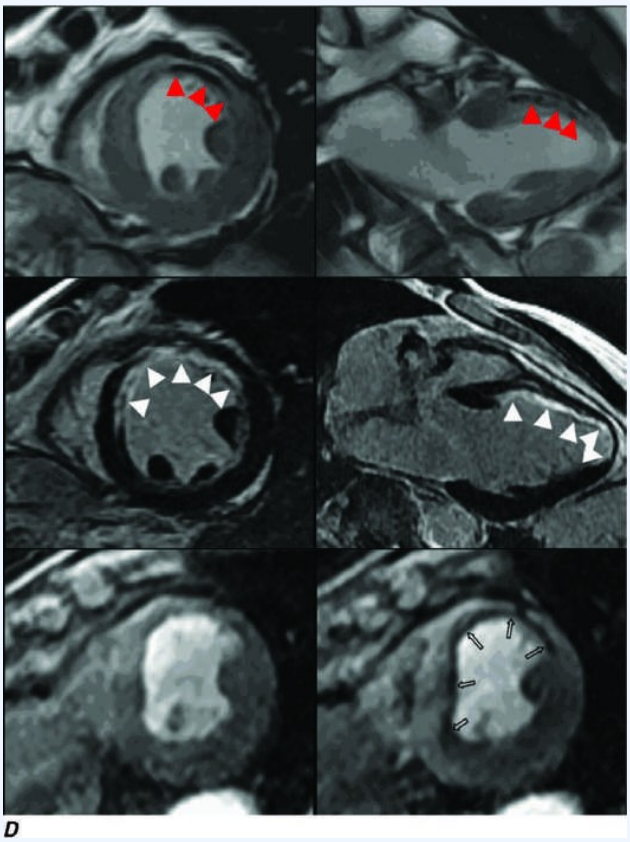
Harrison's 22e · Figure 1

FIGURE 284-3 Selecting appropriate testing patients with angina and suspected coronary artery disease (CAD). On the left of the figure is an algorithm for selecting from among testing options. In patients who are at low risk, in whom prior testing was equivocal, or in whom the diagnosis of is CAD uncertain, noninvasive functional stress testing with imaging for myocardial ischemia or computed tomography angiography (CTA) is reasonable to establish the diagnosis of CAD prior to initiation of treatment. Patients with a high clinical likelihood of CAD, patients with symptoms despite antianginal therapy or with low-level activities, and patients with high-risk features based on the initial clinical evaluation may proceed directly to invasive coronary angiography without further diagnostic testing. (Adapted from J Knuuti et al: 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 41:407, 2020.) Panels A–F are examples of the data obtained with electrocardiogram (ECG) monitoring and specialized imaging procedures. CMR, cardiac magnetic resonance; EBCT, electron beam computed tomography; ECHO, echocardiography; FFR, fractional flow reserve; IHD, ischemic heart disease; iwFR, instantaneous wave-free ration; MIBI, methoxyisobutyl isonitrite; MR, magnetic resonance; PET, positron emission tomography. A. Lead V at rest (top panel) and after 4.5 min of exercise (bottom panel). There is 3 mm (0.3 mV) of horizontal ST-segment depression, indicating a 4 positive test for ischemia. (Adapted from BR Chaitman, in E Braunwald et al [eds]: Heart Disease, 8th ed, Philadelphia, Saunders, 2008.) B. A 45-year-old avid jogger who began experiencing classic substernal chest pressure underwent an exercise echo study. With exercise, the patient's heart rate increased from 52 to 153 beats/min. The



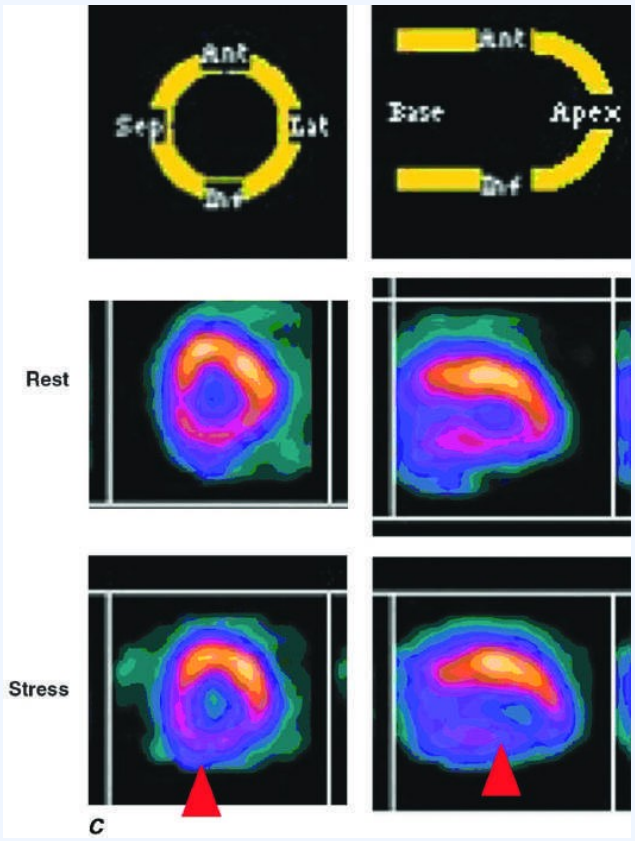
Harrison's 22e · Figure 2

FIGURE 284-3 (Continued)



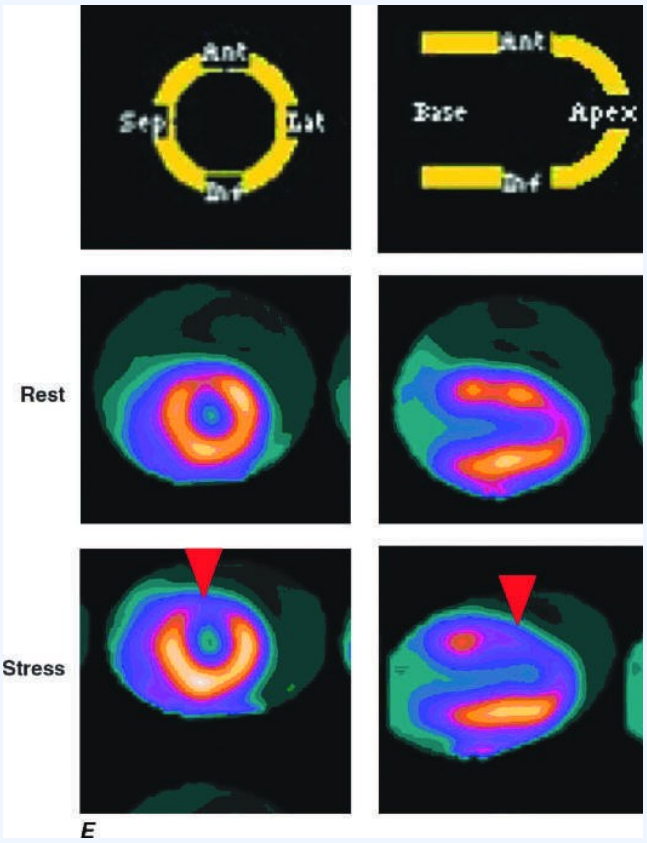
Harrison's 22e · Figure 3

FIGURE 284-3 (Continued)



Harrison's 22e · Figure 4

FIGURE 284-3 (Continued)

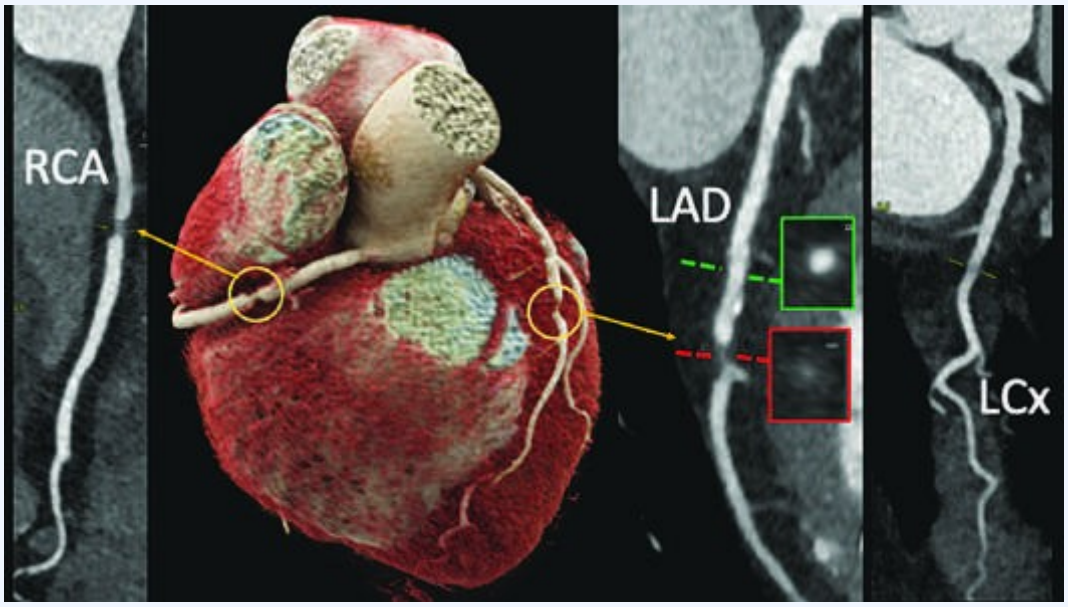


Harrison's 22e · Figure 5

FIGURE 284-3 (Continued)

Harrison's 22e · Figure 6

FIGURE 284-2 Cascade of mechanisms and manifestations of ischemia. (Reproduced knowledge. J Am Coll Cardiol 54:1561, 2009.)



Harrison's 22e · Figure 7

reason, methods for detecting coronary calcium have been developed as a measure of the presence of coronary atherosclerosis. These meth- ods involve CT applications that achieve rapid acquisition of images (electron beam [EBCT] and multidetector [MDCT] detection). Coro- nary calcium detected by these imaging techniques most commonly is quantified by using the Agatston score, which is based on the area and density of calcification. FIGURE 284-3 (Continued) in

Harrison's 22e · Figure 8

FIGURE 284-1 Macrocirculation and microcirculation across segments and sizes of the at the top. Vasomotion of the arterial segments occurs in response to the stimuli shown. depiction of the relative resistance to antegrade flow. (Adapted from J Knuuti et al: 2019 Eur Heart J 41:407, 2020/.)

Harrison's 22e · Figure 9

FIGURE 284-1 Macrocirculation and microcirculation across segments and sizes of the at the top. Vasomotion of the arterial segments occurs in response to the stimuli shown. depiction of the relative resistance to antegrade flow. (Adapted from J Knuuti et al: 2019 Eur Heart J 41:407, 2020/.)

Harrison's 22e · Figure 10

FIGURE 284-1 Macrocirculation and microcirculation across segments and sizes of the at the top. Vasomotion of the arterial segments occurs in response to the stimuli shown. depiction of the relative resistance to antegrade flow. (Adapted from J Knuuti et al: 2019 Eur Heart J 41:407, 2020/.)