Cardiology Consult Manual

Hanna Z. Mieszczanska
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ISBN 978-3-319-89724-0 ISBN 978-3-319-89725-7 (eBook)
https://doi.org/10.1007/978-3-319-89725-7

Library of Congress Control Number: 2018950435

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Preface

Cardiology consultation is frequently requested as part of multidisciplinary patient care. With the aging population, the prevalence of cardiovascular disease is increasing. However, despite great advances in the field of cardiology, cardiovascular diseases remain the leading cause of death. The knowledge base in cardiovascular medicine expands very rapidly, and it is important to summarize it in an easy-to-read format for busy healthcare practitioners. Rapidly developing technological advances transform diagnostic modalities as well as the procedures and result in new and updated ACC/AHA/HRS guidelines. Cardiologists are increasingly being asked to take care of cardiac issues in patients with a multitude of general medical problems, malignancy, perioperative complications, trauma, or cardiac issues during pregnancy.

The manual will provide a practical approach to diagnosis and management of common and uncommon cardiology conditions, which can be encountered on the cardiology consult service. The new ACC/AHA guidelines for management of various cardiac conditions will be outlined in a short and easy format in the manual, facilitating practice of evidence-based medicine.

We hope that the information in the *Cardiology Consult Manual* can be used as a reference for medical providers such as hospitalists, residents, fellows, medical students, and also cardiologists—anyone who works on the cardiology consult service and in the cardiac care unit treating patients with cardiovascular disease.

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Contents

Chapter 1
Cardiovascular Physical Examination

Michael Hannon and J. Franklin Richeson

Visual Inspection

- The general appearance of the patient is of great importance and can provide clues about the underlying illness and state of hemodynamic compensation [1].
- Patient's gait can be assessed when patient is walking into the exam room. In some selected patients, especially when associated with other neurologic deficits (e.g., facial droop, aphasia, hemiparesis), it can be suggestive of stroke.
- Body habitus should be assessed: obesity and cachexia [2].
- Mental state is of importance: anxiety, delirium, and altered mental status.
- Presence of pallor, cyanosis, diaphoresis, or cool extremities.
- Respiratory status should be observed. Is the patient tachypneic, orthopneic, speaking in full sentences, coughing, wheezing? Using accessory muscles.
- Occasionally hemodynamic state can be diagnosed in the instance of a hyperdynamic circulatory state by observing head bob, etc.
- Neck pulsations can be noted when talking to the patient (the rapid "y" descent of constrictive pericarditis and restrictive heart disease, for example, is often evident from afar) [3].
- Volume status can often be assessed by noting peripheral edema, distended abdomen, and weeping leg ulcers.
- Peripheral stigmata of endocarditis (splinter hemorrhages, Osler nodes, Janeway lesions) or arterial embolism can occasionally be seen especially in association with fever and heart murmur [4].

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H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7_1

- Presence of xanthomas (yellowish plaques or nodules composed of lipid-laden histiocytes in the skin), especially around the eyelids (xanthelasmata), can be diagnostic of hyperlipidemia [5].
- Corneal arcus: lipid deposit in cornea. Common in elderly (arcus senilis) but can be present earlier in life in hypercholesterolemia.
- Presence of digital clubbing (defined by nail fold angle >180° can be observed when talking to the patient [6]. Can be present in different disorders including cyanotic congenital heart disease.

Vital Signs

- Heart rate—usually assessed by palpation of peripheral pulse, but auscultation or electrocardiography is more accurate if atrial fibrillation or premature beats are present (as many beats will not be transmitted to the periphery).
- Blood pressure (BP)—one should use an appropriately sized cuff as falsely high readings will be obtained if cuff is too narrow. A manual assessment of BP is often more accurate.

Peripheral Pulses

- Palpate peripheral pulses radial, brachial, femoral, popliteal, posterior tibial, and dorsalis pedis. Diminished or absent peripheral pulses can be suggestive of peripheral arterial disease.
- Palpation of the peripheral pulse can detect irregular heart rate and be a good screening tool for atrial fibrillation.
- Symmetry of left- and right-sided pulses should be assessed. Asymmetry may signify stenosis or compromise from a dissection. A palpable pulse deficit of the carotid or upper limb pulses can be present in patients presenting with aortic dissection [7].
- Normally pulses are brisk and monophasic.

Pathologic waveforms

- "Parvus et tardus"—slowly rising carotid waveform of critical aortic stenosis.
- "Corrigan's pulse"—water hammer pulse of aortic regurgitation or other high-flow state, such as thyrotoxicosis and severe anemia. This is a high amplitude pulse that strikes and then briskly falls away from the palpating finger. It may be best appreciated at the brachial artery while holding the arm above the patient's head.
- "Pulsus bisferiens" (spike and dome)—double arterial upstroke (with a concussive, then tidal wave) seen in obstructive cardiomyopathy.
- Pulsus alternans can be present with severe left ventricular dysfunction.

Inspection/Palpation of the Precordium [8]

- Oblique lighting and positioning of the examiner so that a tangential view of the precordium can be obtained will maximize the information obtained.
- Apex—the apex beat can be seen/felt about half the time in slender patients. One should feel a monophasic outward motion in the midclavicular line in the fourth-fifth interspace. Displacement to the left signifies cardiomegaly. If outward motion of apex persists for longer than one-half of systole, this is a "sustained" apex beat and signifies LVH or a pressure overload state, such as aortic stenosis. When present, there is also usually lateral displacement of the apex. If the amplitude of the apex beat is exaggerated, it is called a "hyperdynamic beat" and signifies a volume overload of the ventricle, as in severe aortic or mitral regurgitation. When present, the impulse is usually displaced downward and to the left. If a "double impulse" (two outward motions/cycle) is seen/felt, this is tantamount to the auscultation of a gallop (S3 or S4).
- Thrills (systolic vibrations) can rarely be palpated over the precordium. At the apex, the palpation of a thrill usually connotes a Grade IV (at least) mitral regurgitation. Closer to the left lower sternal border, a thrill may stem from the jet of a ventricular septal defect (either congenital or acquired after MI).
- RV impulse is not normally palpable or visible. When it is, it is seen along the left lower sternal border and usually connotes either severe pulmonary hypertension or (more commonly) severe tricuspid regurgitation. When it is a sign of tricuspid regurgitation, there may also concomitant hepatic systolic pulsation and a giant "v" wave in the jugular waveform as well.
- Obviously, one should be observant for the presence of the scars of previous surgery and the protrusion of subcutaneous devices (ICDs, pacemakers).

Jugular Venous Pulse (JVP)

- Since most other aspects of the CV exam can be accurately assessed with readily available imaging techniques, evaluation of the JVP, in the early twenty-first century, is the single and most important (and most difficult) component of the exam. In most cardiac inpatients, it varies from day to day and should predicate daily management of patients with heart failure.
- While body habitus may limit one's ability to inspect the jugular venous column, it should be visible in 80–90% of patients.

Keys to successfully viewing the meniscus of the JVP are correctly positioning the examiner and the patient:

- Stand in a position that affords a tangential view of the sternomastoid (pulsations are most easily appreciated if crossing the examiner's visual field left-right,

rather than toward-away). Oblique lighting may cast a shadow of the pulsation and make it more readily apparent.

- The patient's torso should be wherever in the 90° arc from supine to upright that brings the meniscus of the JV column into view. For many patients, the JVP can be seen only when supine; for others, it may be above the ear when sitting bolt upright. If the waveform is not apparent, one should change the patient's posture through this arc until the meniscus becomes visible [9].
- Recognize the JVP. The venous waveform is soft and undulant. Relatively light pressure applied with a tongue blade below its meniscus will damp its undulations (but will not damp arterial pulsation). Arterial pulsations are generally more brisk, and one can easily palpate the underlying artery. Contraction of respiratory muscles can sometimes confuse the examiner, and pulsations during the expiratory phase must then be sought.
- If the JVP is thought to be low: apply pressure to the liver or ask patient to perform the Valsalva maneuver, thus distending the external jugular. If that distention collapses with relief or pressure or termination of Valsalva, then the JVP is very low. If it remains distended, it does not necessarily mean jugular pressure is high, as tortuosity may prevent its collapse.
- If the JVP is thought to be high: sit the patient bolt upright, and inspect the earlobe for pulsations. If that fails, inspecting the veins of the hands is sometimes useful. In patients with venous distention of the dorsum of the hand (a minority of patients), ask the patient to make the arm limp, while the examiner slowly elevates the hand and forearm. The vertical height above the right atrium at which collapse occurs is the venous pressure [10].

Calculating and Reporting the JVP

- In the arc of the torso between supine and upright, the right ventricle is 5 vertical centimeters below the sternal angle, so the sternal angle is always used as a reference point.
- One should always report the vertical height of the column numerically (saying "halfway up the neck" or "no JVD," etc. is worthless). If the meniscus is seen 3 vertical cm above the sternal angle, one may either report that or say that it is 8 cm above the right ventricle (having added the additional 5 cm).

Waveforms

- Arterial: As noted, they are usually brisk and monophasic. Height of carotid pulse will not change with height of patient's head or torso elevation. Gentle pressure on sternocleidomastoid will obliterate venous pulse but not carotid.

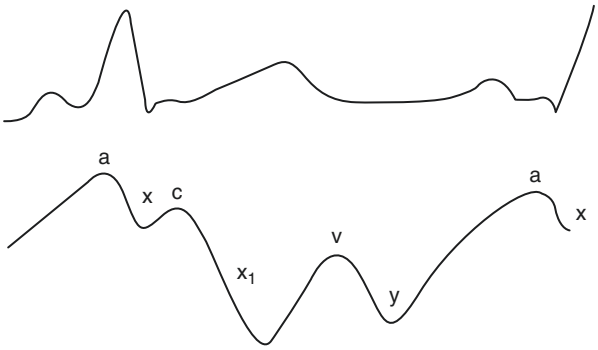

Fig. 1.1 Simultaneous recording of an electrocardiogram (top recording) and normal jugular venous pressure waves (lower tracing). Reproduced with permission from Cook et al. [11]

- Venous (normally biphasic): "*a* wave" corresponds to atrial contraction, and the "*v* wave" represents atrial filling and is inscribed during ventricular ejection. Figure 1.1 demonstrates simultaneous recording of an electrocardiogram and normal jugular venous pressure waves.
- Many diagnoses may be inferred from inspecting the JVP waveform, but the most common include [9]:
  - Absent "a" wave: atrial fibrillation
  - Giant "v" wave: tricuspid regurgitation
  - "Cannon *a*" wave: seen A-V dissociation or in SVT such as AVNRT (with simultaneous atrial and ventricular contraction) when RA contracts against a closed tricuspid valve or ventricular tachycardia
  - Large "a" waves: tricuspid stenosis, pulmonic stenosis, pulmonary HTN
  - Attenuation of the "y" descent: in pericardial tamponade
  - Accentuation of the "y" descent: in constrictive pericarditis and restrictive cardiomyopathy

Kussmaul's sign

- Kussmaul's sign is seen in constrictive pericarditis [12] and is present if the venous pressure does not fall (or rises) during inspiration.

Hepatojugular reflux

- An increase in the jugular venous pressure >3 cm that is sustained for 15 s with pressure applied in right upper quadrant
- Present when the increased venous return cannot be accommodated by RV (can be present in patients with heart failure
- Can also be seen in pericardial constriction, restriction, and RV infarct ([13])

JVP

- Ordinarily, when treating an exacerbation of heart failure, one should try to

- diuresis the patient until JVP normalizes (5–7 cm above the right atrium).
- Many heart failure patients also have tricuspid regurgitation (with a giant "v" wave); "normalizing" the JVP may not be possible or desirable. Recall that the nadir of the "y" descent is equal to the RV end-diastolic pressure, and if that is below 5–7, stroke volume will fall; hypotension and renal dysfunction may ensue. When diuresing a patient with tricuspid regurgitation, one must use the nadir of the "y" descent, rather than mean JVP as one's yardstick of success.

Auscultation

- Auscultate for bruits over the carotids, femorals, and abdomen. Using the bell when auscultating over the carotids will avoid the "pseudo-bruit" of "whiskers scratching against the diaphragm."
- Carotid bruits are suggestive of clinically relevant carotid stenosis. Complete occlusion or even very severe stenosis may cause decrease and disappearance of a bruit.
- In patients with hypertension, abdominal bruits are strongly supportive of a diagnosis of renovascular disease [7].
- Auscultation of high-pitched sounds, such as S1, S2, and most murmurs is best done with the diaphragm.
- Low-pitched sounds such as gallops (e.g., S3 and S4) and the rumble of mitral stenosis are best heard with the bell.

Precordial Auscultation Sites (Fig. 1.2)

Aortic area (second right interspace): systolic murmur (aortic stenosis and sclerosis)
Pulmonic area (second left interspace): systolic ejection murmur (PS, flow murmur)
Left sternal border: diastolic murmur (aortic regurgitation, pulmonic regurgitation), systolic murmur (hypertrophic cardiomyopathy)
Tricuspid area (left lower sternal border): holosystolic murmur (tricuspid regurgitation, ventricular septal defect), diastolic murmur (tricuspid stenosis, atrial septal defect [increased flor across tricuspid valve])
Mitral area (apex): holosystolic murmur (mitral regurgitation), diastolic murmur (mitral stenosis)

Other areas of auscultation [14, 15]:

- Neck: systolic ejection murmur (SEM) of valvular aortic stenosis (AS) can be transmitted to the neck. Carotid bruit suggestive of carotid stenosis is usually louder higher in the neck.
- Clavicle: SEM of AS can be also heard in the clavicular region, as the bone is a very good transmitter of sound.

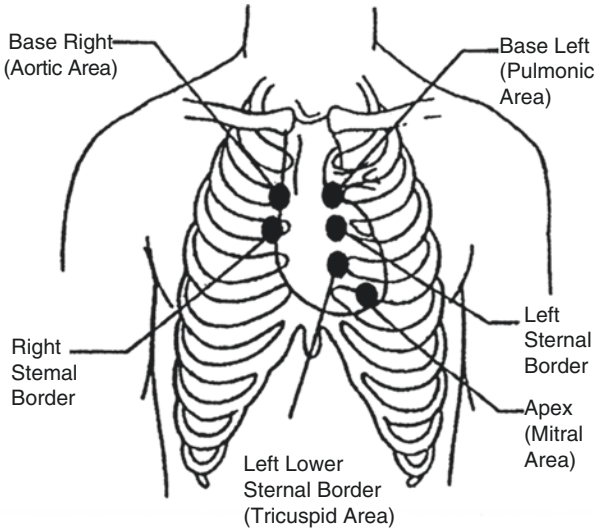

Fig. 1.2 Precordial auscultation sites. These are the specific sites on the chest wall principally used for cardiac auscultation. Reproduced with permission from Chizner [14]

- Left axilla: the holosystolic murmur of chronic mitral regurgitation (MR) can radiate to the left axilla.
- Abdomen: abdominal bruit suggestive of renal artery stenosis can be heard.

S2 is usually louder than S1. At physiologic heart rates, diastole is longer then systole, but at faster heart rates, one may need to simultaneously feel carotid pulse to distinguish S1 from S2.

S1 represents the closure of mitral and tricuspid valves. Ordinarily this is heard as a single sound and loudest at the apex.

Accentuated S1

- Short PR interval
- Mild mitral stenosis (can be delayed as well)
- Tachycardia

Diminished S1

- Lengthened PR interval
- Mitral regurgitation
- Severe mitral stenosis

S2

- Represents the closure of the aortic and pulmonic valves at the end of systole. Aortic component (A2) normally before pulmonic closure (see below).

- Intensity of S2 dependent on diastolic pressure—louder in systemic HTN or pulmonary HTN. P2 over the pulmonic area is often louder than A2 in pulmonary HTN. A2 can be absent in severe aortic stenosis.

S2 varies with the respiratory cycle

- Normally a single sound is heard during expiration. As increased venous return distends the right heart during inspiration, S2P is somewhat delayed, splitting S2. This is normal "physiologic splitting."
- Widened S2 splitting (the split does not fully close with expiration) occurs in conditions that delay S2P throughout the respiratory cycle but which allow the right heart to be sensitive to varying venous return, such as right bundle branch block or pulmonic stenosis, or conditions that cause earlier activation of the LV, such as WPW with LV insertion of the bypass tract.
- Fixed S2 splitting occurs in atrial septal defect: the increased venous return during inspiration delays P2, and the left-to-right shunting across the ASD delays it during expiration.
- Paradoxical splitting of S2 (splitting during expiration but with S2 being a single sound during inspiration) occurs in conditions that either delay LV emptying (left bundle branch block, severe LV systolic dysfunction, severe aortic stenosis) or cause the RV to activate earlier than normal (WPW with RV insertion of bypass tract).

Gallops [15, 16]

- Low-pitched diastolic sounds (therefore best heard with the bell—usually quite soft and difficult to hear) that represent vibration of the ventricular myocardium. While an S3 gallop may normally be heard in patients under 25 and in pregnancy, it is otherwise highly pathologic. An S4 gallop is always pathologic.
- S3 is mid-diastolic, occurring at the end of the rapid filling phase. Increased stiffness of the LV from scarring commonly mediates its appearance, and it is most commonly heard in patients with heart failure with reduced ejection fraction (HFrEF).
- S4 emanates from a presystolic vibration of the LV myocardium as blood from atrial contraction resonates against the LV muscle. It usually indicates reduced ventricular compliance. Commonly, this results from conditions that can lead to ventricular hypertrophy (e.g., HTN). A fourth heart sound is never heard in the presence of atrial fibrillation because the contraction of the atria is ineffective in this condition.

Pericardial Friction Rub [16]

- A coarse, low-pitched sound that signifies inflammation of the pericardium. It has a leathery sound, akin to the noise of walking on wet snow. If not heard with the patient supine, it can sometimes be brought out by leaning the patient forward.

- An audible friction rub is highly specific for pericarditis.
- Pleural rubs can occasionally occur over the precordium, but of course their timing is linked to the respiratory, not cardiac, cycle.

Clicks [14, 17]

- May be heard in systole and are of two varieties.
- Ejection clicks occur shortly after S1, are high-pitched, short sounds that may stem from the ejected blood striking the proximal aortic wall. These are uncommonly heard in hypertensive patients or in those with dilation of the proximal aorta.
- Non-ejection clicks occur in mid-systole, vary in timing with loading conditions, and probably emanate from tensing of chordae tendineae, in mitral valve prolapse. They tend to occur before the murmur of prolapse begins and may be single or multiple.

Snaps

- Opening snap is an early diastolic high-pitched sound heard in mild mitral stenosis at the apex. It shortly follows S2P, introduces the rumble of mitral stenosis, and is heard at the apex. It arises from the deceleration of the stenotic mitral cusps.
- The more severe the MS, the higher the LA pressure, the earlier the OS (shorter A2-OS interval).
- Since it implies some mobility of the cusps, it often disappears as the valve thickens and calcifies.

Tumor Plop

- An early diastolic heart sound, which may also be due to left atrial (LA) myxoma

Cardiac Murmurs [3, 14, 17–19]

Murmurs are often graded on the following scale [15] (intensity bears little relationship to the severity of the valvular lesion).

Grade I: heard after several seconds of auscultation
Grade II: faint but heard immediately
Grade III: moderately loud

Grade IV: loud with palpable thrill
Grade V: heard with only edge of stethoscope on chest
Grade VI: heard with no contact of stethoscope and skin

Systolic

- Early-mid: "innocent flow murmur," aortic sclerosis, aortic stenosis (AS), pulmonic stenosis (PS)
- Hypertrophic obstructive cardiomyopathy (HOCM)
- Holosystolic: mitral regurgitation (MR), tricuspid regurgitation (TR), VSD

Diastolic

- Early (high frequency): aortic regurgitation (AR), pulmonic regurgitation (PR).
- Diastolic blowing murmur of AR heard louder at the third right interspace when compared with the third left interspace suggests aortic root disease (e.g., dissection) rather than aortic valvular disease (Harvey's sign).
- Mid-late: mitral stenosis (MS), flow rumble is severe AR.
- Late systolic: mitral valve prolapse (MVP).

Continuous murmurs

- Patent ductus arteriosus, arteriovenous fistula

Most cardiac murmurs emanate from left-sided structures and will be described here.

- Since loading conditions of the right side are respirophasic, murmurs from the pulmonic and tricuspid valve will also vary with respiration (Carvallo's sign: increase of TR murmur with inspiration), and they are best heard over the pulmonic and tricuspid areas, so they are usually distinguishable from left-sided murmurs [17].
- The murmur of TR is often quite silent, and the giant "v" wave in the JVP or, less commonly, pulsatile liver is the most reliable diagnostic sign of TR.

Systolic Murmurs [17]

Flow murmur

- Usually soft systolic murmur and can be position dependent. Benign and does not imply cardiac disease.

Aortic sclerosis/stenosis and mitral regurgitation are the two most common left-sided systolic murmurs.

- The most reliable discriminator of the two is the presence or absence of the murmur during the pre-ejection phase of the cardiac cycle. As systole begins, LV pressure rises and first closes the mitral valve as it exceeds LA pressure.

- There is then a pre-ejection period as pressure rises to aortic pressure. If a murmur is heard during this period, it cannot be aortic in origin, as the aortic valve has not yet opened (it must be mitral regurgitation). Thus, the murmur of mitral regurgitation is said to begin immediately with S1, and the murmur of aortic stenosis begins later (after the pre-ejection period). We call this an ejection murmur.
- While these two murmurs differ in other respects, the time of onset is the most reliable discriminator.
- The murmur of MR tends to be loudest at the apex and axilla, is higher pitched, and has a blowing quality (not as coarse).
- The murmur of AS (ejection murmur) has a crescendo-decrescendo intensity and encompasses S2A; it is loudest at the base and usually radiates to the neck.
- As indicated earlier, if it is critical AS, the upstroke of the carotid pulse becomes diminished and delayed.

HOCM

- There are auscultatory features of both MR and AS, but it is also sensitive to changes in loading conditions.
- Maneuvers that make the LV cavity smaller, for example, such as the late strain phase of the Valsalva maneuver, will intensify the murmur (the obstruction worsens) [20].
- Maneuvers that increase afterload and widen the outflow tract (such as squatting or isometric handgrip) will lessen the intensity of the murmur. The murmur increases with changing position from squatting to standing [14, 17].
- It sounds similar to the murmur of mitral regurgitation (blowing, fine), but its onset is usually not at the time of mitral closure, but begins in mid-systole (late systolic murmur).
- It is also sensitive to LV volume, becoming a longer, louder murmur with a small LV (late strain phase of Valsalva) and shortening and softening with maneuvers that expand LV volume (handgrip, squatting).
- The systolic click of MVP moves earlier in systole (closer to S1) during the strain phase of the Valsalva maneuver [14].

VSD

- The murmur of VSD has the timing and pitch of mitral regurgitation, but it radiates to the left lower sternal border, rather than to the axilla.
- Since both VSD and papillary muscle rupture (with severe MR) are both complications of acute MI, distinguishing these two can be problematic when a new murmur and hemodynamic deterioration occurs 3–5 days after MI.

Diastolic Murmurs [14]

Diastolic murmurs are in general more difficult to hear than are systolic murmurs.

- The murmur of AR is a high-pitched decrescendo diastolic murmur that is best heard along the left or right sternal border. It is best heard with the patient is upright or leaning forward to bring the heart closer to the stethoscope.
- When it emanates from primary valvular disease, its radiation is louder to the left of the sternum; when aortic root pathology is to blame, it radiates more loudly to the right.
- The intensity of the murmur has no correspondence to the severity of the regurgitation (as is true of all murmurs).
- There is an inverse relationship between the length of the murmur and its severity. In acute severe AR, the LV diastolic pressure rises, and the murmur becomes shorter.
- The murmur of MS is often extremely difficult to hear. One listens at the apex using the bell and often with the patient in the left lateral decubitus position.
- If the valve remains pliable, the murmur will be introduced by an opening snap. It is low-pitched and resembles distant thunder, often increasing in intensity prior to S1 if the patient remains in sinus rhythm.

Bedside Maneuvers

Decrease preload

- Valsalva maneuver and standing up from squatting
  - Increases intensity of HOCM murmur
  - Decreases intensity of most murmurs (including AS)
  - MVP: earlier onset of click

Increase preload

- Squatting
- Decreases intensity of HOCM murmur
- Increases intensity of most murmurs (including AS)
- MVP: later onset of click

Increased afterload

- Handgrip, squatting
- Increased intensity of MR, AR, VSD murmurs
- Decreased intensity of HOCM
- MVP: later onset of click

Inspiration (increased venous return)

- Increased intensity of right heart murmurs

Other Findings

- Assessment of capillary refill time and other markers of peripheral perfusion is helpful in the initial evaluation of circulatory status [7, 21]. Pressure is applied to the nail bed until it turns white. If there is good blood flow to the nail bed, a pink color should return in less than 2 s after pressure is removed. A prolonged capillary refill time (>2 s) may be a sign of volume depletion and decreased peripheral perfusion. However, there is limited reliability and high interobserver variability in adults.
- Presence of the fine inspiratory crackles at the base of the lungs can be suggestive of pulmonary edema. Wheezing (cardiac asthma) can be also noted.
- Presence of pleural effusions (common finding in heart failure) can be detected by diminished or inaudible breath sounds, dullness to percussion, decreased tactile fremitus.
- Egophony (known as "E-to-A" changes) can be detected at the superior aspect of the pleural effusion [22].
- Ascites can be present in the setting of passive liver congestion in the setting of increased right-sided filling pressures or RV diastolic dysfunction.
- Hepatomegaly may be a result of right ventricular failure.
- Palpable pulsatile abdominal mass may be suggestive of abdominal aneurysm and should prompt consideration of imaging [7].

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Chapter 2
Evaluation and Management of Chest Pain and Acute Coronary Syndrome (ACS) in the Emergency Department

Maria Finke, Dylan Norton, and John Gassler

Epidemiology

- Prevalence and Significance
  - Non-traumatic chest pain responsible for 8–10 million ED visits per year—second most common chief complaint of patients presenting to the ED [1].
  - Coronary heart disease accounts for 102.6 deaths/100,000 persons per year in the USA [2].
  - 1.35 million patients per year hospitalized with acute coronary syndrome [3].
  - 51.7% of patients diagnosed with "nonspecific chest pain" [1].
- Economic Burden
  - Direct costs of cardiovascular disease estimated at $193.1 billion per year in the USA [2].
  - Estimated cost of non-cardiac chest pain is $8 billion dollars per year in the USA [4].

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H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7_2

General Approach

History

- Key elements: onset, severity, provoking and palliating factors, quality, location, radiation, severity, and associated symptoms such as diaphoresis or nausea. Attempt to distinguish cardiac from non-cardiac causes. Table 2.1 describes characteristics which may help distinguish typical cardiac chest pain from atypical chest pain.
- Risk factors: assist in risk stratification for acute coronary syndrome (ACS) and other disease processes. Lack of risk factors does not exclude the diagnosis of ACS [5]. ACS risk factors include:
  - Advanced age
  - Male sex or postmenopausal female
  - Tobacco smoking and any prior or recent drug use (especially cocaine)
  - Family history of coronary artery disease, especially early onset (age <55 males, <65 females)
  - Medical history
    Hx previous thromboembolic disease or vascular disease.
    Hx CAD, MI, PCI/stent, or CABG
    Diabetes, HTN, HLD
    Does the patient take ASA, thienopyridine, or an anticoagulant?
    Prior cardiac testing? Recent coronary angiogram or stress test?

Table 2.1 Typical vs. atypical chest pain [7–10]

History and exam	Typical pain features	Atypical pain features
Quality	Pressure, heaviness, similar to previous MI, or angina	Burning, sharp, tearing, ripping
Location	Central chest, left-sided	Back, right sided, epigastric
Radiation	Arm, shoulder, or jaw	Back
Severity	May be mild to severe	May be mild to severe
Alleviating/ aggravating/ relieving factors	Exertional, better with rest or nitro, not reproducible or positional	Non-exertional, positional, better with antacids, sharp, reproducible, worse after eating or swallowing
Associated symptoms	Nausea, vomiting, diaphoresis, dyspnea	Nausea and vomiting may be related to GI etiology
Physical exam	Diaphoresis, hypotension. Signs of acute heart failure s/a JVD, S3 gallop, S4 HS, edema may be seen in ACS if cardiac function is affected	Extreme hypertension, cough, focal lung findings, reproducible pain, hypoxia, tachycardia, friction rub, crepitus, aortic insufficiency murmur, rash

Physical Exam

- Vital signs: often normal, but patients may be hypotensive with right ventricular MI. Hypertension may cause demand-mediated ischemia. Extreme abnormalities suggest alternative diagnoses (i.e., HTN, aortic dissection; tachycardia, hypoxemia, tachypnea—PE or pneumothorax; fever, pneumonia, esophageal rupture, or myocarditis).
- General appearance: ranging from comfortable appearing to mildly anxious to grossly uncomfortable and diaphoretic.
- Cardiac exam: often normal in ACS.
  - Signs of acute heart failure s/a JVD, edema, and S3 or S4 gallop may suggest ACS with acute heart failure or PE as cause.
  - Murmur of acute aortic insufficiency may suggest aortic dissection as cause of pain; 32% of patients with dissection will have aortic insufficiency murmur [6].
  - Pericardial rub or pain worse in recumbent position suggests pericarditis.
- Pulmonary exam: often normal in ACS, unless in acute heart failure and presenting with pulmonary edema. Wheezing, prolonged expiratory phase, rhonchi, focal lung findings, or localized crackles are typically associated with asthma, COPD, or pneumonia.
- Musculoskeletal: assess for reproducibility of the pain with movement of torso and upper extremities and on palpation of the chest wall. However, presence of reproducibility does not rule out ACS.
- Skin: assess for rash or prodromal herpes zoster (which can cause severe unilateral pain).
- Abdominal: upper epigastric tenderness or RUQ tenderness suggests a GI cause.
- See Table 2.2 for likelihood ratios for factors making ACS more or less likely.

Table 2.2 Findings making acute coronary syndrome more likely [8–11]

Test	Likelihood ratio[a]
Radiation to both arms	2.6–7.1
Radiation to the right arm	4.7–5.4
Radiation to the left arm	1.2–2.3
Worse with exertion	1.5–2.4
Similar to prior MI	1.8–2.2
Findings making acute coronary syndrome less likely	
Pleuritic pain	0.2–0.35
Sharp pain	0.2–0.5
Positional pain	0.2–0.5
Reproducible pain	0.2–0.4

[a]Likelihood ratios: Likelihood ratios help to determine the posttest probability of disease in a particular patient. Likelihood ratios greater than one increase the probability of disease, while those less than one decrease the probability of disease. Generally, likelihood ratios greater than 2 or less than 0.5 are thought to be helpful in ruling in or out disease, while values of 10 or 0.1 make the chance of disease much more likely or unlikely, respectively [12]

Table 2.3 Differential of chest pain [7, 8]

Disease process	History	Physical exam	Testing	Diagnosis	Treatment
Pulmonary embolism	Chest pain and dyspnea, cough, hemoptysis, syncope RF: female, hypercoagulable state, immobility	Tachycardia, tachypnea, hypoxemia. Hypotension if massive and causing obstructive shock	U/S: dilated RV, septal bowing into LV (D-sign) ECG: S1Q3T3 or RBBB/RAD Troponin, BNP	Risk stratification: PERC, Wells, D-dimer Diagnosis: CT angiography or V/Q scan	Anticoagulation Thrombolytics Embolectomy (in selected patients)
Aortic dissection	Sudden onset of tearing CP w/ radiation to the back, pain above and below the diaphragm RF: male sex, hx of HTN, Marfan syndrome, bicuspid aortic valve, smoking	Hypertension, variation in blood pressure or pulse deficit, check for neuro deficits	CXR: ±widened mediastinum, abnormal aortic contour, tracheal shift, L apical cap, often normal U/S: ±pericardial effusion (type A) ECG: ±inferior ST elevation (dissects into RCA)	CT angiography or TEE Type A—involving the ascending aorta Type B—descending aorta *(Stanford classification)*	Beta-blockers first, and then Ca++ blockers to lower blood pressure and heart rate Fentanyl for pain Surgical vs. medical management
Pericarditis	Sharp, pleuritic chest pain. Infectious (often preceded by URI) or noninfectious (systemic inflammatory disease, cancer, post-cardiac injury, or drug related)	Improves when sitting up or leaning forward. Tachycardia, friction rub Tamponade: hypotension, elevated JVP, muffled heart sounds, pulsus paradoxus	ECG: diffuse concave ST elevations with PR depressions U/S: pericardial effusion Troponin elevation = peri-myocarditis	History, exam, ECG, and echocardiogram	Viral (most cases): NSAIDs Pericardiocentesis (if tamponade) Pericardial window (large effusions in recurrent/chronic cases)
Esophageal rupture	Retrosternal chest pain, upper abdominal pain, vomiting. Develops dyspnea, fever, and shock. Recent endoscopy, EtOH	Crepitus, epigastric tenderness	CXR with mediastinal, subcutaneous emphysema, pleural effusion, or peritoneal air	CXR, chest CT, endoscopy	NPO, IV antibiotics, and IVF may need surgery vs. endoscopy if perforation is not contained

Disease process	History	Physical exam	Testing	Diagnosis	Treatment
Pneumothorax	Dyspnea and chest pain Hx trauma, COPD, asthma, positive pressure ventilation, young and thin male	Decreased or absent breath sounds on affected side. Hypoxemia, tachypnea Tension PTX: hypotension, elevated JVP	U/S: absent lung sliding, lung point, barcode sign on M-mode	CXR or chest CT Tension PTX diagnosed clinically w/o imaging	O_2 and observation vs. chest tube (varies with size and etiology) Tension PTX: needle decompression and chest tube
Pneumonia	Fever and chest pain, cough, shortness of breath	Fever, tachycardia, hypoxemia, tachypnea, rales	Leukocytosis	CXR or CT chest	Antibiotics supportive care

Other causes of chest pain to consider, not listed above:

- Myocarditis (recent viral illness, fever, elevated troponin, decreased LVEF)
- Hypertensive emergency (HTN, may have demand ischemia)
- Cocaine-induced chest pain (use benzodiazepines and vasodilators, caution with beta-blockers)
- Pancreatitis (epigastric tenderness, n/v, elevated lipase, hx EtOH, or gallstones)
- Biliary colic (RUQ tenderness, cholelithiasis on US)
- Esophageal spasm (pain related to eating, may be relieved by nitrates)
- Peptic ulcer disease (PUD)/gastritis (pain related to eating, N/V, may be guaiac positive, relieved by antacids)
- Musculoskeletal: costochondritis (reproducible chest wall pain), contusions, rib fracture (hx trauma, point tenderness over the rib)
- Herpes zoster (dermatomal distribution, rash may be absent early)
- Panic attack/psychiatric disease (r/o dangerous causes first, hyperventilation, anxiety)
- Pleurisy: recent viral infection, pleuritic pain. Table 2.3 summarizes the various causes of chest pain that must be considered by the clinician

12 Lead Electrocardiogram (ECG)

- Obtain in any patient with symptoms that could be ACS and in patients with significant risk factors (elderly, known cardiac disease, diabetes, etc.) presenting with atypical symptoms (back pain, abdominal pain, fatigue).
- Obtain within 10 min of presentation.
- Rapidly identify STEMI or STEMI equivalents and treat appropriately.
- Consider right-sided or posterior leads when indicated to assess for RV MI or posterior MI.
- Some ECG findings suggest non-cardiac cause:
  - Sinus tachycardia, right-axis deviation, and S1Q3T3 pattern suggest right heart strain, if these are acute changes, consider PE if clinically appropriate.
  - Inferior MI can present with aortic dissection if there is involvement of the ostial RCA.
  - Diffuse concave ST elevations without reciprocal depressions, ± PR depressions suggest pericarditis.
- An ECG without ischemic changes makes ACS less likely. However, the ECG may be normal in NSTEMI or unstable angina.
- Repeat the ECG if patient's pain or clinical status changes, especially if the initial ECG is non-diagnostic. If there is high suspicion for ACS, serial ECGs can detect dynamic changes of myocardial ischemia.

Cardiac Chest Pain

- Acute coronary syndrome (ACS): spectrum of disease processes caused an imbalance of the availability of oxygen and myocardial oxygen demand.
  - Subdivided into unstable angina, non-ST elevation myocardial infarction (NSTEMI), and ST elevation myocardial infarction (STEMI).
  - Often results from the rupture of coronary plaque-triggering platelet adhesion, activation, thrombus formation, and ultimately vessel occlusion. Plaque erosion is a cause of STEMI in 30% of cases [13]. May also result from coronary artery dissection, arteritis, thromboembolism, or vasospasm.
- Coronary atherosclerotic disease (CAD): the formation of "atherosclerotic plaques" resulting in stenosis of the coronary arteries. Underlies most cases of ACS and is a significant risk factor for acute pathology.
- Stable angina: cardiac chest pain that is predictably triggered by exertion or emotion and relieved by rest or vasodilators (nitroglycerin). Often related to a severe (>70% stenosis) stable plaque that causes demand-mediated ischemia.

- Unstable angina: acute myocardial ischemia without evidence of myocardial necrosis (negative cardiac biomarkers). Chest pain/anginal symptoms that are new, present at rest, or significantly increased from prior stable angina pattern.
- NSTEMI*:* acute myocardial ischemia with positive cardiac biomarkers demonstrating myocardial necrosis, but without ST elevation on ECG.
  - Possible ECG findings: new horizontal or downsloping ST depression ≥0.5 mm in two anatomically contiguous leads and/or T inversion ≥1 mm in two anatomically contiguous leads with prominent R wave or R/S ratio >1.
- STEMI*:* acute myocardial ischemia with myocardial necrosis demonstrated by ST elevation on ECG
  - New ST elevation at the J point in two anatomically contiguous leads. Thresholds include:
    ≥1 mm in any leads other than V2–V3
    Leads V2–V3: ≥2 mm in men ≥40 years; ≥2.5 mm in men <40 years, or ≥1.5 mm in women.
  - Sgarbossa criteria:
    Diagnosis of STEMI in setting of LBBB.
    Scores ≥3 are 90% sensitive for STEMI.
    Concordant ST elevation >1 mm in leads with a positive QRS complex (5 points), concordant ST depression >1 mm in V1–V3 (3 points), discordant ST elevation >5 mm (or >25% the magnitude of the QRS complex) in leads with a negative QRS complex [14, 15].
  - STEMI mimics*:* pericarditis, LV aneurysm, hypercalcemia, early repolarization.
  - Potential STEMI equivalents*:* Wellen's syndrome, deWinter's pattern, diffuse ST depression with elevation in aVR, new LBBB with hemodynamic instability or severe symptoms.

    Cardiac catheterization no longer recommended for all patients with chest pain and an isolated, "not known to be old" LBBB [16].
  - Hyperacute T waves*:* (may mimic hyperkalemia) can be early sign of MI. Check electrolytes and serial ECGs.
  - Repeat the ECG and assess for dynamic changes if there is high suspicion for ACS.
- Wellens' syndrome: deeply inverted or biphasic T waves in the anterior leads (particularly V2–V3) with isoelectric or minimally elevated (<1 mm) ST segments (Fig. 2.1). Must have a history of angina but be pain-free at time of ECG. Suggestive of a critical stenosis of the left anterior descending artery (LAD) [17]. Figure 2.1 shows an example of Wellen's syndrome.

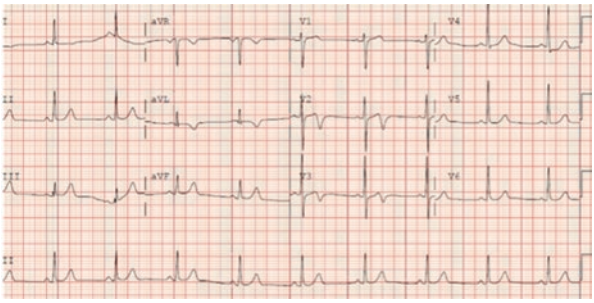

Fig. 2.1 ECG with normal sinus rhythm with biphasic T-wave inversion in V2–V3 (Wellen's syndrome). Pt had a proximal 95% LAD occlusion. Reproduced with permission of the patient

Cardiovascular Effects of Cocaine [18]

Epidemiology

- Cocaine is the second most commonly used illicit drug in the USA after marijuana [19].
- Cocaine is the leading cause of ED visits related to drug abuse—primarily due to cardiovascular complaints.
- Myocardial ischemia and infarction: most common in first hour after use.

Mechanism of Cocaine-Induced Cardiotoxicity

- Increased myocardial oxygen demand.
- Increased heart rate and blood pressure (dose-dependent).
- Coronary vasoconstriction (effect potentiated in cigarette smokers).
- Prothrombotic effect.
- Accelerated atherosclerosis.
- Endothelial dysfunction.
- Vessel wall injury.
- Acute and chronic hypertension (HTN).
- Blockage of catecholamine reuptake in synaptic nerve endings.
- Increased catecholamine release by the CNS.
- Peripheral vasoconstriction results in hypertension, tachycardia, and an increase in afterload. See Fig. 2.2 for a graphic representation of the pathophysiology of the cardiovascular effects of cocaine.

Cocaine Effects on Cardiovascular Disease (Fig. 2.2)

Cardiomyopathy and Heart Failure

- Myocardial infarctions and scarring.
- Acute catecholamine surge with severely elevated BPs. Left ventricular hypertrophy and cardiomyopathy with decreased ejection fraction has been described

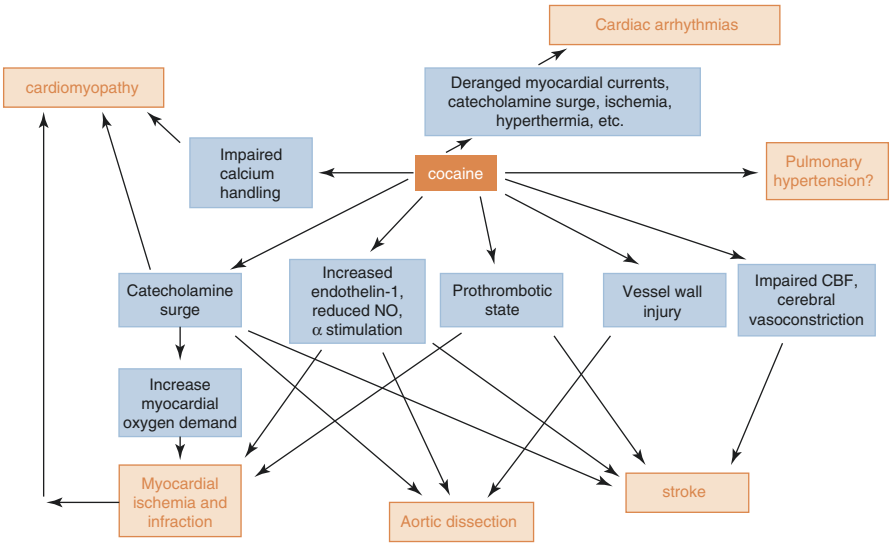

Fig. 2.2 The cardiovascular effects of cocaine (reproduced with permission from: Havakuk [18]) and to endothelial dysfunction. The ample cardiovascular effects of cocaine are exerted through a multitude of mechanisms, with possible consequent deleterious impact on almost every aspect of the cardiovascular system. *CBF* cerebral blood flow, *NO* nitrous oxide

in the setting of chronic cocaine consumption (possibly due to chronically elevated afterload).
- Myocyte apoptosis.

Aortic Dissection

- Patients at risk due to endothelial dysfunction and chronic endothelial injury.
- Acute hypertension leads to acute vascular injury.

Stroke

- Acute hypertension resulting from abrupt catecholamine surge
- Pro-thrombotic effect
- Impaired cerebral blood flow

Arrhythmias

- Sinus tachycardia, AF, SVT, ventricular ectopy, VT due to increased sympathetic tone, myocardial ischemia, MI and scarring.
- Long QT—inhibition of $KCNH_2$-encoded potassium channels inhibition of L-type calcium channels cocaine-induced hyperthermia
- Bradycardia or other conduction disturbance—inhibition of voltage-gated sodium channels disturbances (i.e., Class IC antiarrhythmic effect).
- Brugada type ECG—due to inhibition of SCN5A sodium channels

Cocaine-Induced Chest Pain: Evaluation and Treatment

- Obtain serial ECGs and troponins. Low-risk patients may be discharged after observation. Consider stress-testing and refer for follow-up when appropriate.
- Patients with STEMI on ECG should be referred for coronary angiography and receive revascularization if needed.
  - Increased incidence of stent thrombosis in cocaine abusers (possibly due to the pro-thrombotic effect of continued cocaine abuse or non-compliance with antiplatelet therapy), so bare-metal stents are strongly recommended [20].
  - Treat symptomatic patients with nitroglycerin, benzodiazepines, and calcium-channel blockers. After initial treatment with a vasodilator (nitroglycerin or calcium-channel blocker), nonselective beta-blockade (labetalol) may be considered for patients with persistent hypertension or sinus tachycardia [20].
- Isolated use of cardio-selective beta-blockers can cause unopposed alpha-adrenergic physiology leading to worsened coronary vasoconstriction and increased blood pressure [19].

Risk Stratification for Suspected ACS

- Early assessment of ACS risk is important in guiding management to improve outcomes for high-risk patients and prevent complications of overtreatment in low-risk patients.
- Determine low, medium, or high risk based on clinical presentation, risk factors, ECG findings, and initial cardiac biomarkers.
- Many risk scores have been developed to quantify risk of ACS, including TIMI, GRACE, HEART, PURSUIT, etc. The TIMI and HEART scores are detailed below. Table 2.4 compares the performance of the HEART and TIMI scores.
  - **TIMI** (thrombolysis in myocardial infarction): older risk score initially validated in a high-risk population and may be less applicable to undifferentiated chest pain patients in the ED.
    Scores 1 point for each: age ≥65, ≥3 CAD risk factors, known CAD (>50% stenosis), aspirin use in past 7 days, ≥2 episodes of severe angina in past 24 h, ECG with ST changes ≥0.5 mm, positive cardiac biomarker.
    Total score determines risk: 0 carries 30-day adverse cardiac event rate of 2.3%, 1 is 5%, 2 is 10.1%, 3 is 19.5%, 4 is 22.1%, 5 is 39.2%, 6 is 45%, and 7 is up to 100% [21].
  - **HEART** (history, ECG, age, risk factors, troponin): each category is assigned 0–2 points and then summed. 0–3 is low risk, 4–6 is medium risk, and ≥7 is high risk. HEART was specifically designed for and validated in an undifferentiated ED population presenting with chest pain [22, 23].
    History: highly suspicious = 2, moderately suspicious = 1, slightly or non-suspicious = 0

Table 2.4 Performance of HEART score and TIMI score in predicting ACS

Decision tool	Score	+LR	Risk of MACE[a]	Management
Low				Often suitable for discharge and outpatient management. May use accelerated diagnostic pathways for further risk reduction. Cardiology follow-up and provocative testing can be considered but may not be necessary
HEART score	0–3	0.20	0.9–1.7%	
TIMI	0–1	0.31	2.3–5.0%	
Medium				Generally require admission, serial troponin testing, and cardiology consultation. Select patients may be discharged with outpatient cardiology follow-up. Consider provocative testing
HEART score	4–6	0.79–2.4	16.6–20.3%	
TIMI	2–4	0.94–2.4	10.1–22.1%	
High				Require admission, serial troponin testing, cardiology consultation, and likely early cardiac catheterization or aggressive medical therapy
HEART score	7–10	13	50.1–72.7%	
TIMI	5–7	6.8	39.2–100%	

HEART score: MACE measured at 90 days and 6 weeks, respectively [24]
TIMI score: MACE measured at 30-day ED presentation [21]
[a]MACE (major adverse cardiac event), myocardial infarction, death, or revascularization

ECG: significant ST-depression = 2, nonspecific repolarization disturbance = 1, normal = 0
Age: ≥65 years = 2, >45 to 65 years = 1, <45 years = 0
Risk factors: ≥3 risk factors or history of atherosclerotic disease = 2, 1 or 2 risk factors = 1, no known risk factors = 0
Troponin: ≥3× normal limit = 2 points, >1–3× normal limit = 1 point, ≤normal limit = 0 points

Evaluation for ACS

Initial Testing

- ECG*:* obtain in all patients presenting with chest pain as or possible anginal equivalent symptoms. A great screening tool but cannot rule out ACS. Adept interpretation may allow for early diagnosis of acute MI or provide evidence in support of an alternative chest pain diagnosis.
- Cardiac troponin*:* very sensitive and specific for myocardial injury. May take 4–8 h to rise after onset of symptoms and will peak in 18–24 h. Remains elevated for 10–14 days. Sensitivity 100% at 12 h after symptom onset but limited in the first 6 h [25].
  - Obtain on presentation and at 3–6 h after presentation. High-risk patients should have serial troponin levels beyond 6 h if the initial values are normal [26].

  - Troponin I (cTnI) vs. troponin T (cTnT)*:* troponin I may be more accurate in early presenters. Troponin T may yield higher prognostic accuracy. Either test may be used. Be familiar with institution-specific levels for a positive test.
  - High-sensitivity troponin (hs-cTnT)*:* recently approved by the FDA. Similar "high-sensitivity" troponin has been available in other countries for years. Requires detection of some troponin level below the 99th percentile in a normal population, complicating the identification of an abnormally elevated troponin. Not yet widely available in the USA and unclear how to incorporate these results into existing diagnostic algorithms [27].
  - Troponin in CKD*:* troponin can be used in risk-stratifying and diagnosing ACS in patients with CKD. Troponin is renally cleared, so levels may persist longer after an ischemic insult. Patients with severe cardiovascular disease and CKD may have persistently elevated troponin, which represents poor prognosis and severe disease rather than ACS. Compare troponin to prior levels and trend over time; sharp rises or significant elevations are more likely to support a diagnosis of ACS [28].
  - CK-MB and myoglobin: alternative biomarkers that have previously been used to assess for myocardial injury. Myoglobin is not specific for myocardial injury. CK-MB is less sensitive when compared to troponin. No benefit to use of these biomarkers given the superiority of troponin. Use alternative cardiac biomarkers only if troponin is not available [26].
- Brain natriuretic peptide (BNP)*:* often elevated in CHF and poor prognosis if newly elevated in acute MI. Not useful as a marker of acute MI.
- D-Dimer*:* may be appropriate if PE is being considered. Use with the guidance of validated decision-making tools such as the Wells score and pulmonary embolism rule-out criteria (PERC) rule.

Next Steps in Assessment

- Stress testing*:* recommended for low- and intermediate-risk patients who have a negative ischemic work-up but whose symptoms were likely to represent ACS. Contraindicated in patients with ongoing ischemia. Perform within 72 h, but low-risk patients may have outpatient testing [26].
  - Multiple types of stress testing, depending on the patient's ability to exercise and baseline ECG.
  - Treadmill exercise testing*:* preferred in patients who can exercise and who have a resting ECG without ST changes that would interfere with interpretation (such as a bundle-branch block, LV hypertrophy with ST-T changes, digoxin, or other baseline ST abnormalities).

  - Pharmacological stress test (dobutamine echocardiography or regadenoson nuclear): used in patients who cannot exercise or have baseline ECG changes. In patients with definite ACS, also evaluate LV function.
- CT coronary angiography: noninvasive evaluation of the coronary anatomy. Limited to the detection of anatomic stenosis. Findings may be normal or with non-obstructive or obstructive CAD. Unable to confirm a diagnosis of ACS or determine whether a lesion causes inducible myocardial ischemia.
  - Not appropriate for patients who are high risk or with known CAD.
  - Initial studies for use of coronary CT in low-intermediate risk populations were promising and highlighted the potential for decreased time to diagnosis, high negative predictive value, and decreased length of stay and cost reduction [29]. Coronary CT has been cited to have a sensitivity and specificity of 96% and 83%, respectively [30].
  - May lead to increased rates of invasive procedures compared to standard of care, possibly increasing risk and cost to the patient [31].
- Accelerated diagnostic pathways: identify very low-risk patients who may be discharged directly from the ED without further cardiac testing. These were studied in comparison to serial troponin at 0, 6, and 12 h followed by cardiac stress testing.
  - HEART pathway: HEART score 0–3 with negative troponin at 0 and 3 h. 99% sensitive/99% NPV [32]. Reduces the risk compared to the HEART score alone [33]. Compares favorably to unstructured clinical judgment and NACPR (below) and increases the number of patients for early discharge while remaining sensitive for ACS [34].
  - North American Chest Pain Rule (NAPCR): patients must meet all the following criteria (in either group, based on age) to be safely discharged without further cardiac testing. (1) Age <40, normal ECG, low-risk chest pain characteristics, no history of ischemic chest pain, single negative troponin on arrival. (2) Age 41–50, normal ECG, low-risk chest pain characteristics, no history of ischemic chest pain, a negative troponin level 6 h after onset. Found to have 100% sensitivity/100% NPV. Results are promising, but the tool needs further validation prior to widespread use [35].
  - ADAPT: TIMI score 0, non-ischemic ECG and negative troponin at 0 and 2 h. Initially promising results with 99.7% sensitivity/99.7% NPV, however, the US validation was only 83% sensitive with 99.1% NPV [34]. Also, in one study ADAPT only decreased time to ED discharge by 8.3% compared to standard of care [36].
- Consultation: cardiology consultation in all patients with diagnosed STEMI and NSTEMI with discussion of reperfusion options. Consider early cardiology consultation in high-risk patients, especially in the setting of equivocal ECG findings, elevated cardiac biomarkers of undetermined significance, and for patients who are hemodynamically unstable.

ED Management of ACS

- Ultimately, patients with STEMI require emergent reperfusion/revascularization by thrombolysis, percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG) in consultation with cardiology.
- Patients with NSTEMI are considered for urgent reperfusion/revascularization.

Pharmacotherapy [26]

- Beta-blockers: lower heart rate and decrease myocardial oxygen requirement and may lessen infarct size in acute MI. Initiate oral therapy within 24 h, but not generally in the ED. Use with caution due to potential for cardiogenic shock.
  - Contraindications: bradycardia, second- or third-degree heart block, heart failure. Relatively contraindicated in severe COPD/asthma.
- Anticoagulation: may improve perfusion and prevent re-occlusion at the site of plaque rupture by inhibiting thrombin activity. Choice of anticoagulant and practice patterns vary.
  - Unstable angina and NSTEMI: enoxaparin and unfractionated heparin (UFH) appear to have equal efficacy. UFH may carry a higher risk of bleeding. Bivalirudin or fondaparinux may be used in patients with a history of heparin-induced thrombocytopenia (HIT).
  - STEMI: recommend consultation with cardiology or initiating an institutional protocol.
    Patients undergoing PCI: UFH, enoxaparin, or bivalirudin
    Patients receiving thrombolysis: UFH or enoxaparin
    Patients not receiving reperfusion: UFH or enoxaparin
- Antiplatelets: very important initial management of ACS due to the role of platelets in thrombus formation.
  - Aspirin: unless there is allergy or active life-threatening hemorrhage, administer aspirin 162–325 mg (chewable) as soon as possible in patients with suspected ACS; if oral route is not available, 300 mg aspirin suppository is appropriate.
    Rapid antiplatelet effect through inhibition of thromboxane A2 production.
    Prompt use has shown ~2% reduction in mortality in myocardial infarction with only minor bleeding as a side effect [37].
  - Adenosine diphosphate (ADP) receptor antagonists: clopidogrel (600 mg), prasugrel (60 mg), or ticagrelor (180 mg). Administer one of these antiplatelet agents in addition to aspirin at first medical contact for patients with STEMI and plan for PCI [38].
    Clopidogrel is older, slower in onset, and irreversible.
    Ticagrelor is favorable to clopidogrel in reducing total and cardiovascular mortality.
    Prasugrel may be preferred in patients with STEMI and/or diabetes mellitus but is contraindicated with patients with history of stroke/TIA.

- Nitrates: initial treatment of anginal chest pain with sublingual nitroglycerin every 3–5 min for up to three doses, observing for hypotension. If pain responds and hemodynamics are stable, it can initiate a nitroglycerin drip.
  - Contraindicated in patients with phosphodiesterase inhibitor use within the past 24 h, hypotension, critical aortic stenosis, and with RV infarct.
  - Response to nitroglycerin cannot differentiate cardiac from non-cardiac chest pain.
- Pain control: for pain unresponsive to nitroglycerin in patients with STEMI, IV morphine is first line. Initial dose is 2–4 mg and repeated in 2–8 mg increments.
  - Morphine can be used for refractory pain in UA/NSTEMI but may be associated with increased mortality.
  - In patients receiving oral P2Y12 receptor inhibitors (ticagrelor, prasugrel, clopidogrel), morphine has been shown to delay the antiplatelet effect, and it may be beneficial to abstain from use in patients receiving oral antiplatelet therapy [39].

Monitoring and Supportive Care

- Oxygen therapy: administer to patients with dyspnea, signs of heart failure, shock, or oxygen saturation <90%. In normoxic patients there is no benefit of supplemental O_2, and routine use of supplemental oxygen may result in larger infarct [40].
- Blood pressure management: no specific guidelines available. Treat hypotension (SBP < 90) with intravenous fluids and vasopressors if needed to maintain adequate tissue perfusion. Marked hypertension is rare in ACS and may suggest an alternative diagnosis.
- Electrolytes: check levels of potassium and magnesium. Potassium should be maintained above 4.0 mEq/L and magnesium above 2.0 mEq/L.
- Cardiac monitoring: for patients with high risk for ACS or who are unstable, continuous telemetry and hemodynamic monitoring is appropriate. Defibrillation equipment should be readily accessible. Low-risk patients without evidence of dysrhythmias can have telemetry monitoring discontinued [41].

Discharging Patients with Low-Risk Chest Pain

- Often a specific diagnosis cannot be made.
- Consider involving patients in decision-making about their work-up and disposition, with counseling of the risks and benefits of the various options.
- Counsel patients to call their doctor or return to the ED with any concerns or if the chest pain is accompanied by new or worsening symptoms.
- All patients should have follow-up with a primary care physician who can assist in further work-up, treatment, and risk reduction.
- High-risk patients are appropriate to follow up with cardiology for further cardiac evaluation and risk reduction.

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Chapter 3
Cardiac Electrocardiography

Saki Miwa and Hanna Z. Mieszczanska

As with any data, interpretation must be performed in the context of the clinical picture.

- A normal ECG does not necessarily mean that the patient's cardiac condition is normal, and vice versa.
- Remember that ECGs only provide a snapshot of the heart at one particular point in time. It is prone to error (e.g., lead placements) and can often be difficult to interpret (e.g., body habitus, COPD).
- Further work-up is required if there is clinical suspicion for cardiac abnormalities.

The Normal ECG [1–3]

People often confuse "normal ECG" with "normal sinus rhythm." While it is correct, that a normal ECG is one that is sinus rhythm, not all sinus rhythm ECGs are normal.

- Sinus rhythm is when the heart rate is between 60 and 100 beats per minute.
- Sinus tachycardia is when the rate is greater than 100 beats per minute.
- Sinus bradycardia is when the rate is less than 60 beats per minute.

A stepwise systematic approach to interpret the ECG:

- What is your general impression—any obvious abnormality?

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H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7_3

- Heart rate—beats per minute. Is it normal rate, tachycardia, or bradycardia?
- Rhythm: Sinus, atrial fibrillation, atrial flutter, atrial tachycardia, ventricular tachycardia, etc.
- Axis: Overall direction of the heart's electrical activity.
- Intervals: PR, QRS, QT.
- Atrial size.
- Hypertrophy: LV or RV hypertrophy.
- Ischemia or injury: presence of Q waves, ST elevation MI, ST depression, T-wave abnormalities.
- An ECG lasts 10 s (if paper speed is 25 mm/s).
- Five large boxes (25 mm) is 1 s.
- One large box (5 mm) is 0.2 s.
- One small box (1 mm) on ECG is 0.04 s.
- When the wave of depolarization is moving toward a positive skin electrode, a positive deflection is displayed on the ECG tracing.
- When the wave of depolarization is moving away from a positive skin electrode, a negative deflection is displayed on the ECG tracing.

Components of the ECG [4] (Fig. 3.1):

- Atrial depolarization is represented by the P wave.
- The PR interval (the time from the onset of the P wave to the start of QRS complex) reflects the time required for atrial depolarization and conduction through the AV node.
- Ventricular depolarization is represented by the QRS complex.
- Ventricular repolarization is represented by the T wave (the positive deflection after QRS complex).
- The J point is the junction between the end of the QRS complex and the beginning of the ST segment.
- The ST segment (the flat isoelectric segment between the end of S wave and the beginning of the T wave) represents the time period in which the ventricles are completely depolarized.

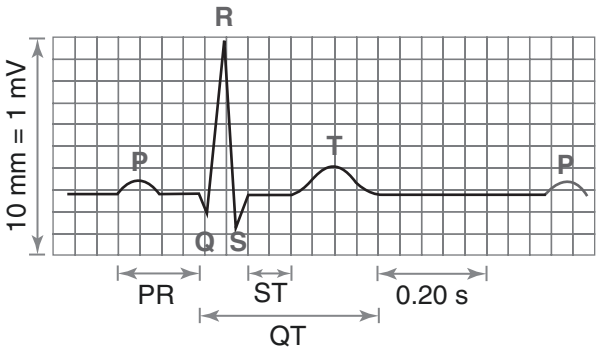

Fig. 3.1 Standard ECG paper. Intervals. Reproduced with permission from Klabunde [4]

- The QT interval (the time from the start of the Q wave to the end of the T wave) represents the overall time required for initiation and completion of ventricular depolarization and repolarization.

Normal features:

- PR interval: 0.12–0.20 s (3–5 small squares).
- QRS duration: 0.06–0.10 s.
- QT interval (corrected for heart rate): <0.44 s. Typically a normal QT is less than half the preceding R-R interval.
- ST and PR segments should be isoelectric.
- T waves should be upright in I, II, V3–V6 and inverted in aVR, V1.

Commonly Seen "Normal" Variants

These ECG patterns are typically nonsignificant, but, as always, it is important to compare with the patient's prior ECGs as well as the clinical picture.

- Juvenile T waves (inverted T waves in V1–V3, often seen in children or females)
- U waves (small deflection following the T wave)
- Q waves in leads V1–V3
- Sinus arrhythmia (variation in heart rate due to inspiratory/expiratory pattern)

Sinus rhythm

- Originates from sinus node.
- Each QRS complex is preceded by a normal P wave.
- The PR interval should remain constant.
- Find P waves: normal is positive P wave in leads II/III/aVF, inverted in lead aVR, and biphasic in lead V1.
- P-wave inversion in inferior leads is seen with ectopic atrial and junctional rhythms.

Calculate the rate (Figs. 3.2 and 3.3):

- In order to determine heart rate: # of beats per minute = # of QRS complexes in ECG tracing × 6.
- Alternatively, when the heart rate is regular, count the number of large (0.2 s) boxes between two successive QRS complexes and divide 300 by this number, and heart rate is calculated in beats per minute. For example, if there are two large boxes between QRS complexes, HR is 150 beats per minute (300/2 = 150), if three large boxes between QRS complexes, the heart rate is 100 beats per minute, because 300/3 = 100. Similarly, if four large time boxes are counted between QRS complexes, the heart rate is 75 beats per minute (300/4). Remember the rule: 300, 150, 100, 75, 60, 50.

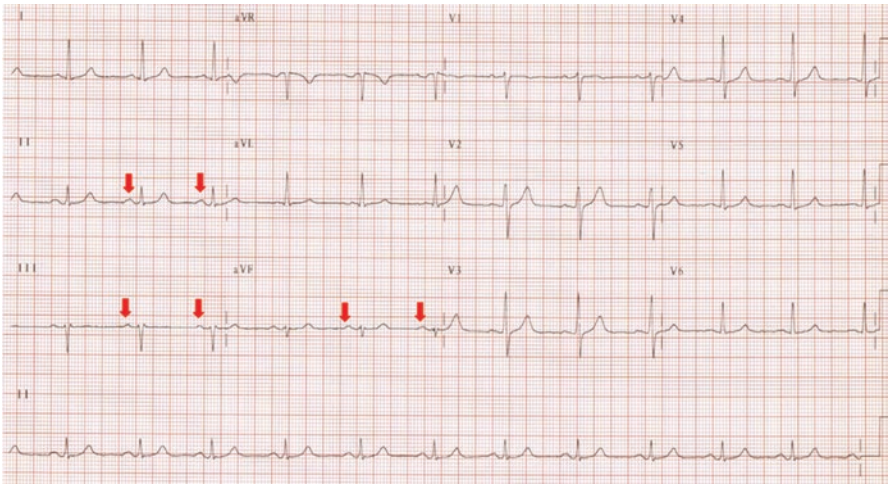

Fig. 3.2 Sinus rhythm (note positive P waves in inferior leads). Heart rate: number of large boxes between two QRS complexes is about four → dividing 300 by the number of large boxes (four) between QRS complexes gives us an estimated heart rate of 75 beats per minute

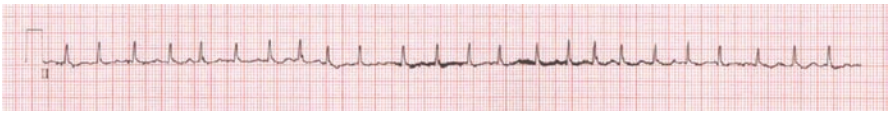

Fig. 3.3 A standard rhythm strip is 25 cm long (i.e., 10 s). Count number of QRS complexes in 10 s rhythm strip × 6. There are 24 QRS complexes in this EKG strip (showing an irregular rhythm c/w A. fibrillation), therefore → heart rate is 24 × 6 = 144 beats per minute

How to Determine QRS Axis (Figs. 3.4 and 3.5)

- The mean electrical axis of the heart is the average of all of the mean electrical vectors occurring during ventricular depolarization. The QRS axis can be determined using all six limb leads.

  First check lead I: if positive, axis is either normal, leftward, or left.

- If QRS complex is up (positive), then electrical activity is moving toward the lead. If QRS complex is down (negative), then electrical activity is moving away from the lead.
- Look at limb leads.
  - Normal axis: leads I and aVF are both positive (−30° to +90°).
  - Left axis deviation (LAD): axis beyond −30°. Leads I and aVL are positive; leads II and aVF are negative (S > R in lead II).
  - Right axis deviation (RAD): axis beyond +90°. Leads III and aVF are positive; leads I and aVL are negative (S > R in lead I).

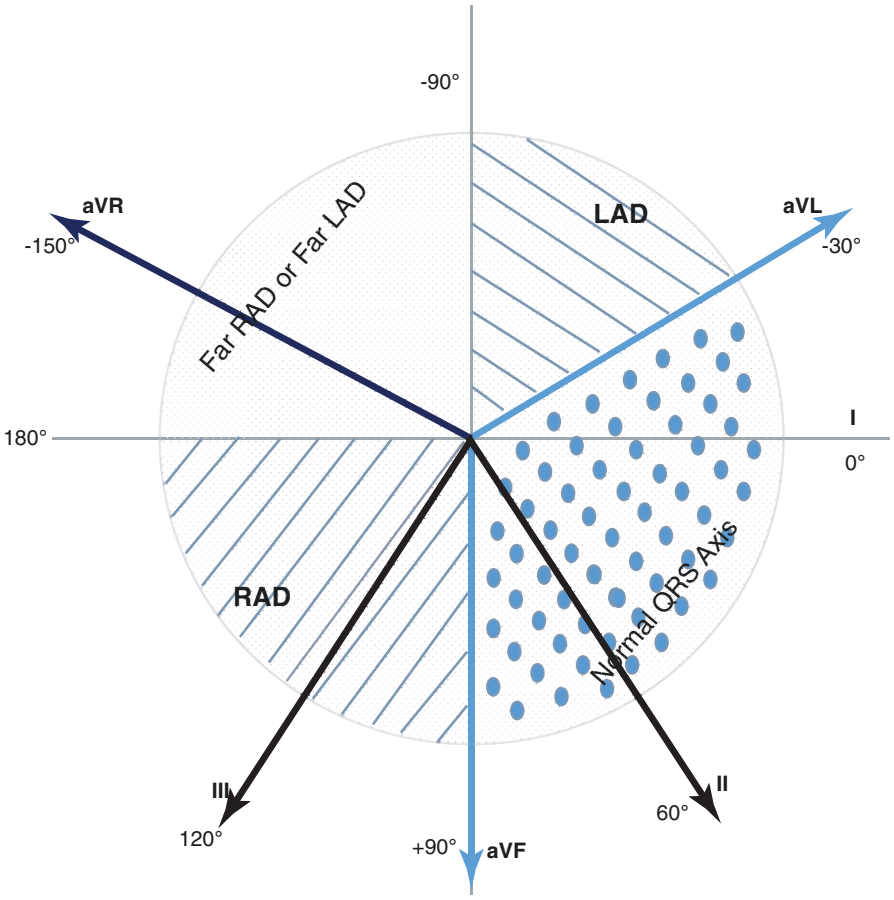

Fig. 3.4 A diagram showing how to evaluate QRS axis

- Left axis deviation (LAD) means electrical activity flows predominantly to the left. It is found in LV hypertrophy (LVH), LBBB, and inferior MI.
- Left anterior fascicular block (LAFB): there is LAD (−45 to −90°) and small q waves with tall R waves
- ("qR complexes") in leads I and aVL) with QRS <120 ms [5] (Fig. 3.6).
- Right axis deviation (RAD) means electrical activity flows predominantly to the right. It is found in right ventricular hypertrophy, RBBB, pulmonary embolism, septal defects (ASD), lateral wall MI, and dextrocardia.
- Left posterior fascicular block (LPFB): RAD (+90 to 180°) and rS in I and aVL and qR in III and aVF with QRS < 120 ms.

Low voltage ECG:

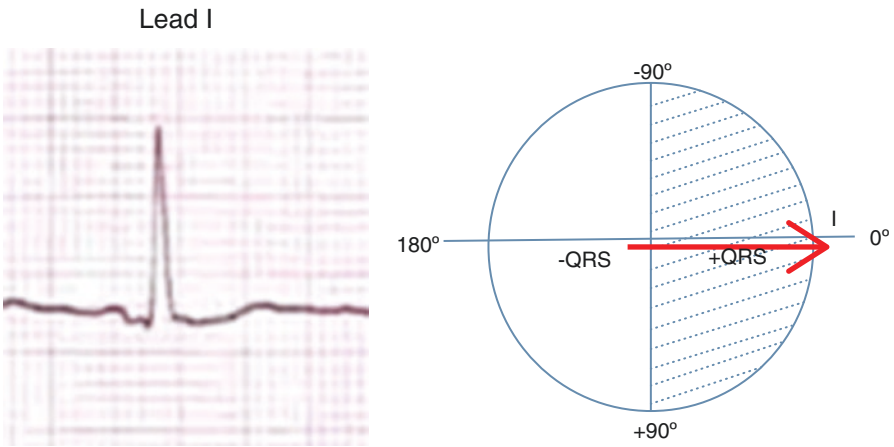

Fig. 3.5 If the QRS complex is positive in lead I, the electrical axis is in the direction of the shaded semicircle above (see arrow)

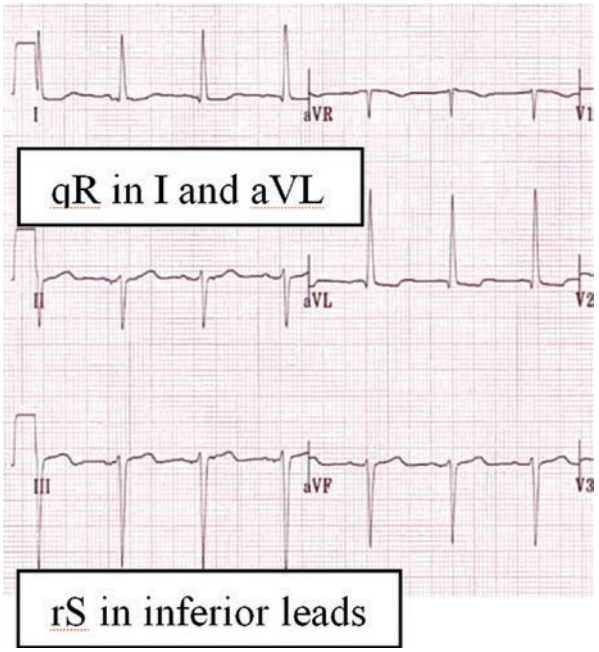

Fig. 3.6 Left anterior hemiblock (LAFB): QRS complexes are positive in leads I and aVL, negative in leads II and aVF → Left axis deviation is present. Left axis deviation, small q waves with tall R waves ("qR complexes") in leads I and aVL)

QRS height (amplitude):

- Low limb lead voltage: less than 5 mm
- Low precordial voltage: less than 10 mm high in all the precordial leads

It can be seen in:

- Pericardial effusion
- Emphysema
- Obesity
- Cardiac amyloid

Left Atrial Enlargement

Features:

- Biphasic P wave in lead I: broad and deep terminal negative portion of the P wave (i.e., >0.04 s and >1 mm in depth) (Fig. 3.7)
- P-wave duration >0.12 s in leads I and/or II. P wave in lead II can have two peaks (P mitrale)

Causes:

- Mitral stenosis
- When present with LVH: hypertensive heart disease, cardiomyopathy, mitral regurgitation, and aortic stenosis

Right Atrial Enlargement

Features:

- P-wave height in leads II, III, or aVF is >2.5 mm.
- P-wave height in leads V1 and V2 is >1.5 mm.

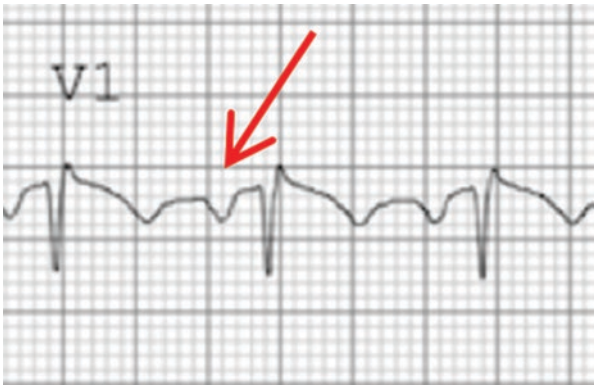

Fig. 3.7 Left atrial enlargement on the ECG assessed in lead V1. The terminal negative portion of the P wave in lead V1 is ≥1 mm in depth and ≥40 ms in duration

Causes:

- Increased right ventricular pressures, pulmonary arterial hypertension, and cor pulmonale
- Valvular disease, e.g., tricuspid regurgitation, tricuspid stenosis
- Congenital heart disease, e.g., Ebstein's anomaly, trial septal defect (ASD), and tetralogy of Fallot
- Dilated cardiomyopathy

Left Ventricular Hypertrophy [6–9]

Features (Figs. 3.8 and 3.9):

- The height of largest S wave in V1 or V2 + height of largest R wave in V5 or V6 >35 mm (or seven large boxes) (Sokolov-Lyon criteria).
- The absolute height of QRS complex is >11 mm if no left axis duration.
- The S in V_3 + R in aVL > 28 mm (men) S in V_3 + R in aVL > 20 mm (women) (Cornell criteria).

Causes:

- Hypertension, aortic stenosis/regurgitation, mitral regurgitation, aortic coarctation, and HOCM

LVH

- Should be confirmed by echocardiography (LVH cannot be diagnosed by ECG alone).
- ECG has poor sensitivity for detecting LVH (patients with LV hypertrophy can have normal ECG).

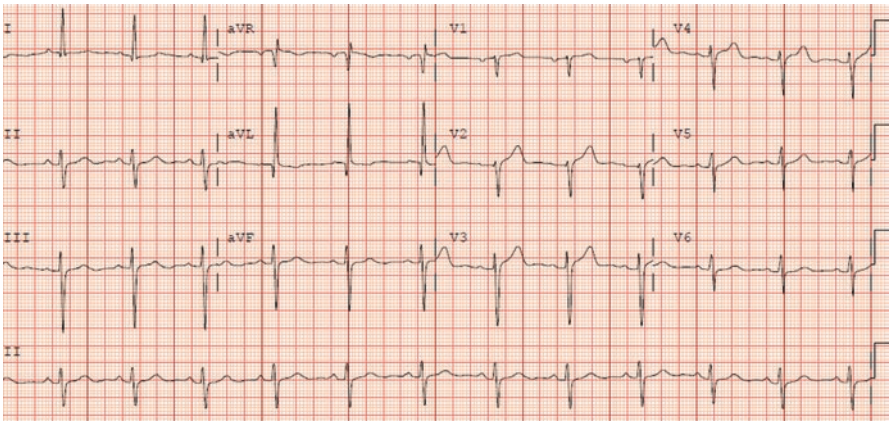

Fig. 3.8 Sinus rhythm, LV hypertrophy (Cornell criteria: note the R wave in lead aVL is >11 mm + S wave in lead V3 = 31 mm), LAFB

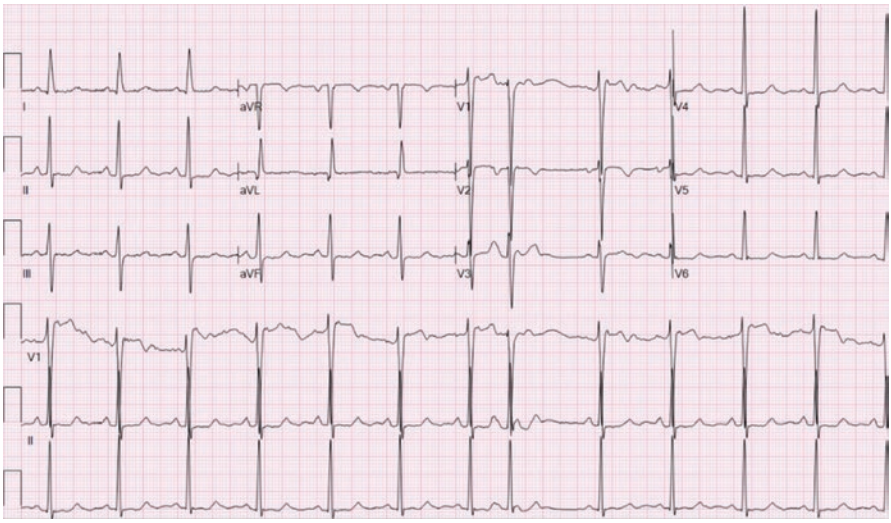

Fig. 3.9 Sinus rhythm, LV hypertrophy. Note that the R wave in lead V5 + S wave in lead V1 is >35 mm (Sokolov-Lyon criteria)

Hypertrophic Cardiomyopathy (HOCM)

Features (Fig. 3.10):

- High-voltage QRS complexes in the precordial leads
- Deep Q waves not corresponding to any coronary anatomy
- ST-T segment changes including deep T-wave inversions

Right Ventricular Hypertrophy

Features (Fig. 3.11):

- Dominant R wave in V1 $\geq$ 7 mm
- Dominant S wave in V5 or 6 (>7 mm deep, or R > S ratio <1)
- R wave in V1 + S wave in V5 or V6 > 10.5 mm
- Secondary ST-T changes in right precordial leads (strain pattern in V1–V4)

Sick Sinus Syndrome (Fig. 3.12)

- Sinus node dysfunction

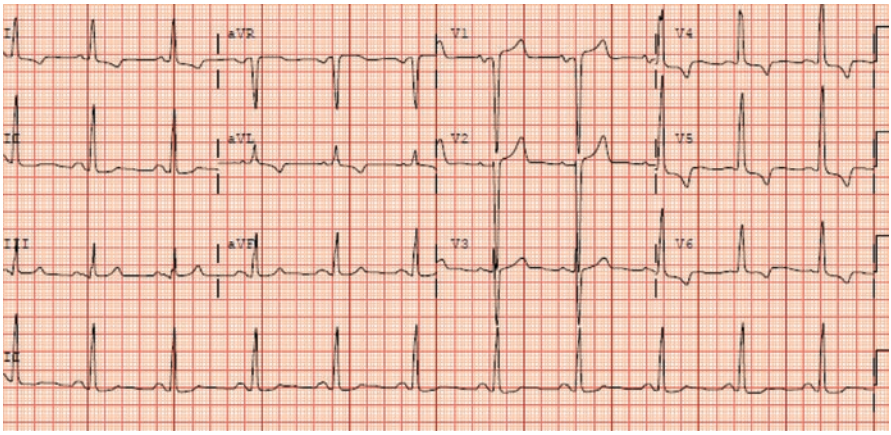

Fig. 3.10 Sinus rhythm. Hypertrophic obstructive cardiomyopathy (HOCM)

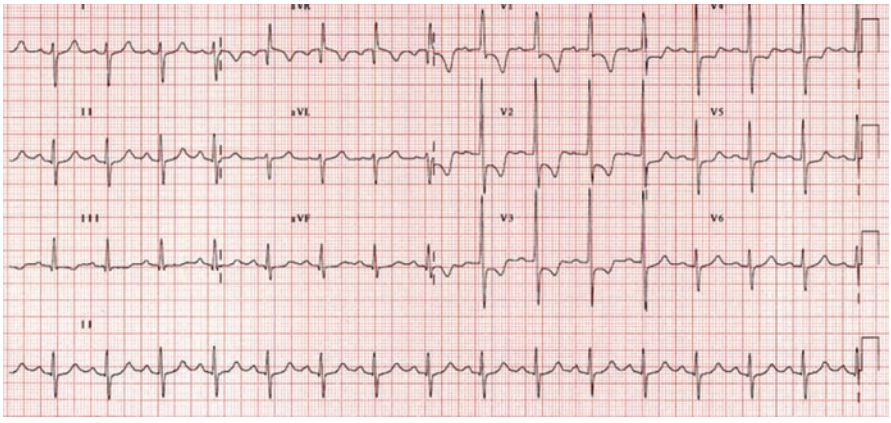

Fig. 3.11 ECG of the patient with cor pulmonale: Right axis deviation (+150°). Right ventricular hypertrophy with dominant R wave in V1 (>7 mm tall; R/S ratio >1). Right ventricular strain pattern with ST depression and T-wave inversion in V1–4

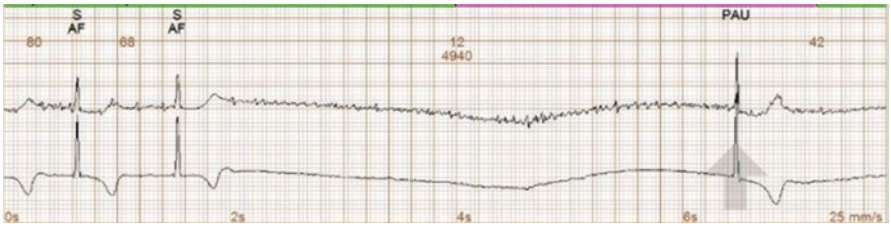

Fig. 3.12 Patient in A. fibrillation with prolonged pause

Features:

- Sinus pause (lack of P waves in the pause >3 s)
- Sinoatrial block
- Sinus bradycardia
- Bradycardia-tachycardia syndrome (alternating bradycardia with paroxysmal tachycardia)

Intrinsic Causes:

- Idiopathic fibrosis (most common cause)
- Ischemia, including myocardial infarction
- Infiltrative diseases, e.g., sarcoidosis
- Congenital abnormalities

Extrinsic Causes:

- Medications, e.g., beta-blockers, calcium-channel blockers, digoxin
- Hypothyroidism
- Electrolyte abnormalities, e.g., hyperkalemia

First degree AV Block

Features (Fig. 3.13):

- PR interval $\geq$ 0.20 s and is fixed.
- Each P wave is followed by a QRS complex.

Causes:

- Multiple etiologies, including high vagal tone, myocarditis, or drugs (e.g., beta-blockers, calcium-channel blockers)
- May also be a normal variant

Second Degree, Type I AV Block (Wenckebach) [6]

Features (Fig. 3.14):

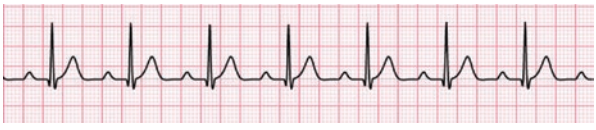

Fig. 3.13 Patient in first degree AV block. Notice prolonged PR interval

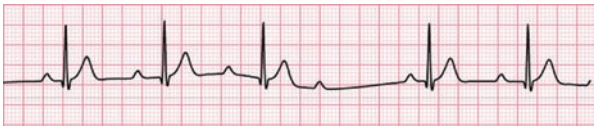

Fig. 3.14 Patient in second degree heart block type I

- Appearance of group beating.
- Progressive prolongation of the PR interval until there is a non-conducted P wave.
- Progressive shortening of the R-R interval.
- The R-R interval spanning the non-conducted beat is less than twice the following R-R interval.

Causes:

- Dysfunction at the level of the AV node.
- Common etiologies include high vagal tone, drugs (e.g., beta-blockers, calcium-channel blockers), myocarditis, and MI.
- Can be seen in well-trained athletes and during sleep, and it is not pathologic.
- Rarely causes hemodynamic instability.
- Low risk of progressing to complete heart block (provided QRS is narrow).

Second Degree, Type II AV Block [10]

Features (Fig. 3.15):

- Intermittent non-conducted P wave without prolongation of the PR interval.
- PR intervals in conducted beats are often constant.
- The R-R interval spanning the dropped beat is multiple of the preceding R to R interval.
- With 2:1 AV block occasionally ventriculo-phasic sinus arrhythmia can be seen. P to P interval with the intervening QRS is shorter than P to P interval without QRS (phenomenon mediated by baroreceptors).

Causes:

- Dysfunction at a level below the AV node (infrahisian disease).
- Mostly associated with underlying heart disease, including MI, myocarditis, cardiomyopathy, and/or structural heart disease.
- Other causes include hyperkalemia, digoxin toxicity, and hypothyroidism.
- More likely to cause symptoms (most often syncope) and hemodynamic instability, which may occur spontaneously.
- High risk of progression to complete heart block or sudden cardiac death.
- Emergent need for pacing may be indicated if symptomatic and/or hemodynamically unstable.

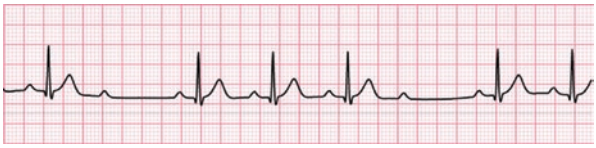

Fig. 3.15 Second degree heart block type II

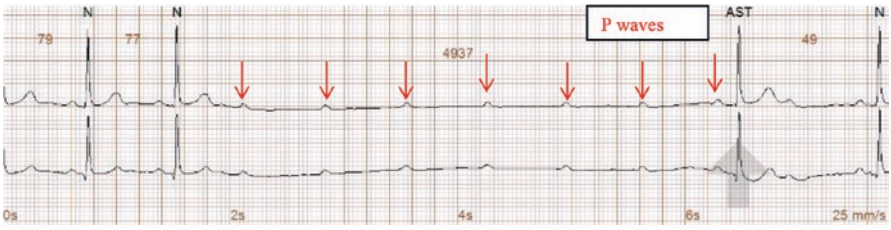

Fig. 3.16 Patient in third degree heart block; non-conducted P waves are indicated with red arrows

Third Degree AV Block (Complete Heart Block)

Features (Fig. 3.16):

- P waves consistently fail to conduct, causing P waves and QRS complexes to be independent of each other.
- P-P intervals (most of the time) and R-R intervals are constant.

Causes:

- Damage to the conduction system, either through infiltrative or degenerative disorder.
- Myocardial infarction (usually inferior distribution).
- Lyme disease (reversible with antibiotic treatment).
- Sarcoidosis, particularly in younger patients.
- Other causes include severe hyperkalemia, hypothyroidism, endocarditis, and digoxin toxicity.
- Congenital.

Intraventricular Conduction Abnormalities

Right Bundle Branch Block (RBBB) [11]

Features (Fig. 3.17):

- Wide QRS (≥0.12 s)
- RSR' pattern in leads V1–V3 representing delayed activation of the right ventricle

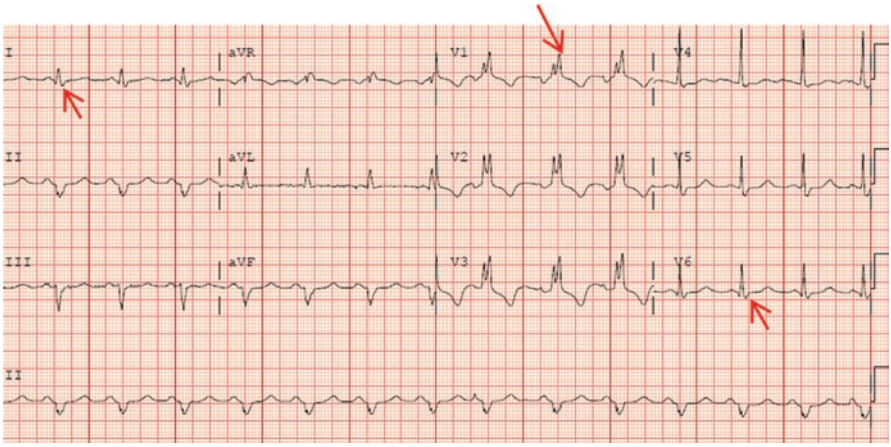

Fig. 3.17 Right bundle branch block. rSR' pattern indicated in lead V1 (red arrow). Note prominent S waves in I, aVL, V5–V6 (red arrows)

- Wide, slurred S wave in leads I, aVL, V5, and V6 (lateral leads)
- Sometimes associated with T-wave inversions and ST depressions in leads V1–3

Causes:

- Delayed depolarization of the RV compared to the LV.
- May be found in patients without any cardiac disease, but comparison with patient's prior EKGs and the clinical picture needs to be considered before it can be considered "normal."
- Also associated with RV hypertrophy/cor pulmonale, pulmonary embolus, hypertensive heart disease, cardiomyopathy, myocarditis, ischemic heart disease, and congenital heart disease.

Left Bundle Branch Block (LBBB) [12]

Features (Fig. 3.18):

- Wide QRS (≥0.12 s)
- Dominant S wave in V1
- rS complex or QS pattern in leads V1–V3
- Broad, or notched ("M-shaped") R wave in leads I, aVL, V5, and/or V6 (result of the delayed activation of the left ventricle)
- Lack of Q waves in leads I, V5, and V6
- ST segments and T waves in the opposite direction to the major QRS deflection

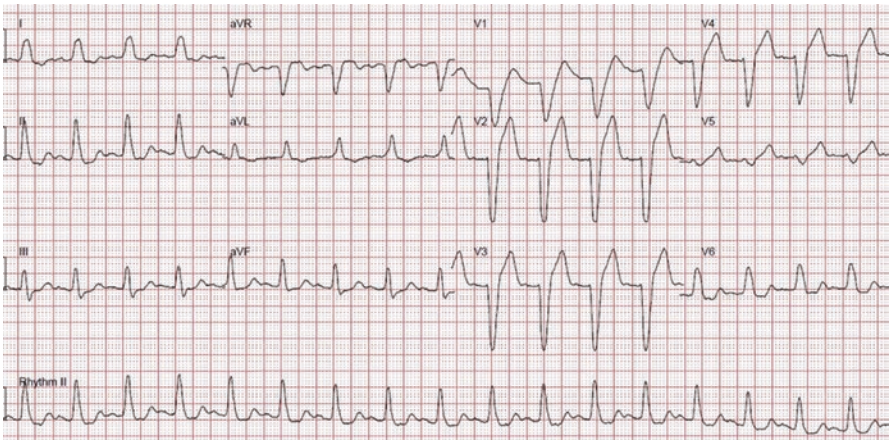

Fig. 3.18 Left bundle branch block. QRS duration >120 ms, QS in lead V1, monophasic R wave with no Q waves in leads V6 and I

Causes:

- Delayed depolarization of the LV compared to the RV (conduction occurs down the septum from the right to the left).
- Most often due to underlying cardiac disorder and rarely found in normal adults.
- Can be initial presentation of an acute anterior MI.
- Other associated disorders include ischemic heart disease, cardiomyopathy, congenital heart disease, and aortic stenosis.

Intraventricular Conduction Delay (IVCD)

- If the QRS complex does not resemble either right or left bundle branch block but has a duration that is greater than 0.10 s, then it is considered "nonspecific intraventricular conduction disease" or IVCD.

Premature Atrial Complex (PAC)

- Arises from an ectopic focus in the atrium.
- It is preceded by an abnormal (non-sinus) P wave. P-wave morphology different from the normal sinus P-wave morphology.
- Followed by a pause, but unlike PVC, it is not a full compensatory pause.

- The QRS complex of an APC is usually normal (narrow).
- The QRS complex of an APC can be broad because of aberrant ventricular conduction, RBBB, or LBBB.

PACs can occur in repeating patterns:

- Atrial bigeminy: every other beat is PAC
- Atrial trigeminy: every third beat is PAC.
- Couplet: two consecutive PACs.
- Triplet: three consecutive PACs.

Premature Ventricular Complexes (PVC)

- Arises from an ectopic focus in the ventricle.
- Multifocal PVCs arise from multiple ectopic foci (PVCs with multiple morphologies).
- Broad QRS complex (≥120 ms) with abnormal morphology and discordant ST and T wave changes, not preceded by a premature P wave.
- The sinus P-P cycle is not disturbed by PVC.
- Followed by a full compensatory pause (the next normal beat occurs after an interval double of the preceding R-R interval).

PVCs can occur in repeating patterns (Fig. 3.19):

- Ventricular bigeminy: every other beat is PVC.
- Ventricular trigeminy: every third beat is PVC.
- Couplet: two consecutive PVCs.
- Triplet: three consecutive PVCs.

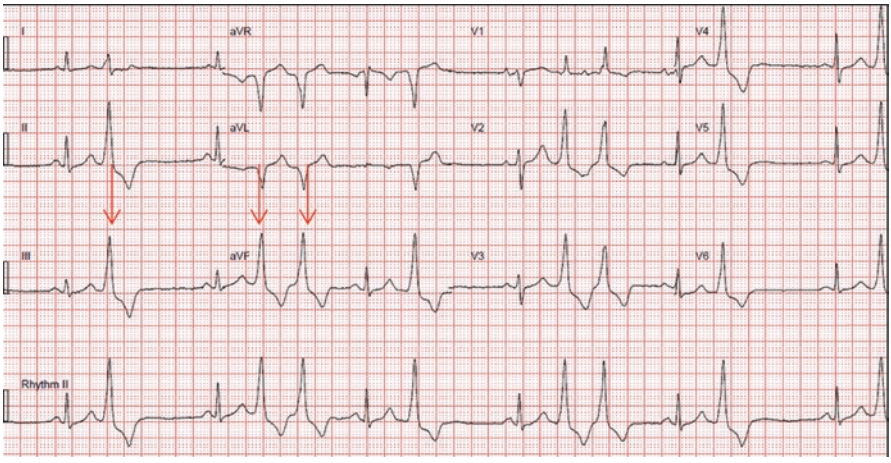

Fig. 3.19 PVCs (marked by arrows) in bigeminal pattern and occasional ventricular couplets

Prolonged QT Interval [13]

Features (Fig. 3.20):

- QT should be measured from beginning of the QRS complex to where the tangent of the T-wave downslope meets the baseline.
- QTc (corrected QT interval) ≥0.44 s in men and ≥0.46 s in women.
- QT interval is dependent on heart rate; it lengthens with faster HR and shortens with slower HR (except in congenital long QT syndromes).
- Significance should be determined by the corrected QT interval, which is the interval corrected to a heart rate of 60 beats per minute. Different formulas exist for calculating the corrected value. There are multiple formulas used to estimate QTc. Different formulas exist for calculating the corrected value with Hodges and Fridericia proving prognostic data with regard to the risk of ventricular arrhythmias.
- In most cases, the QT interval is normal if it is less than half the duration of the R-R interval.
- Increases risk of developing sudden cardiac death and ventricular arrhythmias (particularly torsades de pointes), especially if QTc ≥ 0.50 s.

Causes:

- Represents the time it takes for the ventricles to depolarize and repolarize
- Electrolyte imbalances: hypokalemia, hypomagnesemia, and hypocalcemia
- Drugs: amiodarone, procainamide, sotalol, tricyclics, lithium, etc.
- Intracranial hemorrhage
- Hypothermia
- Myxedema
- Congenital long QT syndromes

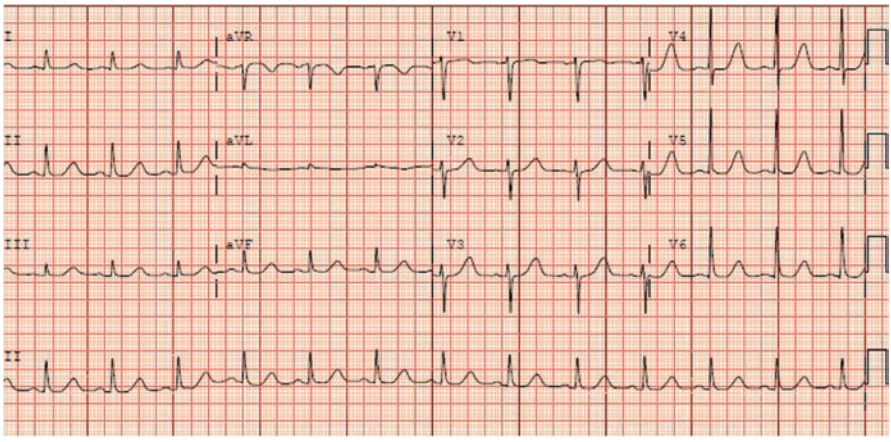

Fig. 3.20 Prolonged QT interval

Torsades De Pointes

- A form of polymorphic ventricular tachycardia occurring in the setting of QT prolongation (Fig. 3.21)
- A rapid ventricular rhythm characterized by a waxing and waning QRS amplitude, in which the QRS complexes "twist" around the isoelectric line ("twisting of the points")

Preexcitation [14, 15]

Features (Fig. 3.22):

- Delta wave: slurring of the onset of the QRS complex resulting in short PR interval
- Widened QRS complex (>0.12 s)
- ST-segment and T-wave changes occurring in direction opposite of the delta wave and major QRS vector

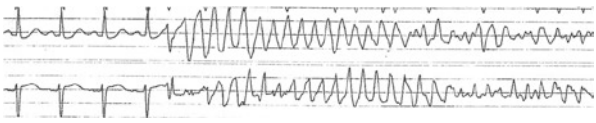

Fig. 3.21 Torsade de pointes in the setting of prolonged QT interval

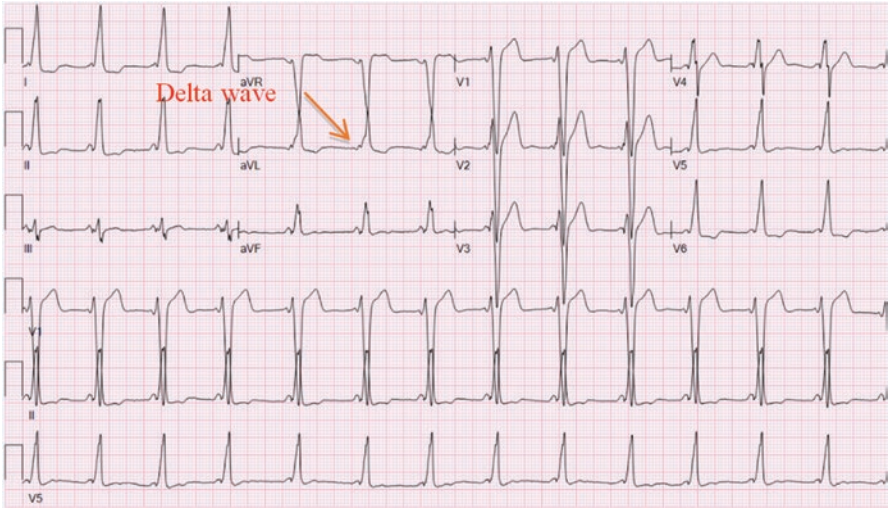

Fig. 3.22 ECG showing preexcitation. Note slurring of the initial portion of the QRS complex (delta wave)—red arrow

Causes:

- Congenital condition in which abnormal cardiac tissue creates a pathway for conduction, most commonly, from the atria to the ventricles.
- Conduction occurs through this accessory pathway competing with the AV node, thereby resulting in preexcitation of the ventricles.
- High risk for developing arrhythmias, most commonly AV reentry tachycardia, atrial fibrillation, and sudden cardiac death.
- Can be seen at any age.
- More common among males.

Myocardial Ischemia [16, 17]

Features (Fig. 3.23):

- T-wave inversions or flat T waves
- New horizontal or downsloping ST-segment depressions ≥0.5 mm in at least two contiguous leads

ST depressions on the ECG do not localize the ischemic area.

Exceptions:

- Wellens syndrome: deeply inverted or biphasic T waves in the anterior leads (particularly V2–V3) with isoelectric or minimally elevated (<1 mm) ST segments. Suggestive of myocardial ischemia with a critical stenosis of proximal left anterior descending artery (LAD)
- De Winter's sign: upsloping ST-segment depressions with prominent/peaked T waves in the precordial leads (chest leads). Suggestive of myocardial ischemia with a critical stenosis of left anterior descending artery (LAD)

Acute Myocardial Infarction

Features (Fig. 3.24):

- Acute myocardial ischemia with myocardial necrosis demonstrated by ST elevation on ECG.
  - New ST elevation at the J point in at least two contiguous leads:
    ≥2 mm (0.2 mV) in men or ≥1.5 mm (0.15 mV) in women in leads V2–V3
    ≥1 mm (0.1 mV) in any contiguous chest leads other than V2–V3, or the limb leads
  - Hyperacute T waves: (may mimic hyperkalemia) can be early sign of MI

ST elevations on ECG can localize acute myocardial infarction (MI) (Table 3.1). Figures 3.25 and 3.26 show examples of acute myocardial infarction.

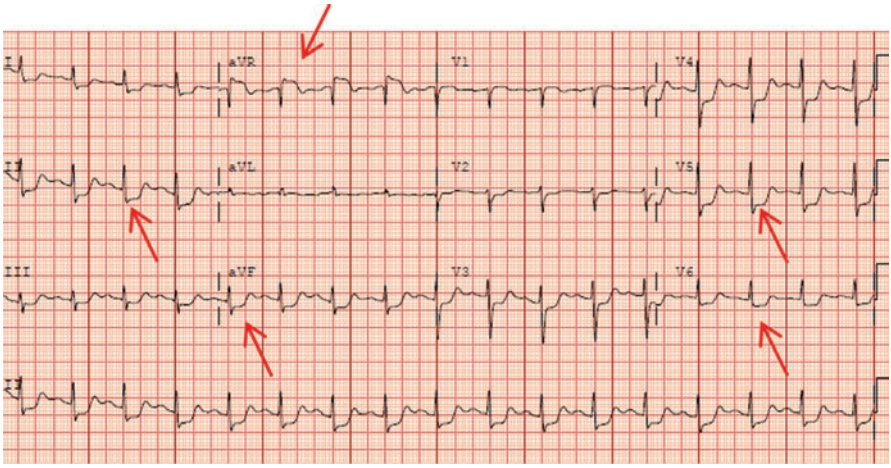

Fig. 3.23 Myocardial ischemia—note diffuse ST depressions, ST elevation in aVR (can be suggestive of left main disease)

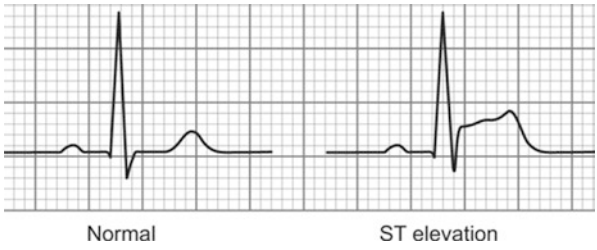

Fig. 3.24 ST-segment elevation resulting from ventricular transmural ischemia. The ST segment is normally isoelectric (zero voltage). Reproduced with permission from Klabunde [4]

Table 3.1 Localization of MI on ECG

MI localization	Leads with ST elevation
Anterior	V2–V5
Extensive anterior/ anterolateral	V1–6, I + aVL
Septal	V1–V2
Anteroseptal	V1–V4
Lateral	I, aVL, V5, V6
Inferior	II, III, aVF
Posterior	High R in V1–V3 with ST depression V1–V3 > 2 mm (mirror view) ST elevations in V7, V8, V9
Right ventricle Suspect in patients with IWMI	ST elevation in V1 + ST depression in V2 (highly specific for RV MI) ST elevation in right-sided leads V3R–V6R

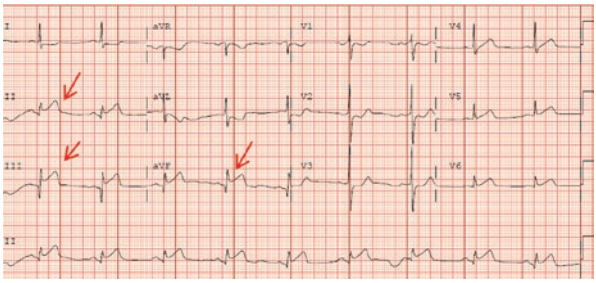

Fig. 3.25 Inferior wall MI (IWMI): ST elevations in leads II, III, and aVF (red arrows). Reciprocal changes in I, aVL, and V2–V3

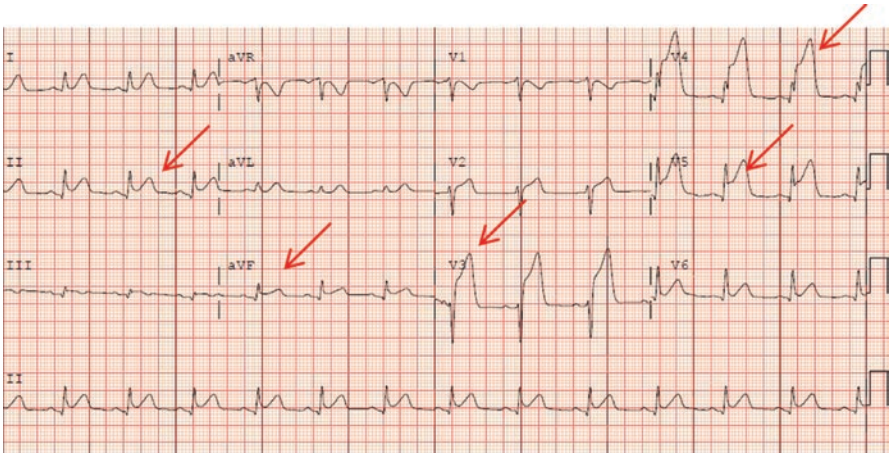

Fig. 3.26 Anterior wall MI: ST elevations in leads V3–V5 (red arrows). Note also mild ST elevations in the inferior leads. Patient found to have occluded LAD that supplied also the distal inferior wall ("wraparound" LAD)

Necrosis

Pathologic Q waves= Remote infarct (old MI) (Fig. 3.27):

- Q-wave amplitude 25% or more of the subsequent R wave
- >0.04 s (1 small box) wide AND >2 mm (two small box) deep in more than one lead
- 0.02 s (1/2 small box) in V1–V3

Acute Pericarditis [18]

Features:

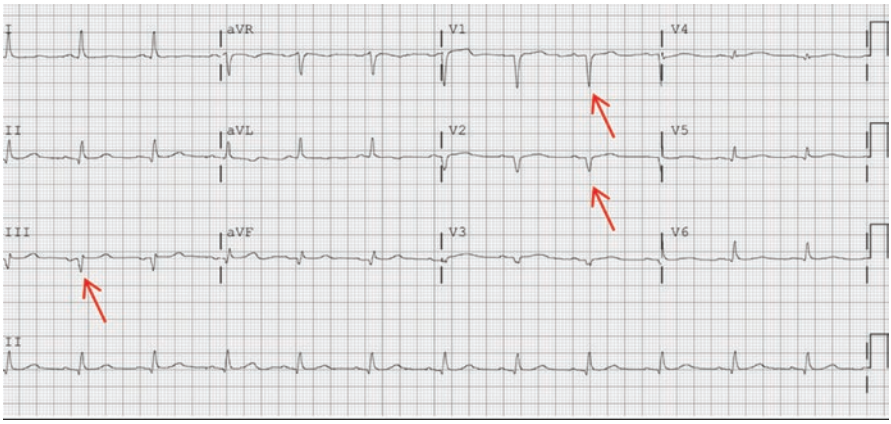

Fig. 3.27 Sinus rhythm, Q waves in the anterior and inferior leads (red arrows) consistent with old inferior and anterior MI

- Diffuse concave ST elevation in all leads without reciprocal ST depressions except in lead aVR.
- Diffuse PR depressions in all leads except lead aVR, which may show PR elevation.
- Low voltage.
- Sinus tachycardia.
- T-wave inversions seen after ST elevations return to baseline (compared to STEMI, when T-wave inversions occur while ST segments are still elevated).

Causes:

- Inflammation of the pericardium may be due to multiple etiologies, including infection, immunological disease, uremia, malignancy, trauma, post-MI, iatrogenic, or idiopathic.

Atrial Fibrillation [19]

Features (Fig. 3.28):

- Continuous chaotic atrial activity.
- Occasional atrial impulse conducts through AV node to initiate a QRS complex with "irregularly irregular" ventricular response to atrial rate of 300–400 beats per minute.
- No P waves.

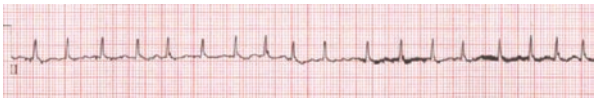

Fig. 3.28 Atrial fibrillation. The ventricular rate is irregularly irregular. Absent P waves

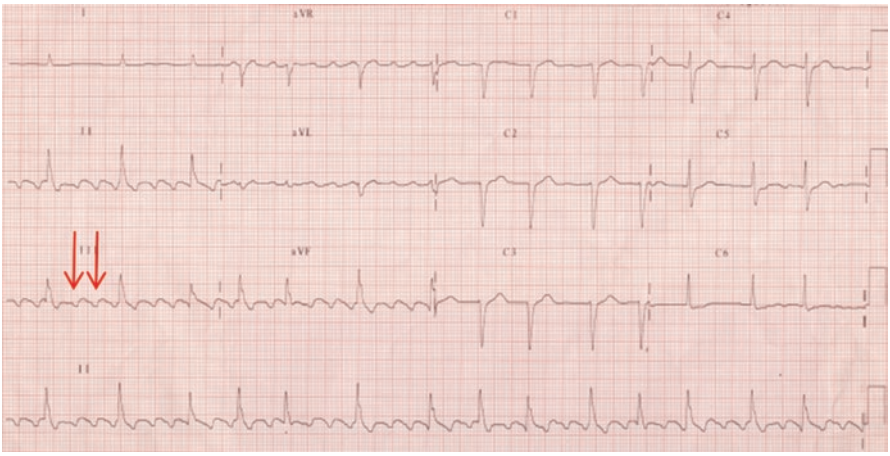

Fig. 3.29 Typical atrial flutter with variable conduction. Red arrows point to flutter waves

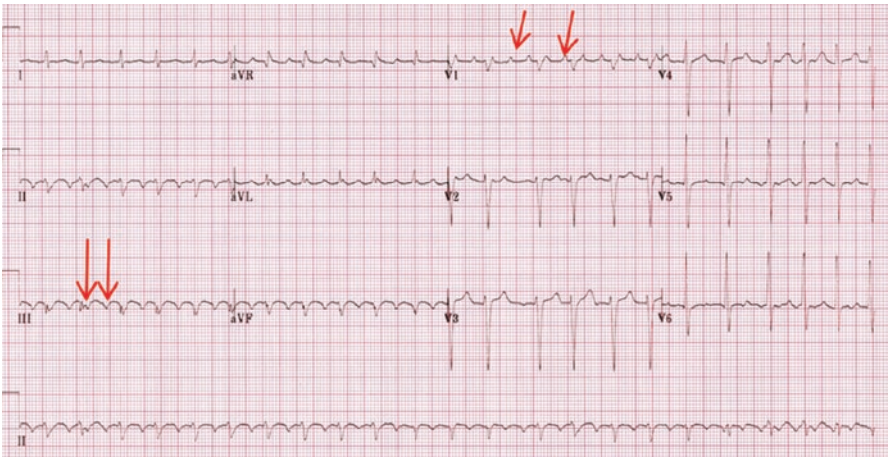

Fig. 3.30 Typical atrial flutter. There are inverted flutter waves in II, III (red arrows) + aVF at a rate of 300 beats per minute (one per big square). There are upright flutter waves in V1 and negative flutter waves in inferior leads (red arrows)

Atrial Flutter [20]

Features (Figs. 3.29 and 3.30):

- Atrial rate 220–350 beats per minute with ventricular rhythm often regular (however, can be irregular with variable conduction)
- Continuous activity (no isoelectric lines between atrial deflections—F waves)
- Some tachycardias have typical heart rates, e.g., a narrow complex tachycardia of 150 beats per minute that is very regular is likely an atrial flutter. **If HR close to 150 beats per minute**—NEVER assume it is sinus rhythm: look for atrial flutter waves!
- flutter with variable conduction can be irregular.

Multifocal Atrial Tachycardia (MAT)

Features:

- Irregular heart rate
- Tachycardia (HR > 100 beats per minute)
- Three different P-wave morphologies

AV Nodal Reentry Tachycardia (AVNRT) [21]

Features (Figs. 3.31 and 3.32):

- Typically, paroxysmal. Abrupt onset and offset.
- Can be interrupted by vagal maneuvers or adenosine.
- Regular with HR typically 180 beats per minute (140–280 beats per minute).
- It is more common in women than men (~75% of cases occurring in women).
- May occur in young and healthy patients.

Two sensitive characteristics to identify AVNRT on the EKG are:

- A retrograde P wave following the QRS complex in V1: Pseudo R′ waves in V1
- RP ≤ 70 ms (the distance between the R and P waves is less than 70 ms, so the P waves fuse with the QRS complex)

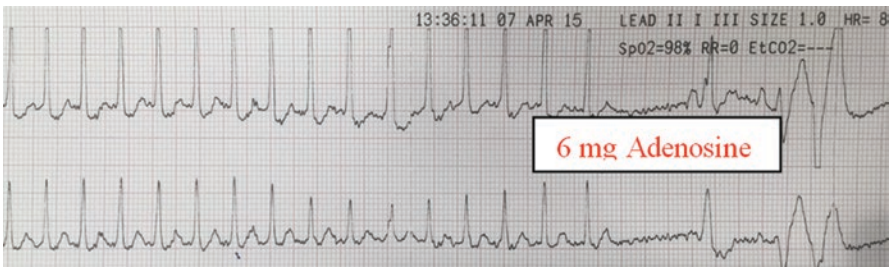

Fig. 3.31 Termination of SVT with adenosine

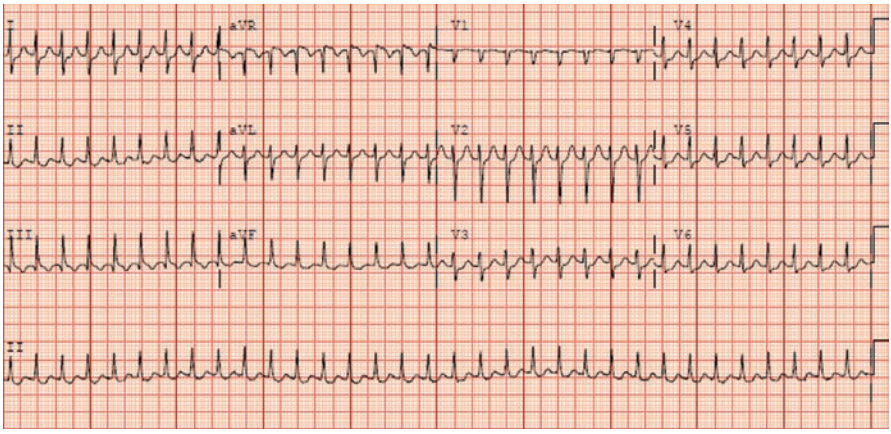

Fig. 3.32 Supraventricular tachycardia. A regular, narrow QRS complex is present

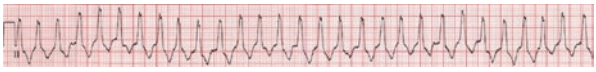

Fig. 3.33 Monomorphic VT

Ventricular Tachycardia [22–25]

Features (Fig. 3.33):

- Tachycardia (HR > 100 beats per minute) with wide QRS complex (>0.12 s), lasting more than 30 s (sustained VT)
- Extreme axis deviation (major QRS vector is positive in lead aVR and negative in leads I and aVF)
- AV dissociation (P waves and QRS complexes are independent of each other; atrial rate is less than ventricular rate)
- Fusion beats (sinus beat conducted via AV node fuses with ventricular activation arising from ventricular focus resulting in intermediate QRS morphology neither resembling sinus nor VT morphology)
- Capture beats (when sinus beat is conducted to the ventricle and results in narrow QRS).
- May be monomorphic (QRS complexes are mostly identical) or polymorphic (QRS complexes are variable in axis, duration, and/or amplitude). Torsades de pointes is a type of polymorphic VT in which the QRS complexes oscillate around an isoelectric line.
- Non-sustained VT refers to three or more consecutive beats that resolve spontaneously, lasting less than 30 s.

Causes:

- Ischemic heart disease needs to be ruled out; treat as acute coronary syndrome unless it can be ruled out (e.g., with coronary angiogram) or another cause is much more likely.

- Cardiomyopathy and heart failure.
- Structural heart disease.
- Metabolic disturbances (e.g., hyperkalemia).
- Congenital disorders (e.g., Brugada syndrome, long QT syndrome), especially in patients with a family history of sudden cardiac death.
- Idiopathic.
- Non-sustained VT usually has same underlying causes as sustained VT and, if not addressed, can lead to sustained VT.

Ventricular Fibrillation

Features:

- Chaotic and irregular deflections of varying amplitudes.
- Heart rate can be anywhere from 150 to 500 beats per minute.
- No distinguishable P waves, QRS complexes, or T waves.
- If prolonged, amplitudes likely to eventually decrease over time until no deflections are seen (coarse VF → fine VF → asystole).

Causes:

- Ventricles are not contracting in an organized, synchronized manner, and there is essentially no cardiac output.
- Multiple etiologies, including any that can cause cardiac or respiratory arrest, as well as drugs (especially those causing prolonged QT with torsade de pointes).

Hyperkalemia

Features:
Early ECG changes of hyperkalemia (serum potassium level of 5.5–6.5 mmol/L):

- Tall, peaked T waves with a narrow base (usually the earliest sign of hyperkalemia)
- Shortened QT interval
- ST-segment depressions

ECG changes (serum potassium level of 6.5–8.0 mmol/L):

- Peaked T waves
- PR interval prolongation
- Widening and flattening of P waves
- QRS prolongation

ECG changes (serum potassium level higher than 8.0 mmol/L):

- Absence of P waves.
- The progressively widened QRS eventually merges with the T wave, forming a sine wave pattern. Ventricular fibrillation or asystole follows.
- Intraventricular/fascicular/bundle branch blocks.

Hypokalemia

ECG changes (serum potassium <2.7 mmol/L)

- The presence of U waves, flattened T waves, prolongation of the PR interval, ST depression

Hypercalcemia

- Shortened QTc, mostly due to decreased ST-segment duration

Hypocalcemia

- Prolonged QTc, mostly due to increased ST-segment duration without significant increase in T-wave duration

Digoxin

Features:

- EKG can show sagging ST depression and flattened, inverted, or biphasic T waves (digoxin effect). It only indicates that patient is on digoxin and is not a marker of digoxin toxicity.

Digoxin toxicity:

- Multiple dysrhythmias can be associated with digoxin toxicity including brady-arrhythmias, AV blocks (first, second, or third), frequent PVCs (including bigeminy and trigeminy), ventricular tachycardia (including polymorphic and bidirectional VT), regularized A. fibrillation (with complete heart block and junctional escape rhythm), paroxysmal atrial tachycardia with AV block, etc.

Paced Rhythms [26]

Features (Figs. 3.34 and 3.35):

- May show atrial pacing and/or ventricular pacing.
- Atrial pacing refers to when the pacing artifact precedes the P wave.

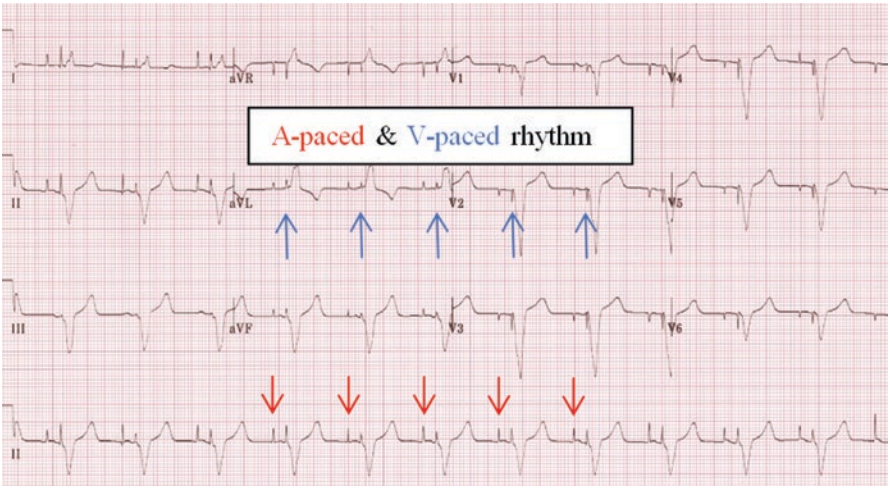

Fig. 3.34 Example of atrial and ventricular paced rhythm

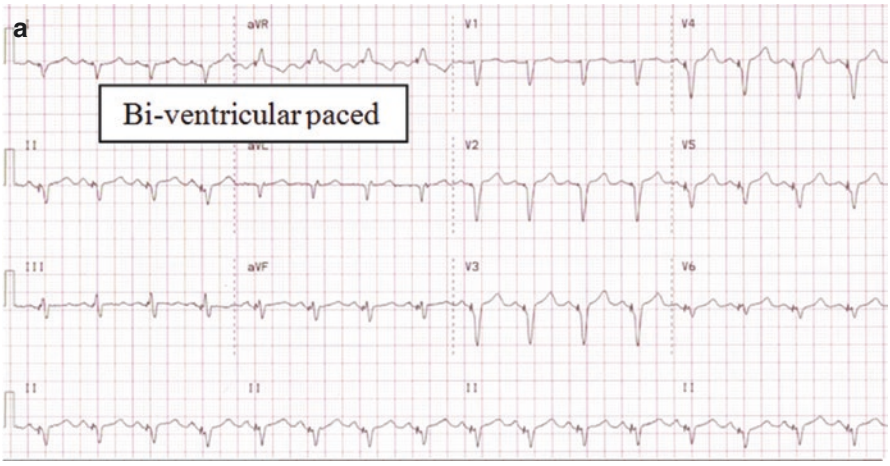

Fig. 3.35 Examples of biventricular paced rhythm. (**a**) Upper ECG: atrial sensed, biventricular paced rhythm. (**b**) Lower ECG: biventricular paced rhythm, underlying rhythm is atrial fibrillation. Note difference in QRS morphology related to variable timing of RV to LV pacing

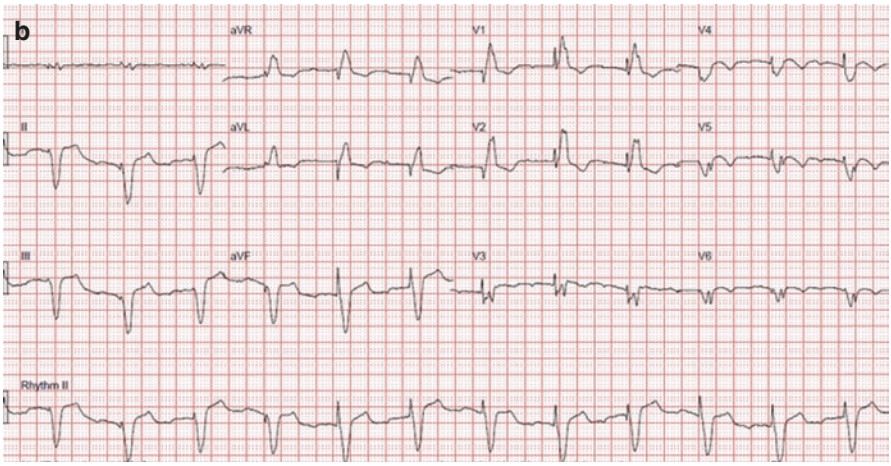

Fig. 3.35 (continued)

- Ventricular pacing is when the pacing artifact precedes the QRS complex. The QRS complex has LBBB morphology since ventricular activation is initiated in the RV.
- In BiV pacing, the QRS complex may appear to have either RBBB, LBBB, or IVCD as pacing is occurring in both the RV and LV.

Acknowledgments I would like to thank Dr. Miluska O Mejia for helping with the Figs. 3.4 and 3.5 and for reviewing the chapter.

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Chapter 4
Primary and Secondary Prevention of Cardiovascular Disease

Brandon Bader and Ronald G. Schwartz

Key Terms

Primary Prevention: Cardiovascular risk reduction strategies involving lifestyle and medical interventions in patients *without* known CVD.

Secondary Prevention: Cardiovascular risk reduction strategies involving lifestyle and medical therapies in patients *with* known CVD.

Epidemiology

- Since 1975, CVD mortality in the United States has declined by 24–28% [1].
- However, in the United States and worldwide, CVD remains the leading cause of death.

Risk Assessment

- Risk factor screening should occur beginning at age 20.
- Several 10-year, multiple-risk calculators are available, with the most popular being the Framingham Risk Calculator and the 2013 ASCVD risk estimator (based on risk factors described in Table 4.1).

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© Springer International Publishing AG, part of Springer Nature 2018

H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7_4

Table 4.1 Risk factors for CAD

Common risk factors for CVD
Age
Sex
Pack-years smoking history (packs per day × number of years)
Systolic blood pressure
LDL cholesterol
Total cholesterol:HDL cholesterol ratio (TC:H most powerful risk predictor) TC:H < 3.0 optimal (desirable) TC:H 4.2 normal or average (not desirable) TC:H > 5.0 high risk [2, 3]
Diabetes
CKD
Family history (parent or sibling)

Table 4.2 Summary of disease prevention strategies

Primary prevention disease-modifying interventions			Secondary prevention
Low-risk patients (10-year risk <5%)	Moderate-risk patients	High-risk patients (Familial hypercholesterolemia, diabetes, CKD)	
Lifestyle modification	Lifestyle modification	Lifestyle modification	Lifestyle modification
Smoking cessation	Smoking cessation	Smoking cessation	Smoking cessation
BP goal <120/80	BP goal <120/80	BP goal <120/80 or < 130/90	BP goal <120/80 or < 130/90
	Antiplatelet therapy	Antiplatelet therapy	Mono or dual antiplatelet therapy
	Low- to moderate-intensity statin	Moderate- to high-intensity statin	High-intensity statin LDL-C goal <70 mg/dL
		Glycemic control in accordance with hemoglobin A1c goals in diabetics	Consideration of second-line anti-lipid therapy

General Disease Prevention Strategies

Targeted Disease Prevention (Table 4.2)

Glycemic Control

- Both microvascular and macrovascular complications from diabetes contribute to morbidity and mortality:
  - Tight glycemic control reduces risk of microvascular complications in both type 1 and type 2 diabetes mellitus [4, 5].

  - Tight glycemic control has shown a risk reduction of macrovascular complications in diabetes mellitus type 1 [6].
  - However, the data are less conclusive for type 2 diabetes and tight control may even be harmful [7].
- All patients at risk or >45 years of age should be screened for diabetes with hemoglobin A1C or fasting blood glucose.
- Those at risk of developing diabetes should be counseled on lifestyle modifications to avoid developing the disease.
- The glucagon-like peptide 1 (GLP1) receptor agonist, liraglutide (Victoza), has been shown to reduce the risk of nonfatal MI, stroke, and cardiovascular mortality over placebo (13.0% vs. 14.9%, HR 0.87) [8].
- Similarly, the sodium glucose cotransporter 2 (SGLT2) inhibitors canagliflozin (Invokana) and empagliflozin (Jardiance) have also been shown to reduce the risk of cardiovascular mortality compared to placebo (HR 0.86) [9, 10].

ADA-Recommended Glycemic Targets for Nonpregnant Adults [11]

Hemoglobin A1C

- 6.5% for patients who meet the following criteria:
  - Short duration of diabetes
  - Long life expectancy
  - Otherwise healthy
  - Goal achievable without significant hypoglycemia or other adverse effects
- 7.0% reasonable goal for many patients
- <8.0% for patients who meet the following criteria
  - Elderly/limited life expectancy
  - Extensive comorbidities
  - Advanced microvascular or macrovascular complications

Fasting plasma glucose (FPG)

- 80–130 mg/dL

2-h postprandial glucose

- <180 mg/dL

T2DM Trials

- United Kingdom Prospective Diabetes Study (UKPDS) [12, 13]
- Action to Control Cardiovascular Risk in Diabetes (ACCORD) [7]

- Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-release control Evaluation (ADVANCE) trial [14]
- Veterans Affairs Diabetes Trial (VADT) [15, 16]

T1DM Trials

- Diabetes Control and Complications Trial (DCCT) [4]
- DCCT Epidemiology of Diabetes Interventions and Complications (EDIC) [6]

Hypertension Control

- The 2017 ACC/AHA hypertension guideline redefines hypertension [17].
  - Normal blood pressure is defined as <120/80.
  - Elevated blood pressure is between 120 and 129/80.
  - Hypertension stage 1 is defined as systolic BP 130–139 mmHg and diastolic BP 80–89 mmHg.
  - Hypertension stage 2 is defined as systolic BP >140 mmHg or diastolic BP >90 mmHg.
  - Blood pressure readings should be performed in a relaxed patient on >2 readings obtained on ≥2 occasions to diagnose hypertension.
  - Home and ambulatory readings are encouraged in addition to office visit readings.
- The guidelines place an emphasis on lifestyle modifications, such as a balanced diet, weight loss, regular exercise, smoking cessation, and alcohol moderation, as hallmarks of hypertension treatment (discussed below).
- For those without significant comorbidities who have a 10-year ASCVD risk <10%, BP goal should be <120–140/80 (SPRINT Trial) [17, 18].
- For diabetics, blood pressure goal is <130/90 (ACCORD Trial) [17, 19].
  - All first-line antihypertensive agents (diuretics, calcium channel blockers, ACE inhibitors, ARBs) are useful and effective in diabetics.
  - For those with albuminuria, ACE inhibitors or ARBs should be first line, unless contraindications present.
- Additionally, those with known CVD, renal disease, or 10-year ASCVD risk >10% should also target a BP goal of <130/90 [17].
- Suggested sequence of medications
  - Thiazide diuretic (a loop diuretic, e.g., torsemide for creatinine >1.5 or CKD ≥ III)
    Chlorthalidone is preferred, as longer lasting than HCTZ.
    Start at 12.5 mg titrate to 25 mg.
  - Beta-blocker: carvedilol 3.125–25 mg BID

Alternative: Atenolol 25–100 mg daily, metoprolol 12.5–200 mg BID.

  - ACE inhibitor: Lisinopril 5–40 mg daily
    ARB: e.g., valsartan 80–320 mg daily (for patients with ACEi cough or hypersensitivity)
  - Calcium channel blocker: amlodipine, felodipine 2.5–10 mg daily
  - Spironolactone (can cause breast tenderness, gynecomastia in men) or eplerenone 12.5–200 mg daily, as tolerated by stable creatinine and K+ <5.4
  - Alpha blocker: guanfacine 1 mg daily, can be uptitrated after 1–2 weeks to 2 mg daily
    Use of clonidine should be avoided due to labile hypertension.
- Methyldopa, nifedipine, and/or labetalol is recommended in pregnant women [17].

Antiplatelet Therapy

- Daily low-dose aspirin is not recommended for low-risk patients (<10% 10-year absolute risk), as the risk of major bleeding exceeds the absolute benefit of risk reduction of CVD.
- For moderate- and high-risk patients (10-year absolute risk >10% of first coronary heart disease event), 75–160 mg/day aspirin is recommended for those that can tolerate aspirin [20].
- Clopidogrel 75 mg is more effective than aspirin for secondary prevention (CAPRIE, MATCH trials) [21, 22]:
  - CAPRIE: Clopidogrel 75 mg outperformed 325 mg daily of aspirin in preventing stroke, MI, or vascular death in those with established disease (those with prior stroke, MI, or known peripheral vascular disease) [21].
  - MATCH: Addition of aspirin to clopidogrel 75 mg daily added bleeding risk without incremental therapeutic benefit for secondary stroke prevention [22].
- Clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes (CHARISMA) [20]:
  - A suggestion of benefit with clopidogrel treatment in patients with symptomatic atherothrombosis and a suggestion of harm in patients with multiple risk factors were found.
- $P2Y_{12}$ receptor blockers (clopidogrel 75 mg) can be used alternatively for those who cannot tolerate aspirin.
- Dual antiplatelet therapy with aspirin and $P2Y_{12}$ receptor blockers is recommended for at least 12 months after MI (Pegasus and DAPT trials) [23, 24].
- For those with prior TIA or CVA: clopidogrel 75 mg daily without aspirin (MATCH Trial) [22]:
  - Clopidogrel with aspirin associated with excess bleeding risk and no clinical benefit compared to 75 mg daily of clopidogrel alone.

- Anticoagulation with warfarin (INR 2.5–3.0), apixaban, rivoraxaban, or dabigatran is routinely recommended for those with atrial fibrillation and CHADS2VASC ≥ 2:
  - Current guidelines no longer recommend antiplatelet therapy alone or in combination with warfarin or target-specific oral anticoagulants for CVA risk reduction associated with cardio-embolism due to atrial fibrillation or flutter due to lack of efficacy [25, 26].
  - However, thrombotic occlusion of cerebrovascular disease indicates the need for clopidogrel 75 mg daily without aspirin (MATCH Trial) [22].

Dyslipidemia

HMG-CoA Reductase Inhibitor (Statin) Therapy *(Fig. 4.1 and Table 4.3)*

- In patients with elevated hs-CRP >2, average lipid levels: anti-inflammatory effectiveness (reducing hsCRP) of high-intensity rosuvastatin 20–40 mg daily in patients with average lipid levels substantially reduced rate of CV events including CVA (Jupiter Trial) [29]

Statin Intolerance

- The most common side effects of statins include myalgias, myositis (5–15%), and hepatotoxicity (<1%); rhabdomyolysis is rare ($1:10^6$).
  - However, there is only a slight increased risk of side effects compared with placebo, suggesting there are many contributing factors to muscle-related symptoms.
  - Observational data show many patients who had statins discontinued for adverse side effects will tolerate same or another statin [30].
- More hydrophilic statins (i.e., pravastatin, pitavastatin, rosuvastatin) may be associated with less incidence of statin intolerance compared to lipophilic statins.
- Muscle-related symptoms, the most common reason to stop statins, have been associated with vitamin D deficiency [31].
  - Vitamin D should be checked and treated in all individuals who report statin intolerance due to myopathy.
- Elderly and those with chronic kidney disease are also at higher risk of developing statin intolerance.
  - Given lack of evidence for increased benefit of high-intensity statins and higher risk of intolerance, those >75 should be started on moderate-intensity statins [27].

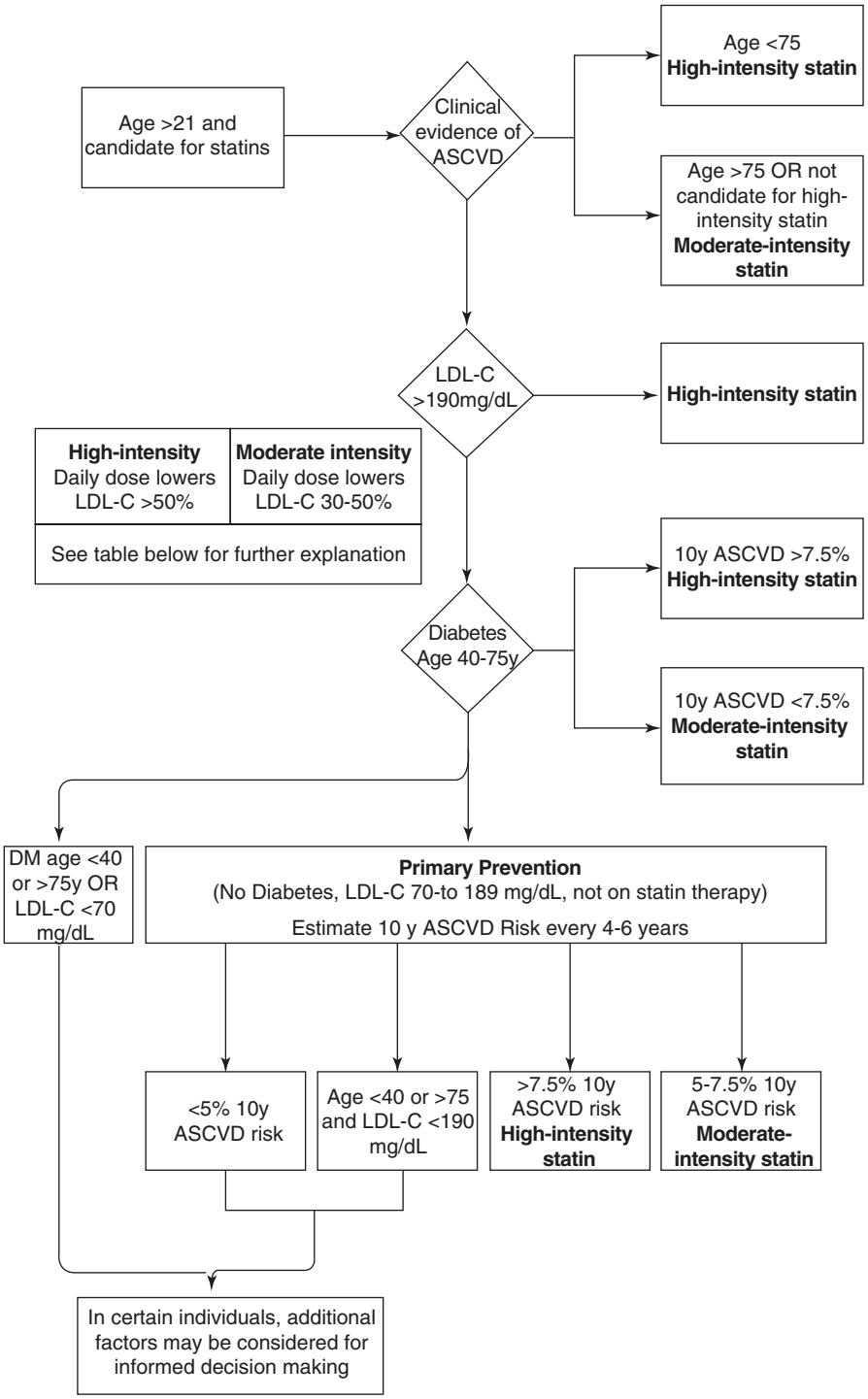

Fig. 4.1 Statin therapy algorithm. Reproduced from Stone et al. with permission [27]

Table 4.3 Statin therapy by intensity

High-intensity statin therapy	Moderate-intensity statin therapy	Low-intensity statin therapy
Daily dose lowers LDL-C on average, by <50%	Daily dose lowers LDL-C on average, by approximately 30–50%	Daily dose lowers LDL-C on average, by <30%
Atorvastatin 40–80 mg Rosuvastatin 20–40 mg Simvastatin 80 mg[a]	Atorvastatin 10–20 mg Rosuvastatin 5–10 mg Simvastatin 20–40 mg Pravastatin 40–80 mg Lovastatin 40 mg Fluvastatin 40–80 mg Pitavastatin 2–4 mg	Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg

Table adapted from Stone et al. with permission [27].
[a]FDA recommends against starting or titrating new patients to 80 mg of simvastatin daily due to the increased risk of myopathy (A to Z trial) [28].

- Other risk factors for statin-related myopathy include female sex, frailty, alcoholism, liver disease, and excessive grapefruit juice intake.
- Drugs that can interact with statins (through cytochrome P450 3A4 isoenzyme catabolism) include fibrates, cyclosporine, antifungals, macrolide antibiotics, HIV protease inhibitors, steroids, amiodarone, and some calcium channel blockers.
- For those who cannot tolerate statins, PCSK9 antibodies or ezetimibe may be considered (see below).

Nonstatin Lipid Therapy

Proprotein Convertase Subtilisin/Kexin 9 (PCSK9) Inhibitors

- Early studies demonstrate a risk reduction of cardiovascular events by up to 50% for both evolocumab (Repatha) and alirocumab (Praluent) [32, 33].
- Evolocumab with statin (in those with LDL-C > 70) resulted in 20% reduction in cardiac death, MI, or stroke compared to statin alone (Fourier trial) [34].
  - May reduce LDL-C by as much as 60% in patients on statin therapy (mean reduction from 90 mg/dL to 30 mg/dL).
- Considered second- or third-line secondary prevention therapy for those that are especially high risk (familial hypercholesterolemia, recurrent atherosclerotic CVD while on statin, diabetes, CKD 3, 4, or 5).
- Currently cost-prohibitive in many patients (up to $14,000 per year).
- No increase in cancer or dementia associated with ultra-low levels of LDL cholesterol (30–40 mg/dL) on PCSK9 therapy.
- Insurance may cover high-risk patients who are statin intolerant with familial hyperlipidemia.

Ezetimibe

- Modestly lowers LDL-C by approximately 17% [35, 36].
- In combination with statins, confers modest (2% absolute risk) reduction in CV events (but not all cause or CV mortality, IMPROVE IT trial) [37].
- Considered second-line secondary prevention therapy for those that are at very high risk.

Fibrates

- Major effects to raise HDL-C levels and lower plasma triglyceride levels; no major effect on LDL-C.
- Improvement in CV endpoints in patients with atherogenic dyslipidemia (MI, CVA, mortality; VA-HIT, BIP trials) [38, 39].
- Increased risk of developing muscle toxicity in patients taking fibrates and statins; however, this is most common in those with CKD ≥3.
- Particularly useful treatment in those with diabetes mellitus type 2 and atherogenic dyslipidemia.
- Incremental value of fibrates with high-intensity statin therapy may reflect study limitations:
  - ACCORD showed a trend of improved CV outcomes in the subpopulation of atherogenic dyslipidemia (High TG > 150 and low HDL <40) [40].
  - FIELD Trial failed to show reduction in mortality; however, study conclusions were likely limited by the high rate of statin drop-ins in the placebo group [41].

Nicotinic Acid (Niacin)

- Raises HDL-C, modestly lowers LDL-C, and lowers TGs [42].
- In combination with statins, substantially reduces angiographic stenosis severity and clinical endpoints were substantially improved vs. placebo controls (FATS, HATS trials) [43, 44].
- May be used with familial hypercholesterolemia in conjunction with statins and ezetimibe.
- Flushing, itching, and burning are common side effects of niacin, which can be attenuated by taking niacin with a large glass of water and increasing dose gradually (50 to 500–1000 mg TID) over several weeks and taking with low-dose aspirin to attenuate prostaglandin-mediated vasomotor symptoms.

Bile Acid Sequestrants

- Not widely used, not well tolerated
- May lower LDL-C by 32% [45]
- Effective when used in combination with a statin with markedly elevated plasma LDL-C levels
- Does not affect clinical endpoints (Cardiac death, MI, CVA)
- May impair absorption of digoxin, warfarin, and fat-soluble vitamins

Lifestyle Modifications

An integral component to all risk reduction strategies.

Smoking Avoidance and Cessation

- Tobacco use is the leading avoidable cause of premature death.
- Use substantially increases morbidity and mortality from CVD.
- Benefits of cessation for CVD prevention, even in elderly, begin within months and reach that of nonsmokers in several years.
- All smokers should be counseled regularly to quit in accordance with guidelines of the ACC/AHA [46].
  - Nicotine replacement with gum, lozenges, tablets, patches
  - Medications such as varenicline or buproprion
  - Counseling
  - Avoidance of second-hand inhalation
  - Meditation

Diet

- Emphasis on plant-based diet with high fiber consumption.
  - Dark-colored, non-starch vegetables (not including corn, white potatoes).
- Eliminate intake of trans-fatty acids (processed fatty foods).
- Carbs are worse than fats for CV mortality (PURE Trial) [47].
  - This large current study raises questions about traditional consideration of CV risks of saturated fats.
- Food sources with omega-3 fatty acids.
- Foods with a low glycemic load.
  - Foods that reduce glycemic load: nuts (walnuts, pecans, almonds), vinegar, cinnamon, fiber.

- Cooking: Avoid cooking foods in oils and fats to reduce risk of free radical formation which may contribute to inflammation, atherosclerosis, and cancer.
  - Best to steam, boil, or bake and then add small amounts of olive oil.

Physical Activity

- Individuals are recommended to engage in at least 30 min of moderate-intensity exercise at least 4 days per week.
- There is a decline in CV outcomes at highest level of reported exertion [48].
  - More recent data demonstrate the greatest increment of health benefit of exercise is associated with mild to moderate exertion.
  - Short duration of intermittent high-intensity exercise can reduce exercise time required to achieve CV survival benefit.
  - Beware of risks of muscle and orthopedic injury of exercise patients not accustomed to exercise, particularly those middle age and elderly.

Overweight and Obesity

- Patients should be counseled on evidence-based weight loss strategies.
  - Plant-based, balanced nutrient diets attenuate glycemic response of meals and avoid metabolic fatigue and hypertension associated with postprandial glycemia.
  - Encourage hydration with water.

Alcohol Consumption

- Small amount of daily alcohol consumption have lower risks of morbidity and mortality from CVD ($\leq$1 oz. for women, $\leq$2 oz. for men) [49].
- However, moderate to heavy consumption has a negative effect on CVD morbidity and mortality.
  - Increases risk of hypertension, atrial fibrillation, ventricular tachycardia, CNS depression

Snoring, Sleep Apnea, and CV Risk

- High correlation with atrial fibrillation, hypertension, pulmonary hypertension, and sudden death [50]

- Consider sleep medicine evaluation/sleep study if:
  - Resistant hypertension (≥3 antihypertensives, including diuretic)
  - Loud snoring or apneas reported during bedtime
  - Onset of atrial fibrillation
  - Occult stroke
  - Morbid obesity

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Chapter 5
Stable Ischemic Heart Disease

Erik H. Howell and Christopher J. Cove

Epidemiology

- Approximately 15.5 million Americans have coronary artery disease, and more than 7 million Americans have angina [1].
- Nearly 50% of patients with coronary artery disease present with angina as their initial clinical manifestation [2, 3].
- Angina approximately doubles the risk of major cardiovascular events [2, 3].
- Stable angina is the most common initial presentation of CAD in women and more common than in men [4].

Pathophysiology

- Caused by a "demand-supply mismatch."
- The myocardial oxygen demand increases with exertion, emotion, or wall stress.
- Unmet myocardial oxygen demand can potentially cause angina, heart failure, arrhythmias, and sudden cardiac death.
- Stable angina most commonly involves atheromatous plaques of epicardial coronary arteries with a small lipid core and an overlying thin or thick fibrous cap that reduces the propensity to plaque rupture.

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© Springer International Publishing AG, part of Springer Nature 2018

H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7_5

Definition

- Angina is defined as substernal chest discomfort (pressure, pain, or tightness) that gradually increases over several minutes. The chest discomfort is provoked by exertion or emotional stress and is relieved by rest or by administration of nitroglycerin (see Table 5.1).

  Angina can further be classified into stable angina and unstable angina.

- Unstable angina is defined as angina that occurs at rest, new-onset angina, or a change in frequency and/or duration of angina.
- Stable angina is defined as angina that occurs with exertion, often in a predictable manner (see Table 5.2).

Table 5.1 Clinical classification of chest pain [5]

Typical chest pain (definitive)	Three features: • Substernal chest pain that has a characteristic quality or duration • Provoked by exertion or emotional stress • Relieved by rest or nitroglycerin
Atypical chest pain (probable)	Meets two of the above criteria
Non-cardiac chest pain	Meets one or none of the above criteria

Table 5.2 The Canadian Cardiovascular Society (C.C.S) grading that is frequently used to assess angina severity [34]

Grade 1	Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation
Grade 2	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions
Grade 3	Marked limitation of ordinary physical activity. Walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace
Grade 4	Inability to carry on any physical activity without discomfort; anginal syndrome may be present at rest

Adapted from Campeau L. Circ. 1976

Approach to Patient with Suspected or Known Stable Ischemic Heart Disease (SIHD)

History

- Determine pretest likelihood of coronary artery disease based on presence of risk factors such as hypertension, diabetes mellitus, smoking, family history, hyperlipidemia, claudication, and advanced age (see Table 5.3).
- Typical angina is suggestive of coronary artery disease [5, 6].
- Important questions regarding chest discomfort:
  - Location
  - Severity
  - Character/Quality
  - Duration
  - Situation in which it occurred
  - Associated symptoms (nausea, diaphoresis, dyspnea)
  - Exacerbating or relieving factors

Physical Examination

- Vital assessment: Check blood pressure in both arms. Determine heart rate and rhythm.
- Tachycardia and high blood pressure due to ischemia-induced reflex sympathetic stimulation.
- Neck: carotid artery bruits.
- Xanthomas/xanthelasma and arcus senilis indicative of hyperlipidemia, diabetic retinopathy or hypertensive retinopathy indicative of poorly controlled hypertension and diabetes, and peripheral vascular disease may be present.

Table 5.3 Pretest likelihood of coronary artery disease based on age, sex, and clinical symptoms

Pretest likelihood of coronary artery disease in symptomatic patients stratified by age and sex						
	Non-cardiac chest pain		Atypical chest pain		Typical chest pain	
Age (years)	Men	Woman	Men	Woman	Men	Woman
30–39	4	2	34	12	76	26
40–49	13	3	51	22	87	55
50–59	20	7	65	31	93	73
60–69	27	14	72	51	94	86

Adapted from Fihn et al. JACC 2012 [5]

- Cardiopulmonary examination during angina may reveal third or fourth heart sound; systolic murmur of mitral regurgitation or increase in intensity of an existent systolic murmur of mitral regurgitation may be present.
- Rales can be suggestive of pulmonary edema.
- Extremities: peripheral pulses, femoral artery bruits, and peripheral edema.

Blood Tests

- Complete blood count
- Comprehensive metabolic panel
- Troponin, BNP (brain natriuretic peptide), or pro-NT BNP levels
- Thyroid function tests

Electrocardiogram (ECG)

- Presence of pathologic Q waves (at least 1/3 the area of the QRS wave) is suggestive of old myocardial infarction (MI) but does not necessarily imply full thickness scar. ST-T abnormalities can be noted.
- Many patients with stable angina do not have new or acute repolarization changes on the ECG. A normal ECG does not reliably rule out cardiac ischemia.

Echocardiogram

- It may show left ventricular dysfunction and regional dysfunction suggestive of ischemia or an old myocardial infarction.
- Mitral valve regurgitation may reflect ischemic papillary muscle dysfunction.
- Other causes of angina such as aortic stenosis and hypertrophic obstructive cardiomyopathy can be identified.

Diagnosis and Evaluation

- In patients with suspected SIHD, it is important to both make diagnosis and assess prognosis. Stress testing can determine whether CAD is present and help optimize risk stratification in patients with known SIHD [7].
- Bayes theorem teaches us:

  - Testing is most useful when we do not know the answer to the question and we are at equipoise for determining the presence or absence of the condition for which we test.
  - The pretest likelihood of a condition influences the posttest assessment of the presence of the condition.
  - For CAD diagnostic purposes, noninvasive testing is most useful clinically in patients with intermediate risk of disease, in whom we are quite uncertain as to whether or not CAD is truly present.
  - If our pretest likelihood of CAD is very high or very low, testing is unlikely to alter our impression of the presence or absence of disease.

    A normal study in a high-risk population results in an intermediate posttest probability of disease, and the chance of a falsely negative study is increased.

    Conversely, an abnormal study in a low-risk population results in an intermediate posttest probability of disease, and the chance of a false-positive test is increased.

- Stress testing is used to provoke ischemia, or produce coronary vasodilation, followed by a functional assessment to detect coronary artery disease/ischemia.
- The performance of different stress testing modalities to detect and quantify coronary artery disease/ischemia is dependent on several factors including but not limited to study population, disease definition, stress protocol as well as intra- and interobserver variability.
- Common stress testing modalities (see Table 5.4)[9]
  - Stress ECG or exercise treadmill test (ETT): Continuous ECG monitoring is used to measure ECG changes (i.e., ST segment depression and/or elevation) and symptoms associated with exercise/increased myocardial oxygen demand. It requires a "normal" baseline ECG and performs poor in patients with an "abnormal" baseline ECG such as LVH, paced-rhythm, LBBB, or interventricular conduction delay [10].
  - Stress echocardiography: Enables assessment of exercise-induced regional wall motion abnormalities or LV dilatation. For those unable to perform physical exercise, chemically induced myocardial stress can be achieved by administering dobutamine. Interpretation can be limited by poor acoustic

Table 5.4 Performance of common, noninvasive tests for coronary artery disease

Stress testing sensitivity and specificity[a]		
Modality	Sensitivity (%)	Specificity (%)
Exercise treadmill test	68	77
Exercise SPECT	88	72
Adenosine SPECT	90	82
Exercise echocardiography	85	81
Dobutamine echocardiography	81	79

Adapted from Gibbons et al. JACC 2003 [8]

[a]Unadjusted for referral bias

windows, resting regional wall motion abnormalities, and exaggerated hypertensive response to exercise.
  - Radionuclide imaging: Single-positron emission computed tomography (SPECT) can be performed by injecting a labeled radioactive isotope (i.e., thallium 201 or technetium 99 m). Position emission tomography (PET) can be performed using rubidium 82 or 13 N ammonia radiotracers. Nuclear testing performance can be limited by patient obesity, breast tissue, LBBB, and balanced three-vessel disease.
  - Cardiac magnetic resonance imaging: A pharmacologic stress agent (i.e., dobutamine or adenosine) is used to assess jeopardized myocardium during magnetic resonance imaging with gadolinium contrast. It evaluates regional myocardial perfusion and contractility with direct visualization of the epicardial arteries [11].

- Other modalities to evaluate suspected or known CAD:
  - Coronary computed tomography angiography: Provides direct visualization of epicardial arteries. Negative predictive value is 99% in the appropriate patient risk strata with optimal imaging. Accuracy varies significantly based on image quality limitations including severe coronary artery calcification and epicardial artery stent placement [12].
  - Electron beam computed tomography or coronary artery calcium scanning: Allows quantification of coronary artery calcification which is correlated with coronary atherosclerosis but is not frequently used in symptomatic patients with SIHD. An elevated coronary artery "calcium score" is associated with risk of cardiovascular events but does not provide sufficient detail to quantify epicardial lesion severity [13].

- ETT is recommended as first step in assessment of patients with low to intermediate pretest probability of CAD who have an interpretable ECG and good exercise tolerance [6].
- Patients with symptomatic SIHD whose stress test indicates cardiac ischemia may need coronary angiography and may benefit from coronary revascularization.
- Coronary angiography is the standard for anatomic assessment of epicardial artery stenosis and provides both diagnostic and prognostic information regarding CAD (see Fig. 5.1).
  - Patients with at least one severe (>75%) coronary artery stenosis (i.e., obstructive CAD) have reduced survival as compared to patients with nonobstructive (≤50%) CAD (see Table 5.4) [14].

- Indications for coronary angiography in known or suspected SIHD:
  - Severe angina (CCS class III or IV) despite optimal medical management
  - Stable angina patients with intermediate to high-risk or moderate to severe ischemia on noninvasive testing
  - Stable angina patients whose noninvasive testing was inadequate in prognostic risk stratification

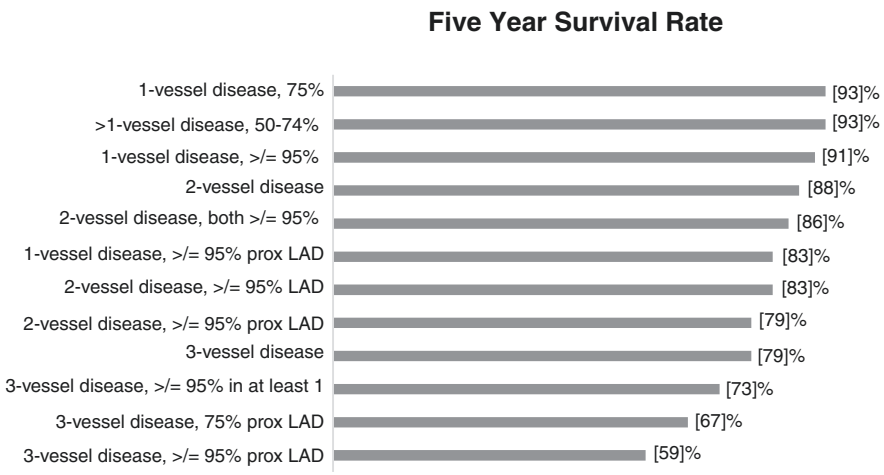

Fig. 5.1 Five-year survival of patients with coronary artery disease stratified by epicardial stenosis. Adapted from Fihn et al. JACC 2012 [5]

  - Patients with changing anginal pattern who survived cardiac arrest or ventricular arrhythmia
  - High pretest probability of three-vessel disease or left main coronary artery disease
  - High suspicion for coronary vasospasm
  - Frequent hospitalizations for angina
  - Unable to perform noninvasive testing
  - Persistent anginal chest pain with negative stress test
- Lesion severity on coronary angiogram is not predictive of plaque stability, and a majority of patients with an acute myocardial infarction have epicardial artery stenosis of less than 70% at site of plaque rupture preceding acute myocardial infarction [5].

Management

- The goal of SIHD treatment is to prevent cardiovascular morbidity and mortality and improve quality of life for those who are symptomatic.
- CAD risk factor modification including obesity, hypertension, diabetes, hyperlipidemia, and smoking is the basis for SIHD management.
  - Lifestyle changes are the first line and foundation of CAD risk factor modification. All patients should be encouraged to engage in 30–60 min of moderate-intensity aerobic activity, such as brisk walking, at least 5 days and preferably 7 days per week; weight management; diet mostly vegetarian, limiting red meat and simple sugars; and annual influenza vaccine.

  - A moderate- or high-dose statin should be prescribed, in the absence of contraindications or documented adverse effects [5].
  - Optimal glycemic control in patients with diabetes mellitus with a goal hemoglobin A1c of 7% or less is reasonable.
  - Systolic blood pressure (SBP) goal <140 mm Hg in patients with hypertension; however, data from a recent randomized control trial indicated that more strict SBP control with a target <120 mm Hg as compared to target SBP < 140 mm Hg significantly reduced the risk of cardiovascular events (acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes) by 25% [15].
  - Emerging CAD risk factors include chronic kidney disease and depression which have been associated with increased risk of cardiovascular morbidity and mortality [16, 17].

- Treatment with aspirin 75–162 mg daily should be continued indefinitely in the absence of contraindications.
- Treatment with clopidogrel is reasonable when aspirin is contraindicated.
- Medical management is the mainstay of antianginal therapy in symptomatic SIHD and is proven to reduce angina occurrence and improve quality of life [18, 19].
  - Nitrates: Reduce left ventricle preload and afterload resulting in decreased cardiac work and oxygen demand.
    Sublingual nitroglycerin: Among the most effective at reducing angina, but no reduction in mortality in patients with SIHD.
    Oral nitrates: Improve exercise tolerance and alleviate symptoms.
    Side effects: Headache, transient dizziness, flushing, and positional hypotension.
    Absolute contraindication: Concurrent use of phosphodiesterase-5 inhibitors can lead to severe hypotension.
  - Beta blockers: Blockade of the beta-1 adrenergic receptors decreases LV wall stress enhancing blood flow to endocardium, as well as decreasing myocardial oxygen demand by reducing rate-pressure product.
    Decreases mortality after myocardial infarction and provides symptomatic relief; however, evidence is lacking for mortality benefit in patients with SIHD without prior myocardial infarction.
    Should be used in all patients with LV systolic dysfunction (EF ≤40%) with heart failure or prior myocardial infarction (evidence supporting reduced mortality derived from studies using carvedilol, metoprolol succinate, and bisoprolol) [6].
    Avoid in patients with known vasospasm to obviate coronary vasospasm from beta-2 receptor blockade.
    Side effects: Bradycardia, precipitate heart failure, decreased libido, impotence, somnolence, lethargy, depression, dyslipidemia (raise LDL and lower HDL).
  - Calcium channel blockers (CCB): Inhibit calcium channels on smooth muscle and cardiac cell, thus, blocking calcium entry resulting in decreased muscle cell contraction.

Numerous studies have shown that calcium-channel blockers improve angina symptoms and are equivalent to beta-blockers.
Avoid short-acting nifedipine because it has been associated with increased mortality in patients with SIHD.
Avoid all calcium-channel blockers in decompensated heart failure.
Side effects: Hypotension, flushing, dizziness, headache, precipitate heart failure, bradycardia.

– Angiotensin-converting enzyme inhibitors (ACEi): Theoretically, may reduce preload and afterload, thus, reducing myocardial oxygen demand and benefiting patients with SIHD.
Use in all patients with SIHD and hypertension, diabetes mellitus, LV systolic dysfunction (EF ≤40%), or CKD.
Angiotensin-receptor blockers can be used in place of ACEi for those patients who are intolerant of ACEi.
Side effects: Cough, hyperkalemia, decreased glomerular filtration rate.
Absolute contraindication: Hereditary angioedema or bilateral renal artery stenosis.

– Ranolazine: Inhibits late sodium channels in myocytes. In ischemia and heart failure, the late sodium channels remain open, so inhibition with ranolazine reduces sodium-dependent calcium entry into cytosol.
Improves angina symptoms, exercise ability, and frequency of sublingual nitroglycerin use
Side effects: Dizziness, headache, gastrointestinal upset, prolonged QT interval
Absolute contraindication: Prolonged QT interval

- Consider structured cardiac rehabilitation program for patients without revascularization and persistent angina despite optimal medical therapy [5].

Revascularization of SIHD

- In general, revascularization should only be considered for patients with persistent angina or severe CAD and/or LV dysfunction despite optimal medical therapy [20].
- In the early days of percutaneous coronary intervention (PCI) and medical therapy, randomized trials indicated symptomatic improvement with PCI compared to medical therapy alone in patients with one- to two-vessel disease but no mortality benefit [21–23].
- In 2007 the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial indicated that there was no benefit to PCI as compared to optimal medical therapy (OMT) when using bare metal stents and excluding subjects with left main disease, and most had normal LV function [24].
  – Significant criticisms include:
  Only 6% of the assessed patients were enrolled.

Potential enrollment bias due to randomization after coronary angiogram.
OMT group had rigorous follow-up to maintain medication adherence.
Approximately 1/3 of the OMT group crossed over to the PCI group while using intention-to-treat analysis.
About 80% of subjects had minimal to no angina symptoms.

- COURAGE substudy indicated that the amount of ischemia was not correlated with adverse events or symptomatic improvement [25]; however, retrospective registry data suggests that significant myocardial ischemia treated with revascularization versus OMT is associated with improved morbidity and mortality [26].
  - Ongoing randomized trial called ISCHEMIA aimed at answering whether extent of ischemia impacts benefit of revascularization versus OMT. Funded by National Heart, Lung and Blood Institute.
- Coronary artery bypass grafting (CABG) improves survival compared to medical treatment among patients with stable coronary artery disease, especially in patients with three-vessel disease, reduced LV function, and significant left main stenosis.
- Network meta-analysis indicated that CABG and PCI with drug-eluting stents are associated with improved survival in patients with SIHD [27].
- Studies comparing CABG and PCI indicated the PCI group often underwent significantly more repeat revascularization as compared to CABG. Additionally, diabetic patients with severe, three-vessel disease yielded the most benefit from CABG versus PCI [28, 29].
- The SYNTAX trial compared PCI with new generation DES vs CABG in patients with 3-vessel CAD or left main. The primary endpoint of death, stroke, MI, and repeat revascularization favored CABG [30]. Mostly driven by repeat revascularization in PCI group, however, stroke rate was significantly lower in PCI group.
  - SYNTAX score: grades coronary anatomy based on lesion location, complexity, and function impact. In the trial, outcomes were assessed by SYNTAX score tertiles. Low (0–22) and intermediate (23–32) SYNTAX scores indicated no difference between PCI vs CABG regarding primary outcome. An elevated SYNTAX score (>32) favored CABG.
- FREEDOM trial compared multivessel PCI vs CABG in diabetic patients. Composite primary endpoint of death, MI, or stroke was significantly better for CABG [31].
- Patients with multivessel CAD should be evaluated by a Heart Team consisting of interventional cardiologist(s) and cardiothoracic surgeon(s) so patient can make a well-informed decision regarding revascularization.
- Clinical guidance for revascularization in SIHD is outlined in the 2017 Coronary Revascularization Appropriate Use Criteria (AUC) publication with an online and smartphone application to enable quick patient-specific assessment [32, 33].

- The AUC writing group assigned a numeric score from 1 to 9 to various commonly encountered clinical scenarios where 7 to 9 indicate "Appropriate care," 4 to 6 indicate "May be appropriate," and 1 to 3 indicate "Rarely appropriate."
- AUC score is determined by level of ischemic symptoms, antianginal therapy use, results of noninvasive testing, and coronary anatomy augmented by invasive testing.

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Chapter 6
Non-ST-Segment Elevation Acute Coronary Syndromes (NSTE-ACS)

Justin Lee, Felix Reyes, and Hanna Z. Mieszczanska

Epidemiology

- NSTE-ACS is responsible for approximately 1 million hospital admissions in the USA annually. Seventy percent of these patients present with a non-ST-elevation myocardial infarction (NSTEMI) [1].
- The male to female ratio is approximately 3:2 [2].
- In the USA, the median age at ACS presentation is 68 years (interquartile range 56–79).
- NSTEMI is associated with an in-hospital mortality of approximately 5% [3].
- About 10% of patients presenting to the emergency room with acute chest pain are ultimately diagnosed with acute coronary syndrome (ACS) [4].

Introduction

- Acute coronary syndrome is a spectrum of clinical presentations, including unstable angina (UA), non-ST-elevation MI (NSTEMI), and ST-elevation MI (STEMI). UA and NSTEMI are differentiated from STEMI by absence of ST-segment elevations.

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H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7_6

Table 6.1 Spectrum of pathologic and clinical ST-segment elevation acute myocardial infarction (STEMI) and non-STEMI acute coronary syndromes

	STEMI	NSTEMI	UA	Chronic stable angina
ST segment elevation	+	–	–	–
Cardiac enzyme elevation	+	+	–	–

- Presentation can be similar in both conditions; however in patients with non-ST-segment elevation myocardial infarction, evidence of myocardial necrosis is present (with elevation of cardiac biomarkers) (Table 6.1).
- These differences are mainly due to the differing severity of the myocardial injury, in which the ischemia is severe enough to cause sufficient myocardial damage to release detectable quantities of a marker of myocardial injury, most commonly, troponin I (TnI), troponin T (TnT), or the MB isoenzyme of creatine phosphokinase (CK-MB) (Table 6.1).

Pathophysiology

- Non-STEMI or unstable angina (ACS without ST-segment elevation) usually is a result of the sudden demand-supply mismatch, which usually results from partial coronary artery obstruction or occlusion in the presence of collateral circulation [5, 6].
- Plaque rupture of a vulnerable, lipid-laden, atherosclerotic coronary plaque remains the most common cause of coronary thrombosis, but plaque erosion is also a commonly recognized cause of more recent cases of ACS (in some studies 30%). Plaque erosion is increasingly prevalent, especially among younger women [5].

Myocardial infarction (MI) as a result of MVO2 imbalance is defined as Type I MI, secondary to obstructive lesion in the coronary vasculature. Other causes of myocardial ischemia/NSTE myocardial infarction (other than atherosclerotic plaque rupture) include:

- Excessive myocardial oxygen demand (e.g., anemia, tachycardia, severe HTN, aortic stenosis) or reduced supply (hypotension, severe anemia, hypoxia) in the setting of a stable, flow-limiting lesion
- Nonischemic myocardial injury (e.g., myocarditis, cardiac contusion, cardiotoxic drugs) and multifactorial causes that are not mutually exclusive (e.g., stress-induced [takotsubo] cardiomyopathy, pulmonary embolism, severe heart failure [HF], sepsis)
- Coronary spasm (Prinzmetal's variant)
- Cocaine use, which can cause ACS by inducing coronary vasospasm, dissection, thrombosis, positive chronotropic and hypertensive actions, direct myocardial toxicity, peripheral vasoconstriction resulting in hypertension, and tachycardia [7]

Myocardial infarction caused by "demand-supply mismatch" *not* secondary to obstructive lesion is defined as Type II MIs. For more types of MIs, refer to the chapter on ST-elevation MI (STEMI) [8].

Factors that increase the probability of NSTE-ACS:

- Older age, male sex
- Positive family history of CAD
- Presence of peripheral arterial disease
- Diabetes mellitus
- Renal insufficiency
- Prior MI
- Prior coronary revascularization

Clinical Presentation

- ACS most commonly presents as a pressure-type chest pain that typically occurs at rest or with minimal exertion lasting ≥10 min [2].
- Chest pain is most frequently retrosternal and can radiate to the arms, the neck, or the jaw. The patient can also have pain in these areas with no chest pain. Patients frequently describe symptoms as not only including pain but also discomfort, pressure, and a squeezing sensation in the chest.
- Patients with NSTE-ACS may also present with diaphoresis, dyspnea, nausea, abdominal pain, or syncope. Unexplained new-onset or increased exertional dyspnea is the most common angina equivalent.
- The relief of chest pain with nitroglycerin is not predictive of ACS.
- Patients with unstable angina (UA) may present with chest pain at rest, while patients with chronic stable angina are more commonly asymptomatic at rest.
- Older patients (>75 years of age) and women usually present with typical symptoms of chest pain but have a higher frequency of atypical symptoms (epigastric pain, back pain, stabbing or pleuritic pain, and increased dyspnea in the absence of chest pain) as well.
- Physical exam findings (may range from normal to):
  - Presence of diaphoresis, new mitral regurgitation (MR) murmur
  - Cold, clammy skin and diaphoresis in patients with cardiogenic shock
  - Pulmonary edema and other signs of left heart failure (jugular venous distention, rales, a third heart sound—S3)
  - Hypotension: Indicates ventricular dysfunction due to myocardial ischemia, myocardial infarction (MI), or acute valvular dysfunction
  - Hypertension: May precipitate angina
  - A systolic murmur related to dynamic obstruction of the left ventricular outflow tract

  - Evidence of peripheral vascular disease
  - Age > 75
- Post-MI angina: Patients present with ischemic chest pain occurring either at rest or during minimal activity 24 h or more following an acute MI.

Initial Diagnosis

Differentiation between types of acute coronary syndrome (ACS), based on diagnostic findings, is demonstrated in Fig. 6.1.

Electrocardiogram (ECG) [2, 9]

- A 12-lead ECG should be obtained and read within 10 min of patient's arrival to the emergency department (ED). Serial ECGs at 15- to 30-min intervals during the first hour should be performed in symptomatic patients when initial ECG is nondiagnostic.
- A normal ECG does not exclude ACS, as it can still be present in 1–6% of patients with ACS.
- ECG changes in patients with NSTE-ACS include ST depression, transient ST elevation, or new T-wave inversions.
- Q waves on the ECG suggest prior MI and a higher probability of patients having coronary artery disease (CAD).
- In the prospective Global Registry of Acute Coronary Events (GRACE) electrocardiographic sub-study, the presence of ST elevation greater than 1 mm in aVR, along with 1 mm ST depressions in 6 or more surface leads, may be useful in the early identification of left main/three-vessel CAD in ACS patients with ST depression [10].

Cardiac Biomarkers

- Serial measurements of cardiac biomarkers should be done on presentation and repeated at 3 and 6 h after. This helps to differentiate an ACS without ST-segment elevation as non-STEMI or unstable angina.
- Troponin (T and I) is preferred over CK-MB, as they are very sensitive and specific [11].
- Additional troponin level should be checked beyond 6 h in patients with initially normal troponin levels, when changes on ECG and/or clinical presentation suggest an intermediate or high index of suspicion for ACS. Troponin can remain elevated for up to 14 days.

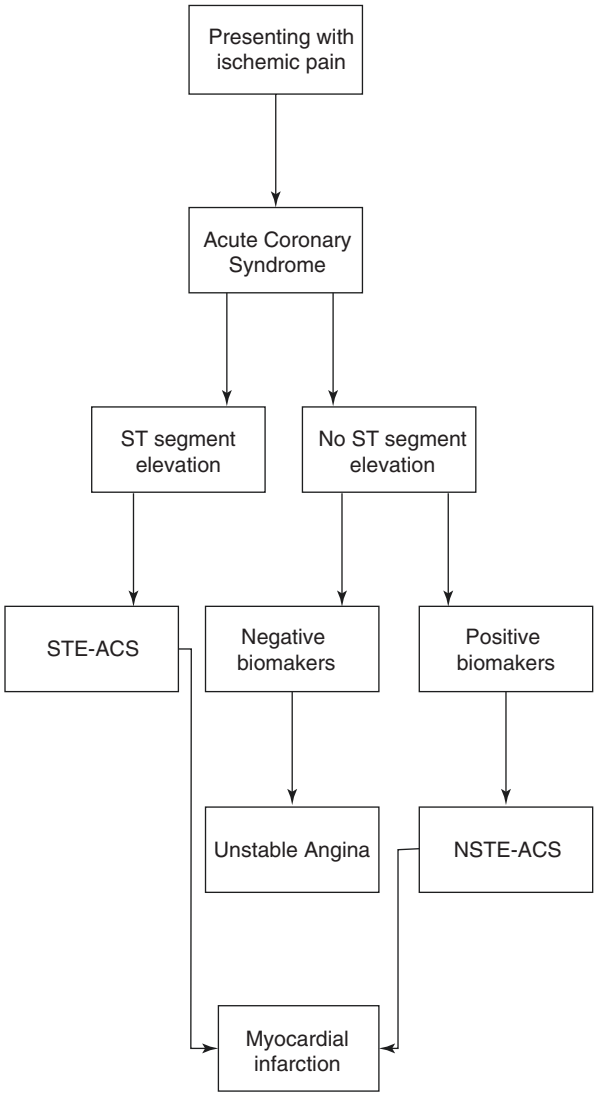

Fig. 6.1 Differentiation between types of acute coronary syndrome (ACS), based on diagnostic findings [2]

- High-sensitivity assays for troponin (recently approved in the USA, beginning January 2017) will increase diagnostic sensitivity and make it possible to effectively rule out myocardial infarction in 1–2 h; however, these assays have decreased clinical specificity [12, 13].
- In patients with chest pain, high-sensitivity cardiac troponin I concentration <5 ng/L at presentation has a high negative predictive value (NPV) of 99.6% for MI. Patients who had hs T < 5 ng/L at presentation had very low rates of adverse cardiac events after 1 year when compared with those with >5 ng/L [14].

- In one study, patients with chest pain but undetectable hsTnT levels and normal electrocardiogram without signs of ischemia were shown to be at minimal risk of MI or death within 30 days (negative predictive value for MI, 99.8%) [15].
- With current troponin assays, concomitant measurement of creatine kinase MB (CK-MB) and myoglobin is no longer recommended (Class III).
- BNP or NT-proBNP may be considered for additional prognostic information in patients with suspected ACS (Class IIb).

Chest X-Ray (CXR)

- Can detect widened mediastinum, which could be suggestive of aortic dissection or presence of pulmonary edema.

Risk scores should be used to assess prognosis in patients with NSTE-ACS.

TIMI risk score calculation is determined by the sum of the presence of seven variables at admission. A higher-risk score indicates worse prognosis and can predict the likelihood of death, MI, or urgent revascularization and as a result can be helpful to guide management. Each of the following criteria constitutes one point for TIMI scoring (Fig. 6.2) [16].

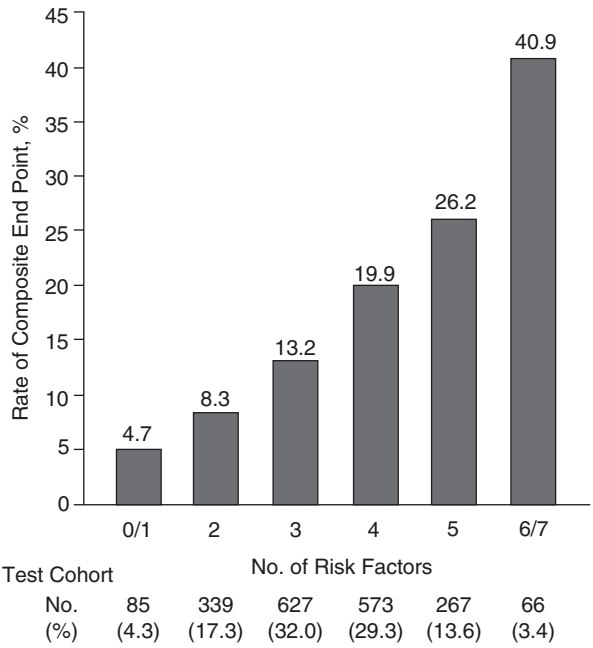

Fig. 6.2 TIMI risk score. Rates of all-cause mortality, MI, and severe recurrent ischemia prompt revascularization at 14 days, after presentation from TIMI 11B and ESSENCE trials according to TIMI risk score. Reproduced with permission from Antman EM, et al. [16]

- Age ≥ 65 years
- Three or more risk factors for coronary artery disease (CAD) (family history of CAD, hypertension, hypercholesterolemia, diabetes mellitus, current smoker)
- Known CAD (stenosis >50%)
- Use of aspirin in the past 7 days
- Severe angina (≥2 episodes in 24 h)
- ST deviation ≥0.5 mm on admission ECG
- Elevated serum cardiac marker level

Long-term prognosis of NSTE-ACS:

From the Global Registry of Acute Coronary Events (GRACE) study conducted in the UK and Belgium, 5-year mortality for NSTEMI (including MI, stroke, and readmissions) was similar to that found in patients with STEMI [17].

High-risk features of NSTE-ACS [3]

- Recurrent angina or ischemia at rest or with low-level activities, despite intensive medical therapy
- Elevated cardiac biomarkers (TnT or Tnl)
- New or presumably new ST-segment depression
- Signs or symptoms of HF or new or worsening mitral regurgitation
- High-risk findings from noninvasive testing
- Hemodynamic instability
- Sustained ventricular tachycardia
- PCI within 6 months
- Prior CABG
- High-risk score (i.e., TIMI or GRACE)
- Reduced left ventricular functions (EF less than 40%)

The above clinical factors can help in determining the use of early invasive or early conservative therapy according to ACC/AHA guidelines. The presence of any of these high-risk features may favor early invasive therapy.

Initial Management

- Bed rest with **continuous ECG monitoring** for ischemia and arrhythmia detection, in patients with ongoing rest pain (Class I).

Antiplatelet Therapy

- **Non-enteric-coated aspirin (ASA)** is the first choice and is administered as soon as possible after presentation (loading, **162–325 mg** [Class I]).
- **Aspirin** should be continued indefinitely (maintenance, **81–325 mg** [Class I]).

- A **P2Y12 inhibitor**
- (**Clopidogrel**—loading, 300–600 mg [5]; maintenance, 75 mg daily [5])
- (**Ticagrelor**—loading, 180 mg [5]; maintenance, 90 mg twice daily [5])
- (**Prasugrel**—loading, 60 mg [5]; maintenance, 10 mg daily [5])
  - The CURE trial [2002] was a large, randomized, placebo-controlled trial in patients with NSTE-ACS that showed 20% reduction in the rate of the combined end point of cardiovascular death, nonfatal myocardial infarction, or stroke when treated with a conservative approach [18].
  - A more recent meta-analysis in 2012 to investigate the efficacy of clopidogrel pretreatment has demonstrated no significant reduction in death or increase in bleeding risk. However, clopidogrel pretreatment has been shown to decrease the risk of major cardiac events (MACE) compared to placebo [19].
  - The AHA/ACC guidelines recommend dual antiplatelet therapy (DAPT), with a P2Y12 inhibitor (either clopidogrel or ticagrelor), in addition to aspirin. All patients with NSTE-ACS should continue DAPT therapy for up to 12 months [11].
  - Daily maintenance dose of aspirin is 81 mg daily in patients treated with P2Y12 inhibitor.
  - In patients undergoing PCI, a loading dose of 600 mg of clopidogrel compared with a loading dose of 300 mg of clopidogrel achieves greater platelet inhibition and decreases the incidence of MACE.
  - Ticagrelor is more potent than clopidogrel. PLATO trial showed a 16% reduction in major cardiovascular events with ticagrelor as compared with clopidogrel in ACS patients [20]. Ticagrelor was also associated with higher incidence of CABG-related bleeding.
  - From PEGASUS-TIMI 54 trial with 21,000 patients, two different doses both significantly reduced the rate of cardiovascular death, MIs, and strokes [21].
  - The most recent AHA/ACC guideline supports the use of ticagrelor over clopidogrel in patients to NSTE-ACS (Class IIa) [2].
  - In patients with acute coronary syndromes with scheduled percutaneous coronary intervention, prasugrel can lower the risk of ischemic complications for myocardial infarction after PCI, to a greater degree than clopidogrel. Use prasugrel only in patients receiving coronary stents in early invasive approach (Class I). Prasugrel should not be used in patients with prior stroke, >75 years of age, or weight < 60 kg [22].
  - In patients with high-risk features not pretreated with clopidogrel or ticagrelor, it is useful to administer a GPIIb/IIIa inhibitor at the time of PCI (Class IIb). However, this is not always the case, as based on the results of clinical trials, 2016 ESC guidelines recommend against the routine upstream use of glycoprotein IIb/IIIa receptor inhibitors (GPIs) before angiography (Class III).
  - In patients with high suspicion of three-vessel CAD (long-standing diabetics, severe HLP, etc.) being sent to the cath lab, clopidogrel may be held prior to PCI, in case the lesion is a three-vessel disease or has a left main coronary involvement.

- A "DAPT score" is a risk score derived from the dual antiplatelet therapy study that is designed to facilitate the management of the dual antiplatelet therapy.
  - In patients treated for 1 year with DAPT without significant bleeding or ischemic events, the benefit/risk ratio with prolonged DAPT may be more favorable for those with a high DAPT score (>2) [23].
  - A score of 2 or greater is associated with a favorable benefit/risk ratio (prevention of cardiovascular events/risk of bleeding) for prolonged DAPT. Meanwhile a score of less than 2 is associated with no significant benefits as compared to the increased risk of bleeding.
    Factors that contribute to a high DAPT score include (points):
  - Diabetes mellitus (1).
  - Current cigarette use (1).
  - Prior PCI or prior MI (1).
  - Congestive heart failure or LVEF <30% (2).
  - MI at presentation (1).
  - Saphenous vein graft PCI (2).
  - Stent diameter < 3 mm (1).
  - Age > 75 years contributes to a low (less favorable) DAPT score (−2).
  - Age 65 to <75 years (−1).
  - Age < 65 (0).
- Of note first-generation DES compared to newer-generation DES have a lower risk of stent thrombosis and appear to require a shorter minimum duration of DAPT.

Anticoagulation

Low molecular weight heparin (LMWH)/enoxaparin—1 mg/kg subcutaneous (SC) q12 h, for the duration of hospitalization or until PCI is performed

Unfractionated heparin (UFH) IV: initial loading dose of 60 IU/kg (maximum 4000 IU) with initial infusion of 12 IU/kg/h (maximum 1000 IU/h), adjusted per activated partial thromboplastin time to maintain therapeutic anticoagulation; can be continued for 48 h or until PCI is performed:

- Selection of the best procedural anticoagulation regimen to balance the risks of ischemia and bleeding during PCI is very important and can affect the outcome.
- LMWH has shown to be more effective than UFH, particularly in patients undergoing noninvasive medical therapy [12].
- Bivalirudin and fondaparinux can be used as alternatives to heparin-based anticoagulation, in accordance with the initial management strategy (invasive or noninvasive) and risk of bleeding.
- Fondaparinux is not approved for the treatment of acute coronary syndromes in the USA (however, it is used in Europe).

  - Bivalirudin is preferred over UFH + GP IIb/IIIa in patients undergoing PCI who are at high risk of bleeding (Class IIa), shown in the HORIZONS-AMI trial [24]. However, a more recent MATRIX trial showed no significant difference in the lowering of net adverse cardiovascular events with bivalirudin rather than heparin, in contrast with the results of the ACUITY and HORIZONS-AMI trials [25].

Fibrinolytic therapy may be harmful in NSTE-ACS and is contraindicated.

Crusade Score Risk for Bleeding

- A risk score designed to assess the risk of major bleeding in patients under acute coronary syndromes, especially NSTEMI [26].
- **Morphine sulfate**
  - Morphine can be administered intravenously when symptoms are not immediately relieved with NTG or when acute pulmonary congestion is present (Class I).
- **Nitrates**
  - Sublingual nitroglycerin (NTG) can be administered (0.3–0.4 mg; may repeat in 5 min, two times, as needed) for ischemic chest pain. For persistent ischemia, heart failure, or hypertension, it can be followed by intravenous NTG administration (Class IIa).
  - The anti-ischemic effects of nitrates are mediated by their reduction of myocardial oxygen demand through reducing the ventricular preload and by vasodilating the coronary arteries [27].
- **Supplemental oxygen**
  - Current evidence does not support benefit in patients with normal oxygen levels. Supplemental oxygen use is recommended only for patients with hypoxemia (oxygen saturation < 90%—Class I) or respiratory distress.
  - Routine use of supplemental oxygen in patients with suspected myocardial infarction who did not have hypoxemia was not found to reduce 1-year all-cause mortality [28].
- **Beta blockers**
  - A **b-blocker** (except in patients with HF, low-output state, risk for cardiogenic shock, or other contraindications to beta blockade) is recommended for its beneficial effects on mortality (Class I).
- **Calcium channel blockers**
  - In patients with continuing or frequently recurring ischemia when b-blockers are contraindicated, a **nondihydropyridine calcium antagonist** (e.g., verapamil or diltiazem) is recommended, followed by oral therapy, as initial therapy in the absence of severe LV dysfunction or other contraindications (Class I).

- **ACE inhibitor**
  - An **ACEI** is recommended, when hypertension persists despite treatment with NTG and a b-blocker, in patients with LV systolic dysfunction or CHF and in ACS patients with diabetes (Class I).
- **Statins**
  - High-intensity statin needs to be initiated or continued (Class I) in all patients with NSTE-ACS, unless contraindicated. Consider 40–80 mg atorvastatin or 20–40 mg rosuvastatin on admission and then daily.

Further Management

- After initial medical management, and upon stabilization of symptoms, a decision can be made on either early invasive or noninvasive (ischemia-guided) initial strategy based on clinical judgment, patient's risk, and preferences.
- Early **invasive** strategy includes **immediate vs. 12–24 h angiography** (Class I).
- If the patient's hemodynamic condition stabilizes after initial medical therapy, and ischemic discomfort is relieved, angiography can proceed within 12–24 h [12, 27] (Fig. 6.3).

- The following clinical features should be used to differentiate low- to high-risk patients for invasive vs. noninvasive strategy:
  - Low-risk features:
    No prior angina
    No ongoing angina
    Little or no prior use of anti-ischemic regimen
    Normal or unchanged ECG
    No detected cardiac enzymes
    Younger age
  - Intermediate-risk features:
    New-onset or accelerated angina
    Angina at rest or ongoing angina >20 min
    No ST-segment change
    No detected cardiac enzymes
  - High-risk features:
    Angina at rest or prolonged angina
    Ongoing angina
    Angina after MI
    Prior use of intensive anti-ischemic regimen
    Older age
    Dynamic ST-segment change
    Detected cardiac enzymes
    Hemodynamic instability

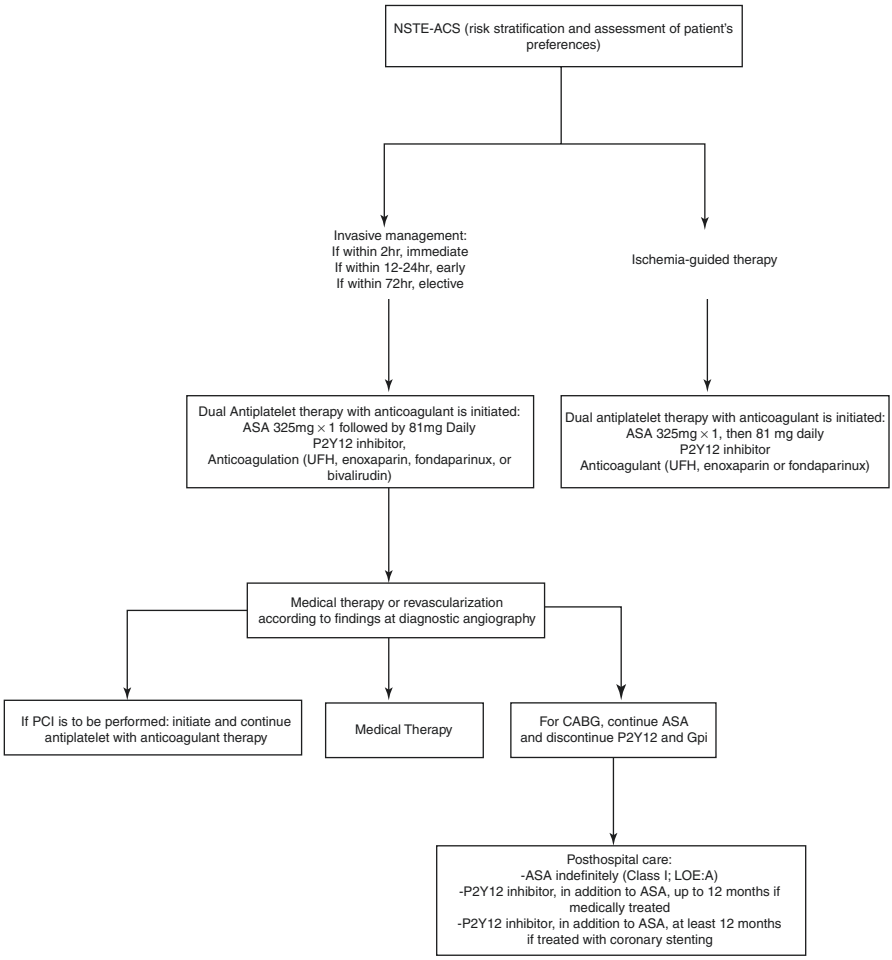

Fig. 6.3 An algorithm for management of patients with definite or likely NSTE-ACS. Adapted from Amsterdam EA [2]

  - Invasive strategy is indicated for patients with higher risk:
    Patients with recurrent angina/ischemia at rest or with low-level activities, despite intensive anti-ischemic therapy
    Recurrent angina/ischemia with CHF symptoms, an S3 gallop, pulmonary edema, worsening rales, or new or worsening mitral regurgitation
    Hemodynamic instability or angina at rest accompanied by hypotension
    Sustained ventricular tachycardia
    PCI within 6 months
- Women with NSTE-ACS and low-risk features should not undergo early invasive treatment, because of the lack of benefit and the possibility of harm (based on the analysis of recent trials, there is evidence that women had higher bleeding complications and contrast-induced nephropathy) (Class III).

- Early **conservative** strategy is recommended for patients at low risk (TIMI score 0–1 or GRACE score < 109) (Class I). These include:
  - **Echocardiogram** to evaluate LV function, followed by **stress test (exercise vs. nuclear)** (Class I)
  - **Ischemia-guided strategy** such as noninvasive stress testing combined with imaging modality (echocardiography, or myocardial perfusion test) that can be used to risk stratify patients with low- to intermediate-risk ACS:
    Patients with LVEF <40% or intermediate- to high-risk stress test results (large anterior or multiple perfusion defects on MPS or wall motion abnormalities on echocardiography, high-risk Duke treadmill score ≤11) will need cardiac catheterization.

Combined Oral Anticoagulant and Antiplatelet Therapy

- In patients who underwent PCI for ACS, especially those with mechanical heart valves, venous thromboembolism, high-risk atrial fibrillation, or hypercoagulable disorders (on oral anticoagulants), the duration of triple therapy (e.g., a vitamin K antagonist and dual antiplatelet therapy with aspirin and clopidogrel) should be as short as possible, due to the increased risk of serious bleeding.
- From the WOEST trial, oral anticoagulant plus clopidogrel without aspirin reduced the risk of clinical bleeding without an increase in thrombotic events, as compared with triple therapy [29].

Use of Proton Pump Inhibitors Together with Plavix

- A significant decrease in the effect of clopidogrel on platelet aggregation, when co-administered with proton pump inhibitor (PPI) omeprazole, has been reported in several pharmacodynamics studies. However, clinical effect of PPIs on cardiovascular outcomes when co-administered with DAPT remains unclear, because of discordant results from observational studies [30].

Secondary Prevention

- Antioxidants and folic acid should not be used for secondary prevention in patients with NSTE-ACS (Class III).
- Hormone therapy should not be given as new drugs for the secondary prevention of coronary events in postmenopausal women after NSTE-ACS and should not be continued in previous users unless the benefits outweigh the risk.

Discharge Planning [12]

- Aspirin 81 mg daily indefinitely.
- P2Y12 inhibitor for ≥12 months (CURE, PLATO, and TRITON TIMI 38; support DAPT duration of 12 months for patients with NSTE-ACS):
  - After PCI with coronary stenting (clopidogrel, ticagrelor, or prasugrel).
  - For medically treated patients (with no revascularization) for up to 12 months (clopidogrel or ticagrelor).
  - In patients with ACS who undergo CABG, clopidogrel or ticagrelor should be resumed and continued for 12 months.
- Referral to cardiac rehabilitation (Class I), which leads to favorable effects on outcomes.
- Evaluations with echocardiography for left ventricular function to evaluate for LV dysfunction.
- In selected patients post NSTEMI (e.g., patients treated with an ischemia-guided strategy), exercise stress testing prior to discharge is recommended. An exercise capacity of ≥5 METS with no evidence of ischemia is an indicator of good long-term prognosis.
- Education regarding risk factor modification (smoking cessation, diet, daily exercise, control of HTN, DM).
- Patients should be discharged on aspirin, a PTY12 inhibitor, beta-blockers, angiotensin-converting-enzyme inhibitors, and statins.

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Chapter 7
Acute ST-Segment Elevation Myocardial Infarction (STEMI)

Justin Lee, Felix Reyes, and Adam S. Budzikowski

Epidemiology and Clinical Significance

- Approximately 550,000 first episodes and 200,000 recurrent episodes of acute myocardial infarction occur annually [1].
- STEMI comprise 25–40% of MI presentations [2].
- Among acute coronary syndrome (ACS), the incidence of STEMI is declining, while incidence of cases without ST elevation appears to be unchanged in the USA [2]. The former may be attributed to more intensive preventive measures, which reduce incidence of ACS, while the latter is related to the higher prevalence of diabetes and chronic kidney disease (CKD) as the population is aging.
- Approximately 30% of patients with STEMI are women, who as a whole have higher mortality and more frequently develop heart failure as a result.
- A sizeable portion of MIs (1–14%) occur in the absence of obstructive CAD (>50% stenosis). MI with non-obstructive CAD (MINOCA) is a working diagnosis, and further investigation for underlying cause must be performed.

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H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7_7

Introduction

ST-segment elevation myocardial infarction STEMI is characterized by the presence of characteristic ECG abnormalities (ST-segment elevation or new LBBB), symptoms consistent with myocardial ischemia, and later on a rise in plasma myocardial necrosis markers [3].

Myocardial infarction (MI) is further classified into five types based on the underlying cause by the Joint ESC/ACCF/AHA/WHF Task [4].

Universal Classification of Myocardial Infarction

Type 1: Infarction due to coronary atherothrombosis
Type 2: Infarction due to supply-demand mismatch (not due to acute atherothrombosis)
Type 3: Infarction due to unknown etiology, secondary to sudden death caused by the infarction, with ECG changes suggestive of MI or new LBBB before biomarkers are available
Type 4a: Infarction related to percutaneous coronary intervention (PCI)
Type 4b: Infarction related to thrombosis of a coronary stent
Type 5: Infarction related to coronary artery bypass graft (CABG)

Pathophysiology

- The usual initiating mechanism for acute myocardial infarction is rupture or erosion of a vulnerable, lipid-laden, atherosclerotic coronary plaque.
- A totally occluding thrombus typically leads to STEMI [5].
- Other conditions that may lead to STEMI include severe coronary vasospasm, spontaneous coronary artery dissection (SCID), and coronary embolism.
- Gender-specific differences in the pathophysiology of STEMI [6]:
  - Regardless of sex, plaque rupture is still the most common cause of acute MI.
  - There is an increased prevalence of plaque erosion, particularly in younger women.
  - Female patients are at higher risk to suffer spontaneous coronary artery dissection.

Clinical Presentation

- Typical presentation is a sudden onset of chest pain, typically severe and crashing in nature.
- Pain is described as heavy, squeezing, or chest tightness. Pain can radiate to the neck, arms, and to the back. Pain is often associated with dyspnea and diaphoresis.
- Approximately a third of patients present with symptoms other than chest pain.
  - Patients with interior wall STEMI may present with abdominal pain, as well as nausea and vomiting.

- Women may have atypical presentation of MI, dyspnea, or sudden fatigue. Dizziness may also be present without chest pain.
  - When presenting with chest pain, pain may also be found in atypical locations such as the shoulders, epigastric region, or back.
  - Women also tend to present later than men.
- Patients with diabetes can present without chest pain and only with hyperglycemia and/or diabetic ketoacidosis.
- It is not unusual to see evidence for transmural MI without prior symptoms.
- Elderly patients may sometimes present without frank chest pain, rather only with change of level of alertness or just fatigue.

Initial Diagnosis

- First step: *EARLY RECOGNITION!*
  - A rapid diagnostic triage of the patient with suspected AMI needs to be performed.
  - Focused history (symptoms consistent with myocardial ischemia (i.e., persistent chest pain)); 12-lead ECG should be obtained and evaluated for ischemic changes, with a goal of performing the evaluation in less than 10 min after the patient's arrival in the emergency department (Class I), before blood is sent for cardiac troponin testing (Class I).
- ECG (Table 7.1)
  - New ST elevation at the J point in at least two contiguous leads of:
    2 mm (0.2 mV) in men or 1.5 mm (0.15 mV) in women in leads V2–V3

and/or

    1 mm (0.1 mV) in other contiguous chest leads or the limb leads
- ST elevation in leads II, III, and aVF and/or reciprocal ST depression in the lateral leads (I, aVL, V5, and V6) are consistent with inferior wall MI (IWMI).
- With the presence of IWMI, the use of additional right precordial leads (V1R to V6R, analogous to the left chest leads) should be considered to identify concomitant RV involvement. ST elevation in V4R (right-sided ECG) is consistent with RV infarction.
- ST elevation in V1—the only standard ECG lead that looks directly at the right ventricle.

Table 7.1 Localization of myocardial infarction based on ECG

ST elevation in ECG	Localization of MI	Culprit vessel (most likely)
Leads V2–V4	Anterior wall	Left main, LAD
Leads II, III, aVF	Inferior wall	RCA
Leads V5–V6	Lateral wall	LCX
Leads I, aVL	High lateral wall	Diagonal or proximal LCX
Leads V1, V2	Anteroseptal wall	Proximal LAD

LAD left anterior descending artery, *RCA* right coronary artery

- The combination of ST elevation in V1 and ST depression in V2 is highly specific for right ventricular MI.
- Right ventricular MI (only seen with proximal right coronary occlusion).
- Up to 40% of patients with IWMI will have concomitant RV infarction:
  - It is important to identify possible RV involvement in IWMI, as these patients' cardiac output is dependent on their preload. IV fluids need to be administered, and use of nitrates (for chest pain) needs to be avoided, as patients may develop severe hypotension in response and generally have worse outcomes.
- New (or presumably new) LBBB has been considered a STEMI equivalent.
  - For EKGs with presence of LBBB, Sgarbossa criteria may be used to diagnose STEMI that is possibly being masked with LBBB. ≥3 points = 90% specificity of MI. Sgarbossa criteria are positive when there is:
    ST elevation ≥1 mm in a lead with a positive QRS complex (concordant ST elevation): 5 points
    ST depression ≥1 mm in leads V1–V3 (concordant): 3 points
    ST elevation ≥5 mm in a lead with a negative QRS complex (discordant ST elevation): 3 points
- Above Sgarbossa criteria also applies to patients with ventricular paced rhythm, although less specific.
- Isolated ST depression ≥0.5 mm in leads V1–V3 and ST elevation ≥0.5 mm in posterior chest wall leads V7–V9 are consistent with isolated posterior MI.
- ST depression ≥1 mm in eight or more surface leads, coupled with ST elevation in aVR and/or V1, suggests left main or left main equivalent coronary obstruction or severe three-vessel ischemia.
- Q waves in contiguous leads may represent old MI.
- Cardiac enzymes (troponin T) every 6 h (these biomarkers may be normal in the early stages).
- Since the beginning of January 2017 in the USA, high-sensitivity assays for troponin were approved by the FDA, to increase diagnostic sensitivity and make it possible to effectively rule out myocardial infarction in 1–2 h [7, 8]:
  - These new hs-c troponin (hs-cTn) test may rule out AMI after a single sample has been obtained
  - Sandoval et al. showed that hs-cTn result below the limit of detection had a 99% negative predictive value. This new test will effectively rule out AMI with 1 h intervals [9].
- Patient should undergo rapid triage in ED based on history, physical exam, ECG, and troponin to differentiate acute coronary syndrome to STEMI and ACS without ST-segment elevation, versus nonischemic chest pain.

Early Risk Stratification

- Patients should undergo the risk assessment of cardiovascular death or recurrent ischemia (high, intermediate, or low risk) based on clinical features, ECG, and troponin testing.

Table 7.2 Killip class risk stratification of MI

Killip Class	Findings	Percentage of patients belonging to class	Mortality
Killip Class I	No clinical signs of heart failure	32% (27–38%)	Mortality rate 6% Current 30-day mortality 2.8
Killip Class II	Rales in the lungs, S3 and elevated jugular venous pressure	38% (32–44%)	Mortality rate 17% Current 30-day mortality 8.8
Killip Class III	Acute pulmonary edema	10% (6.6–14%)	Mortality rate 38% Current 30-day mortality 14.4
Killip Class IV	Cardiogenic shock or arterial hypotension and evidence of peripheral vasoconstriction	19% (14–24%)	Mortality rate 81%

These models are available online and can be useful in initial patient care (Class IIa recommendation)

- Multiple validated models (e.g., TIMI or GRACE score) have been developed to assess the risk of 30-day mortality post-MI:
  - The Thrombolysis in Myocardial Infarction (TIMI) risk score is a bedside clinical risk score for predicting 30-day mortality at presentation of fibrinolytic-eligible patients with STEMI [10].

    Risk Factors

    Age 65–74 years (2 points)
    Age > 75 years
    Systolic BP < 100 mmHg (3 points)
    Heart rate > 100 bpm (2 points)
    Killip Class II–IV (2 points)
    Weight < 67 kg (1 point)
    Anterior STEMI or LBBB (1 point)
    Time to treatment >4 h (1 point)
    DM, HTN, or angina (1 point)
- Risk score/30-day mortality (%). Risk score = total points (0–14).
- Score 0 (0.8%, 30-day mortality), 1 (1.6%), 2 (2.2%), 3 (4.4%), 5 (12.5%), 6 (16.1%), 7 (23.4%), 8 (26.8%), and >8 (35.9%).

The Killip Classification (Table 7.2)

- Killip Class is used to stratify prognosis of myocardial infarction in patients who were diagnosed with AMI [11]. The following table illustrates mortality based on the case series study conducted in 1967 to develop the Killip Class [11].

Initial Management

- Once the diagnosis of STEMI is established, reperfusion therapy needs to be initiated as soon as possible (Fig. 7.1) [12].

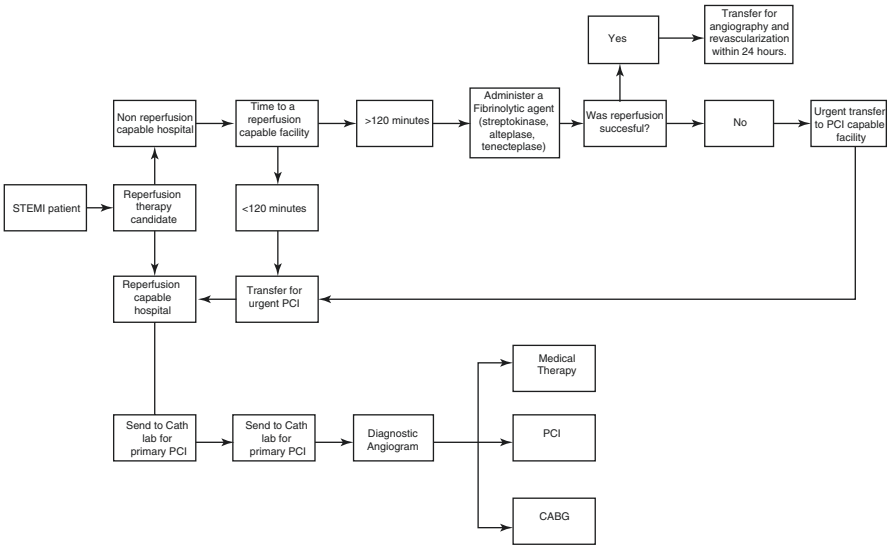

Fig. 7.1 Algorithm for management of patients with STEMI. Adapted from O'Gara PT, et al. [3]

- Immediate reperfusion (opening of the occluded "culprit" artery) is the most important step. This can be accomplished by means of primary percutaneous intervention (PCI) with angioplasty or stenting or administration of intravenous fibrinolytic therapy.
- Patients who present with STEMI within a travel radius of 90 min from a PCI-capable facility, should be referred for emergent coronary angiography and primary PCI.
- If the patient presents to a non-PCI-capable hospital, consider transfer. If travel time is longer than 120 min to a PCI-capable facility, fibrinolysis should be considered.
- Prompt referral to cath lab for **PCI:**
  - **2013 ACC/AHA guidelines**: Door to balloon time—90 min.
  - **2017 ESC guidelines**: In cases where fibrinolysis is the reperfusion strategy, the maximum time delay from the diagnosis of STEMI to treatment has been shortened from 30 min in 2012 to 10 min in 2017.
  - **2017 ESC guidelines now** suggest that new-generation DES have been shown to be superior to BMS in patients with AMI [13].
  - Class I.

  Primary PCI should be performed in patients with:

  STEMI and ischemic symptoms of **less than 12 h duration**

  STEMI and ischemic symptoms of **less than 12 h duration, who have contraindications to fibrinolytic therapy, irrespective of the time delay from FMC**

  STEMI and **cardiogenic shock or acute severe HF**, irrespective of time delay from MI onset
  - Class IIa.

Primary PCI is reasonable in patients with STEMI if there is clinical and/or ECG evidence of ongoing ischemia **between 12 and 24 h** after symptom onset.
  – Class I.

In the absence of contraindications, **fibrinolytic therapy** should be given to patients with STEMI and onset of ischemic symptoms **within the previous 12 h,** when it is anticipated that primary **PCI cannot be performed within 120 min.**

- Absolute contraindications for fibrinolysis [14]:
  – Any prior intracranial hemorrhage (ICH)
  – Ischemic stroke in the last 3 months (except acute ischemic stroke <4.5 h)
  – Known cerebral vascular lesion
  – Known intracranial malignant neoplasm
  – Active bleeding
  – Suspected aortic dissection
  – Significant closed head or facial trauma within 3 months
  – Intracranial or intraspinal surgery within 2 months
  – Severe uncontrolled hypertension
  – Prior treatment within 6 months (for streptokinase)
- Relative contraindications for Fibrinolysis:
  – History of severe, uncontrolled hypertension or SBP >180 mmHg and/or DBP >110 mmHg on presentation
  – Ischemic stroke greater than 3 months prior
  – Known intracranial pathology not listed in absolute contraindications
  – Traumatic or prolonged (>10 min) CPR
  – Major surgery within 3 weeks
  – Internal bleeding within 2–4 weeks
  – Current use of oral anticoagulants
- Fibrinolysis is not useful in patients with vein grafts (post-CABG); PCI is preferred [3].
- **Aspirin** (loading, 162–325 mg [Class I, B]; maintenance, 81–325 mg [Class I, A]):
  – Low-dose aspirin therapy is almost always continued indefinitely in patients with coronary artery disease.
  – For patients with STEMI who are undergoing primary PCI, a loading dose should be given as early as possible or at the time of PCI, followed by a daily maintenance dose for at least 1 year.
- **P2Y12 inhibitor:**
  – Clopidogrel (loading, 600 mg [Class I, B]; maintenance, 75 mg [Class I, B])
  – Prasugrel (loading, 60 mg [Class I, B]; maintenance, 10 mg [Class I, B])
  – Ticagrelor (loading, 180 mg [Class I, B]; maintenance, 90 mg BID [Class I, B])
  – All maintenance doses of P2Y12 inhibitors are continued for 1 year after stent placement [15]
  – TRITON-TIMI 38 and PLATO trials showed that in patients with acute coronary syndromes with scheduled percutaneous coronary intervention, prasugrel and ticagrelor therapy was associated with significantly reduced rates of ischemic events, including stent thrombosis [16, 17].

  - PEGASUS-TIMI 54 trial, 90 mg b.i.d. Ticagrelor (high dose) showed a reduction in MACE compared to 60 mg b.i.d. and placebo in patients with a history of MI 1–3 years previously and with high-risk features [18]. This is included in the new 2017 ESC guidelines.
- **Duration of dual antiplatelet therapy (DAPT):**
  - DAPT duration in NSTE-ACS and STEMI is similar, as both represent different parts of acute coronary syndrome.
  - Ideally all patients with a recent ACS should undergo DAPT for 12 months.
  - Patients who underwent thrombolysis should have a minimum of 14 days of DAPT.
  - All patients with ACS who undergo PCI require at least 12 months of DAPT.
  - Patients post-CABG should also complete 1 year of DAPT.
- **Anticoagulant therapy:**
  Current ACC/AHA guidelines suggest Class I indication for immediate administration of an intravenous anticoagulant agent to all patients diagnosed with STEMI, regardless of treatment strategy. The following are the options:
  - Unfractionated heparin (UFH) (loading, 60 U/kg; maintenance, 12 U/kg/h × 48 h)
    UFH is common practice due to its universal availability, low price, and ease of use as a bolus. Target therapeutic range for aPTT is 50–70 s.
  - Low-molecular-weight heparin (LMWH) (1 mg/kg q12h subcutaneously)
    Intravenous enoxaparin may be a viable alternative to UFH in patients with STEMI undergoing primary PCI, due to difficulty maintaining aPTT within the therapeutic range [19]. Sheath removal considerations should account for its long half-life. LMWH is also less associated with heparin-induced thrombocytopenia (HIT) than UFH [20].
  - Bivalirudin (loading: 0.75 mg/kg, maintenance: 1.75 mg/kg/h)
    From the HORIZONS-AMI trial, bivalirudin monotherapy (with 7% GPIIb/IIIa inhibitor infusion for thrombotic bailout) resulted in significantly lower major bleeding, all-cause mortality, and cardiac mortality than the combination of UFH plus routine GP IIb/IIIa blocker administration in 30-day up to 3-year follow-up [21]. The bivalirudin arm was also associated with a reduction in reinfarction and overall similar stent thrombosis at 3 years (despite a statistically significant ~1% increase within the first 24 h). However, a more recent MATRIX trial showed no significant difference in the lowering of net adverse cardiovascular events with bivalirudin in place of heparin, contrasting the results of the ACUITY and HORIZONS-AMI trials [22].
  - Fondaprinux (2.5 mg daily)
    From the OASIS-6 trial, fondaparinux significantly reduces mortality and reinfarction without bleeding and stroke, suggesting its superiority to placebo and UFH [23]. However, it may increase the risk of catheter thrombosis, so it should not be used with PCI.
    It is recommended that after an uncomplicated PCI, anticoagulant therapies are generally discontinued [1].

- **Beta blockers:**
  - Class I
    Oral beta blockers should be initiated in the **first 24 h** in patients with STEMI who do **not** have any of the following: signs of HF, evidence of a low-output state, increased risk for cardiogenic shock, or other contraindications to use of oral beta blockers (PR interval more than 0.24 s, second- or third-degree heart block, active asthma, or reactive airways disease).
    Beta blockers should be continued during and after hospitalization for all patients with STEMI and with no contraindications to their use.
    Patients with initial contraindications to the use of beta blockers in the first 24 h after STEMI should be reevaluated to determine their subsequent eligibility.
- Nitroglycerin (0.4 mg sublingual every 5 min up to three doses as BP allows) if no contraindications.
  - As needed for chest pain
  - **Avoid** in suspected **RV infarction**
  - **Avoid** with **SBP 90 mmHg** or if **SBP 30 mmHg below baseline**
  - **Avoid** if recent **(24–48 h) use of 5-phosphodiesterase inhibitors**
- Analgesia (e.g., morphine 4–8 mg IV prn) for relief of ischemic pain (Class I).
- Oxygen use is recommended only for patients with hypoxemia (oxygen saturation < 90%) or respiratory distress (Class I). It is not recommended to use oxygen in patients with SaO2 > 90% (Class III) [24].
- ESC guidelines recommend measuring glycemic status at initial evaluation in all patients and maintaining frequent monitoring in patients with known diabetes or hyperglycemia (defined as glucose levels 11.1 mmol/L or 200 mg/dL):
  - However, concerns about overly aggressive glycemic control in critically ill patients were raised by the NICE-SUGAR trial, where tight glucose control (81–108 mg/dL) was associated with increased mortality rate (primarily from cardiovascular causes) and more episodes of hypoglycemia compared to modest control (180 mg/dL) [25].
  - Blood glucose levels should be maintained below 180 mg/dL if possible while avoiding hypoglycemia.
- Patient should be monitored in CCU setting/telemetry for at least 24 h.

Further Management

- **Renin-angiotensin-aldosterone system inhibitors:**
  - Class I
    An angiotensin-converting enzyme (ACE) inhibitor should be administered **within the first 24 h** to all patients with STEMI with **anterior location, HF, or LV ejection fraction (LVEF) less than or equal to 40%**, unless contraindicated.
    An angiotensin receptor blocker (ARB) should be given to patients with STEMI who have indications for but are intolerant of ACE inhibitors.

An aldosterone antagonist should be given to patients with STEMI and no contraindications who are already receiving an ACE inhibitor and beta blocker and who have an LVEF less than or equal to 40% and either symptomatic HF or diabetes mellitus.

– Class IIa
ACE inhibitors are reasonable for all patients with STEMI and no contraindications to their use.

- **Statins:**
  – Class I recommendation: **High-intensity statin (atorvastatin 80 mg or rosuvastatin 40 mg)** therapy should be initiated or continued in all patients with STEMI and no contraindications to its use.
  – Class IIa
  It is reasonable to obtain a fasting lipid profile in patients with STEMI, preferably within 24 h of presentation.
  From Fourier trial, additional lipid control (with evolocumab) to lower LDL < 70 is reasonable—2017 ESC guidelines.
- **Smoking cessation:**
  – A meta-analysis of cohort studies in patients after acute MI has shown that smoking cessation can reduce the mortality rate by nearly 50% on subsequent cardiovascular events, rendering it one of the most powerful secondary prevention strategies [26].
- Diet/exercise.
- Sexual activity is reasonable for patients who can exercise ≥3 to 5 METS without angina, excessive dyspnea, ischemic ST-segment changes, cyanosis, hypotension, or arrhythmia (Class IIa).
- 2013 ACC/AHA guidelines suggest referral to cardiac rehabilitation (Class I).
- About 30% of patients (especially women) who suffered an AMI manifest symptoms of depression and anxiety [27]. Depression is more prevalent in women and increases a woman's risk for cardiac death or MI by ≥50%, particularly in young- and middle-aged women. It is important to recognize and treat it, as it can affect adherence to treatment and cardiac rehabilitation.

Key Changes for STEMI Management in the 2017 ESC Guidelines

- Radial access for PCI: changed from Class IIa to Class I
- Drug-eluting stents (DES) preferred over bare metal stent (BMS): changed from Class IIa to Class I
- Complete revascularization therapy for all patients: changed from Class III to Class IIa
- Thrombus aspiration therapy: changed from Class IIa to Class III
- Bivalirudin administration for anticoagulant therapy: changed from Class I to Class IIa

- Enoxaparin administration for anticoagulant therapy: changed from Class IIb to Class IIa
- Early hospital discharge after STEMI: changed from Class IIb to Class IIa
- Oxygen saturation indication for supplemental oxygen therapy: changed from <95% to <90%

New Recommendations in the 2017 ESC Guidelines

- Additional lipid-lowering therapy if LDL >1.8 mmol/L (>70 mg/dL) despite on maximum tolerated statins (Class IIa)
- Complete revascularization during the index primary PCI in STEMI patients in shock (Class IIa)
- Administration of cangrelor if P2Y12 inhibitors have not been given (Class IIb)
- Switch to potent P2Y12 inhibitors 48 h after fibrinolysis (Class IIb)
- Extend ticagrelor up to 36 months in high-risk patients (Class IIb)
- Use of polypill to increase adherence (Class IIb)

Complications of STEMI (See Chap. 23)

Conclusion

- STEMI is a clinical syndrome that requires early recognition and prompt initiation of therapy, with mortality that is time-dependent. Early mobilization of appropriate services for revascularization of coronary vessel(s) ensures better outcomes.
- With broad application of early reperfusion therapy and ongoing, current medical treatment for STEMI, 30-day mortality rates have progressively declined from more than 20% to less than 5%, with associated major complications declining as well [1, 28].

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Chapter 8
Evaluation of Ischemic Heart Disease: Standard Imaging and Diagnostic Testing Modalities

Imran N. Chaudhary and Ronald G. Schwartz

Introduction

- Coronary artery disease (CAD) is a major cause of illness and death in the United States [1].
- The costs of treating this disease and the indirect costs resulting from lost work and wages are substantial [1].
- Various modalities available for evaluation of clinically suspected IHD include standard exercise tolerance test (exercise ECG, "ETT"), nuclear cardiology techniques including radionuclide PET, SPECT (including high-efficiency CZT [cadmium zinc telluride]) myocardial perfusion/function imaging, MUGA (ERNA) blood pool ventriculography, echocardiography, cardiac CT including coronary artery calcium (CAC) scanning with multidetector CT (to screen for preclinical CAD in asymptomatic patients with multiple coronary risk factors including family history in a sibling or parent and elevated global CAD risk), cardiac MR, and invasive coronary angiography.

Exercise Tolerance Test (ETT)

Protocol

- ECG monitoring with exercise.
- Exercise is usually done on a treadmill, but bicycle ergometry or arm ergometry may also be used.

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© Springer International Publishing AG, part of Springer Nature 2018

H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7_8

- Standard Bruce protocol is most widely used and has a large diagnostic and prognostic database [2].
- Exercise capacity is reported in estimated metabolic equivalents (METs). One MET = resting oxygen consumption for a 70-kg 40-year-old man (equivalent to 3.5 ml/min/kg of body weight).
- 3–5 METs = raking leaves, golf, walking 3–4 miles per hour, and climbing one flight of stairs. 5–7 METs = exterior carpentry and singles tennis. >9 METS = heavy labor, handball, squash, and running at 6 miles per hour.
- The standard Bruce protocol has 3-min stages starting at workload of 4 or 5 METs and increases workload by approximately 3 METs every 3 min. First stage starts at 1.7 mph and 10% grade.
- Modified Bruce protocol is used in older individuals or those in whom exercise capacity is limited. In this case, Bruce protocol is modified by two 3-min warm-up stages at 1.7 mph with 0% grade and 1.7 mph with 5% grade [3].
- Heart rate, blood pressure, and ECG are recorded at the end of each stage of exercise, immediately before and immediately after stopping exercise and for each minute in the recovery phase for at least 5–10 min or till the ECG changes come back to baseline.
- Goal = target heart rate 85% of the age predicted maximum heart rate. Maximum predicted heart rate = 220—age of the patient in years.
- Secondary goals = rate pressure product (RPP) ≥20,000 (RPP = peak exercise HR x peak systolic BP) and completion of 6 min of exercise.

Indications

- Diagnosis of obstructive coronary artery disease in patients with intermediate pretest probability of coronary artery disease
- Evaluation of patients with known coronary artery disease:
  - After myocardial infarction
  - After revascularization, either angioplasty or bypass surgery
- Evaluation of exercise capacity in patients with valvular heart disease (except severe aortic stenosis)
- Evaluation of patients with cardiac rhythm disorders:
  - Identification of appropriate settings in patients with rate-adaptive pacemakers
  - Patients with exercise-induced arrhythmias and evaluation of their response to treatment
- ETT generally discouraged for asymptomatic healthy persons by ACC/AHA guidelines and other organizations
- May be considered in high-risk occupations (e.g., pilots, firefighters, law enforcement officers, mass transit operators, etc.) and in some high-risk asymptomatic individuals with multiple cardiac risk factors [4–7]

Contraindications: Generally a very safe procedure but both myocardial infarction and death have been reported. Complication rate is 1 per 2500 tests [4].

Absolute [4, 7]:

- Acute myocardial infarction (within 2 days)*
- Unstable angina not previously stabilized by medical therapy
- Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise
- Symptomatic severe aortic stenosis*
- Uncontrolled symptomatic heart failure
- Acute pulmonary embolus or pulmonary infarction
- Acute myocarditis or pericarditis
- Acute aortic dissection

Relative [4, 7]:

- Left main coronary stenosis*
- Moderate stenotic valvular heart disease*
- Electrolyte abnormalities
- Severe arterial hypertension* (SBP >200 mmHg and/or DBP >110 mmHg)
- Tachyarrhythmia or bradyarrhythmias
- Hypertrophic cardiomyopathy and other forms of outflow tract obstruction
- Mental or physical impairment leading to inability to exercise adequately
- High-degree atrioventricular block
- *Safe with regadenoson vasodilator stress testing.

Termination: Exercise is often terminated on reaching 85% of maximum predicted heart rate (220—age in years) and RPP > 20,000. Indications to terminate even if 85% of the maximum predicted heart rate is not reached.

Absolute indications [4]:

- Drop in systolic blood pressure of >10 mmHg from baseline blood pressure despite an increase in work load, when accompanied by other evidence of ischemia after the first 2 min of exercise
- Moderate to severe angina
- Increasing nervous system symptoms (e.g., ataxia, dizziness, or near syncope)
- Signs of poor perfusion (cyanosis or pallor)
- Technical difficulties in monitoring ECG or systolic blood pressure
- Subject's desire to stop
- Sustained ventricular tachycardia
- ST elevation (≥1.0 mm) in leads without diagnostic Q waves (other than aVR)

Relative indications [4]:

- Drop in systolic blood pressure of >10 mmHg from baseline blood pressure despite an increase in workload, in the absence of other evidence of ischemia after the first 2 min of exercise

- ST or QRS changes such as excessive ST depression (>2 mm of horizontal or downsloping ST-segment depression) or marked axis shift
- Arrhythmias other than sustained ventricular tachycardia, including multifocal PVCs, triplets of PVCs, supraventricular tachycardia, heart block, or bradyarrhythmias
- Fatigue, shortness of breath, wheezing, leg cramps, or claudication
- Development of bundle branch block or IVCD that cannot be distinguished from ventricular tachycardia
- Increasing chest pain
- Hypertensive response (SBP > 225 mmHg and/or DBP > 110 mmHg)

Interpretation

- **Hallmark of positive ETT = 1 mm (0.1 mv) or more horizontal or downsloping ST-segment depression occurring 80 ms after the J point (slope of ST segment is zero or negative visually) and remaining for three consecutive beats with a stable baseline** [4].
- Normal ECG response during ETT = shortening of P-R, QRS, and QT intervals and J point depression [8].
- Upsloping ST-segment depression increases sensitivity, but causes an unacceptable decrease in test specificity. ST-segment depression noted only in the recovery period has same diagnostic accuracy as ST-segment depression noted during exercise [4].
- ST-segment elevation much less common than ST-segment depression but localizes site of myocardial ischemia [4].
- A 2011 study showed that exercise-induced ST-segment elevation in lead aVR may be suggestive of left main or ostial LAD disease [9].

Confounding Factors

- Resting ECG with left bundle branch block (LBBB) or paced ventricular rhythm cannot be used for assessment of myocardial ischemia.
- Exercise ECG can be interpreted in the presence of right bundle branch block (RBBB) if the right precordial leads (V_1–V_3) are ignored and interpretation is confined to the left precordial leads (V_4–V_6).
- Beta-blocker reduces sensitivity of the stress test by blunting heart rate response to exercise.
- Baseline ST-T abnormalities on the resting ECG, digoxin use, and left ventricular (LV) hypertrophy reduce specificity of the stress test.
- Test accuracy (both sensitivity and specificity) is lower in women than men, which at least in part is due to a lower prevalence of CAD in women and greater

incidence of false-positive results associated with digoxin-like effects of estrogen on ECG repolarization pattern [4]. Although ETT accuracy is lower in women, ACC/AHA guidelines do not consider gender to be a significant determinant for selecting a specific test modality in an individual patient.

Patient Selection

- Consider pretest probability of CAD in selecting patients for ETT [10–12]. See Table 8.1 below.
- Pretest likelihood of CAD depends on patient's age, gender, symptomatic status, and cardiac risk factor profile [13].
- ETT has maximal diagnostic value for patients with intermediate (20–80%) pretest probability of CAD [7, 14].
- ETT has little diagnostic value at extreme ends of pretest probability: low (<10%), primarily women age < 60 years with non-anginal chest pain; high (>90%), primarily men age > 50 years with typical angina.

Adverse Prognostic Findings on ETT

- Low workload achieved (<6 METs or 5–6 min on Bruce protocol)
- Low peak heart rate (<120 beats per minute) without beta-blocker therapy
- Failure to increase systolic blood pressure ≥ 120 mmHg, or a sustained decrease ≥10 mmHg, or below rest levels during progressive exercise

Table 8.1 Pretest probability of coronary artery disease by age, gender, and symptoms [15]

Age (years)	Gender	Typical/definite angina pectoris	Atypical/probable angina pectoris	Non-anginal chest pain	Asymptomatic
30–39	Men	Intermediate	Intermediate	Low	Very low
	Women	Intermediate	Very low	Very low	Very low
40–49	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Low	Very low	Very low
50–59	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Intermediate	Low	Very low
60–69	Men	High	Intermediate	Intermediate	Low
	Women	High	Intermediate	Intermediate	Low

High indicates >90%; intermediate, 10–90%; low, <10%; and very low, <5%.
No data exist for patients <30 or >69 years, but it can be assumed that prevalence of CAD increases with age, and patients with ages at extremes of decades may have probabilities slightly outside the high or low range. Typical or definite angina is defined as substernal chest pain or discomfort that is provoked by exertion or emotional stress and relieved by rest and nitroglycerine. Atypical or probable angina is defined as chest pain or discomfort that lacks one of the three characteristics of definite or typical angina.

- ST-segment depression ≥2 mm, downsloping ST segment starting at <6 METs, involving ≥5 leads, persisting ≥5 min into recovery
- Exercise-induced ST-segment elevation (except in aVR)
- Typical angina pectoris during exercise
- Reproducible sustained (> 30 s) or symptomatic ventricular tachycardia

Recommendations

- Standard ETT recommended as initial noninvasive test for all patients with normal or near-normal ECG who can adequately exercise based on multisociety Guideline for the Diagnosis and Management of Patients with Ischemic Heart Disease [14, 16].
- Stress imaging recommended as initial testing modality in three groups of patients:
- An inability to exercise requiring pharmacological stress
- Significant ECG abnormalities that preclude stress ECG interpretation
- High pretest probability of CAD

Duke Treadmill Score

- The Duke treadmill exercise score (TES) permits prognostic assessment using the exercise ECG [11, 12].
- Duke TES = (# of min on the Bruce protocol) − 4 × angina index (0 = none, 1 = non-limiting angina, 2 = exercise limiting angina) − 5 × the ST-segment deviation from baseline
- A Duke TES -10 to +4 is associated with intermediate risk of 2.5% annual hard cardiac event (HCE) rate (fatal + nonfatal MI) per year.

Augmented Stress Testing

Imaging modalities used with stress testing in conjunction with ECG monitoring:

- Radionuclide myocardial perfusion imaging with SPECT, high-efficiency CZT SPECT, PET
- Echocardiography
- Cardiac magnetic resonance

Stress testing with an imaging procedure (echocardiography, myocardial perfusion, and cardiac MR) is preferable over ETT (ECG exercise testing) in cases of:

Table 8.2 Comparison of various augmented stress testing modalities (stress test with imaging)

	Sensitivity	Specificity	Advantages	Disadvantages
ETT	68%	77%	Lower cost; widely available	Lower sensitivity
SPECT	87%	73%	Higher sensitivity	Radiation often stated as disadvantage but no clinical adverse consequence of diagnostic low-level radiation ever reported [20–22]
Stress echo	84%	81%	Higher specificity	Imaging limited in overweight patients
CZT SPECT			Effective attenuation with supine and upright imaging; accurate in morbidly obese patients; ultra-low dose imaging; rapid, cost-effective stress-only imaging for most studies	High initial cost of CZT SPECT technology

- Patients unable to exercise because of orthopedic, neurological, or peripheral vascular problems by use of various pharmacological agents in place of exercise [17].
- Patients with high probability of false-positive result on exercise test—resting ECG abnormalities, e.g., marked baseline ST-T wave abnormality, left bundle branch block, ventricular paced rhythm, pre-excitation syndromes (WPW), repolarization abnormalities due to left ventricular hypertrophy, and digoxin use that precludes identification of ischemia [18].
- Need for higher sensitivity and specificity than standard ETT, for example, patients with known CAD or with higher likelihood of CAD [19]. Table 8.2 gives comparison of various stress test modalities.
- Need to localize ischemia in patients with known CAD (e.g., with prior revascularization [1]).

Nuclear Cardiology Imaging

Protocol

- Uses a radioactive tracer and an imaging system (camera) to assess perfusion, metabolism, or function of the heart.
- Three types of imaging modalities: single-photon emission computed tomography (SPECT), CZT (cadmium zinc telluride) high-efficiency SPECT, and positron emission tomography (PET).
- Tomographic reconstruction techniques to obtain 3D images.
- SPECT—regional distribution of myocardial perfusion visualized using radioactive pharmaceuticals that accumulate in the myocardium in proportion to regional

myocardial blood flow [17]. Radiopharmaceuticals used technetium-99 m sestamibi, Tc-99 m tetrofosmin, or thallium-201 [17]. Physical exercise if able to exercise or pharmacological vasodilation/stress if unable to exercise (regadenoson, adenosine, dipyridamole, dobutamine).

- PET—fluorodeoxyglucose—(FDG, a glucose analogue) is used to image glucose utilization. FDG rapidly exchanged across cell membrane and phosphorylated, metabolized very slowly, and is essentially trapped inside the myocardium, allowing adequate time to image regional glucose uptake. Patient loaded with glucose after fasting for 6 h to maximize FDG uptake in myocardium for myocardial viability and hibernation imaging.
- Stress agents create "heterogeneity of myocardial blood flow" between vascular territories supplied by normal coronary arteries and those supplied by an artery with significant coronary artery stenosis. This heterogeneity of myocardial blood flow is visualized with radionuclide myocardial perfusion agents and is a requirement for abnormal images.
- *Physical exercise is preferred over pharmacologic stress imaging if a patient is able to exercise to sufficient cardiac workload.* It provides additional useful clinical and physiological information, e.g., duration of exercise, total workload, maximum heart rate, exercise-induced symptoms, ECG changes, and blood pressure response.
- *Pharmacological vasodilation is* used in patients who are unable to exercise adequately due to deconditioning, age, or disability associated with orthopedic, neurological, or peripheral vascular issues.
  - Three agents used for pharmacological vasodilator stress test:
  - Regadenoson is the most widely used pharmacologic agent—selective A2a coronary receptor agonist elicits potent coronary vasodilator response at a fixed dose of 0.4 mg administered over 10 s; routine reversal of adverse symptoms within 3–5 min for completion of stress protocol.
  - Regadenoson has a very high safety profile in patients with asthma, COPD, liver, and advanced kidney failure.
  - Adenosine and dipyridamole, also available but are much less extensively used.

    Longer infusion protocols
    Adenosine or dipyridamole contraindicated in patients with hypotension, bronchospasm, and advanced AV block

  - Pacemaker required if advanced AV block for all vasodilators.
  - All are endogenous vasodilators that increase myocardial blood flow three to four times above the baseline levels.
  - Regadenoson is a selective adenosine A_{2A}receptor agonist that has been developed in an effort to minimize the complications and discomfort from the nonselective activation of A_1, A_{2B}, and A_3 receptors seen with adenosine or dipyridamole.
  - Vasodilatory effect produced by adenosine and regadenoson is much more potent and consistent than that produced by dipyridamole [23].

- *Dobutamine stress* increases myocardial contractility, heart rate, and blood pressure and myocardial oxygen demand.
  - Produces less increment of increased coronary blood flow compared to regadenoson, adenosine, or dipyridamole

Interpretation

- SPECT myocardial perfusion scans interpreted qualitatively by visual analysis aided by computerized quantification.
- Computer-aided quantification of myocardial perfusion imaging improves consistency of image interpretation and decreases intra- and interobserver variability [17].
- High-risk features of a nuclear myocardial perfusion scan:
  - Quantitatively large myocardial perfusion defects
  - Multiple defects in two or more coronary artery territories
  - Increased pulmonary radiotracer uptake after stress (thallium-201)
  - Transient dilation of the left ventricle after stress
  - LV dysfunction (LVEF <45%)
  - Increase of end systolic volume index (ESVI >35 ml/m^2)
  - Reduced global myocardial perfusion reserve

Role of Nuclear Myocardial Perfusion Imaging in Clinical Decision-Making

- **Detection of coronary artery disease** [4, 15, 24]: Fig. 8.1 shows a suggested algorithm for detection of coronary artery disease.
- **Risk stratification and assessment of prognosis in patients with known or suspected coronary artery disease** [25–27]**:**
  - Presence of reversible defects (ischemia) – higher risk of future cardiac events depending on the number and extent of reversible defects and the magnitude of defect reversibility
  - Fixed defects – intermediate risk of future cardiac events
  - Normal SPECT nuclear myocardial perfusion – favorable prognosis, even when coronary artery stenosis is angiographically documented (0.6% per year rate of nonfatal myocardial infarction and 0.5% per year mortality rate)
- **Assessment of benefit of revascularization in addition to medical therapy:**
  - With more than 10% ischemia on SPECT or PET MPI, consider coronary revascularization.
- **Assessment before vascular surgery** [17, 24]**:** Patients with peripheral vascular disease are at risk of co-existing coronary artery disease. In selected cases, preoperative nuclear stress test can identify patients at higher risk of adverse cardiac events during perioperative period.

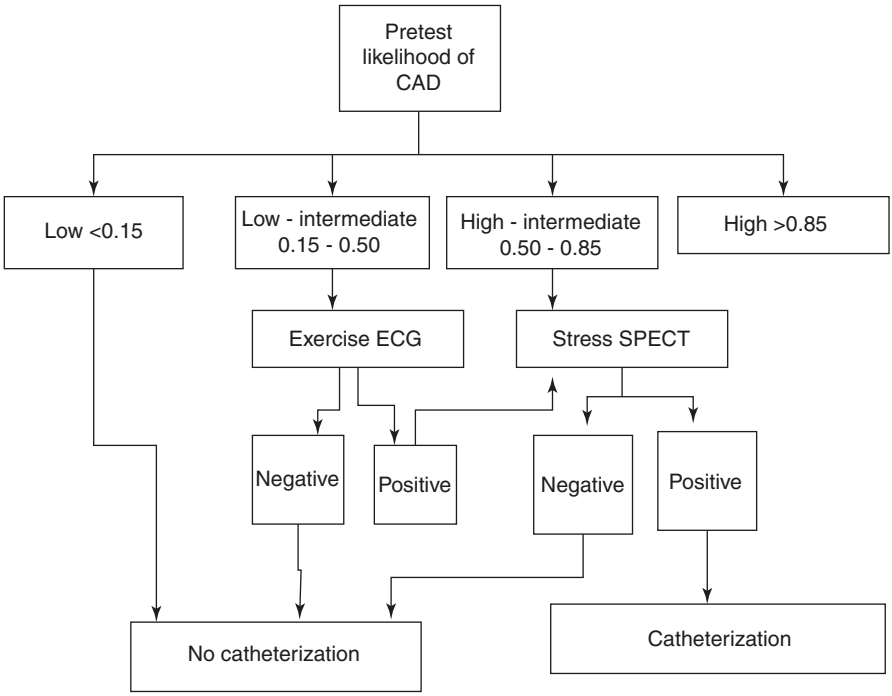

Fig. 8.1 Suggested algorithm for detection of coronary artery disease

- **Post-percutaneous transluminal coronary angioplasty patients:** Nuclear myocardial perfusion imaging is helpful following PTCA to rule out restenosis.
- **Post-coronary artery bypass surgery** [24]: SPECT myocardial perfusion imaging useful in determining the presence and extent of myocardial ischemia in post-CABG patients. Cardiac catheterization recommended whenever there is moderate to severe ischemia.
- **Assessment of myocardial hibernation and viability** [24, 28]**:**
  - Assess hibernation and viability in patients with abnormal LVEF being considered for revascularization. LV function is expected to improve after revascularization if there is myocardial viability.
  - Positron emission tomography (PET) demonstrating perfusion and metabolism mismatch (viable FDG uptake in hypoperfused region) is considered gold standard for detection of myocardial hibernation and viability. Rest and redistribution thallium-201 scintigraphy also considered a reliable method to assess myocardial hibernation and viability.
- **Assessment of therapeutic interventions in ischemic heart disease** [24]**:** well-defined role in initial patient assessment and assessment of therapeutic response to lifestyle, medical, and/or revascularization interventions.
- **Acute ischemic syndrome** [24]**:** acute resting nuclear myocardial perfusion imaging with technetium 99-m sestamibi (injected during or following prolonged

chest pain of the patient) identifies patients with chest pain from acute ischemic coronary syndrome. These patients have resting perfusion defects on sestamibi images.

- **Early assessment of prognosis after myocardial infarction** [17]**:**
  - Early radionuclide myocardial perfusion imaging (first to fourth day) after myocardial infarction.
  - Large resting myocardial perfusion defects or partially reversible defects suggest poorer prognosis and survival.
- **Evaluation of cardiac function** [29, 30]**:**
  - Blood pool imaging (radiopharmaceutical agent directly labels the blood pool—first pass or equilibrium).
  - Tracers label myocardial wall allowing imaging of myocardium through the cardiac cycle.
  - Powerful prognostic information in patients with LVEF <50% [31]. Highly accurate and precise assessment of LV volumes and ejection fraction (<3% variance).

Stress Echocardiography

- Regional left ventricular systolic function measured at baseline and compared with that measured immediately after stress (exercise or dobutamine), using 2D echocardiography.
- In myocardial ischemia, absolute or relative decrease in myocardial perfusion is followed by alteration in diastolic function, abnormalities in regional and global systolic function, ischemic electrocardiographic ST-segment changes, and lastly angina pectoris [19].
- Myocardial ischemia leads to alterations in regional ventricular contraction which are detected on echocardiographic images.
- Initial resting echocardiogram is followed by exercise or dobutamine infusion (if unable to exercise), and echocardiographic images are again obtained immediately after peak stress.
- Peak stress evaluated for new regional wall motion abnormalities compared to resting images. A normal response to stress is improved contractility in all of the ventricular walls. Worsening regional wall motion represents an ischemic response. Wall motion that is unchanged after stress represents a nonspecific response and may indicate mild ischemia [32].
- Stress echo also allows for simultaneous evaluation of left ventricular hypertrophy and valvular structure and function [32].
- Assessment of myocardial viability: in cases of LV systolic dysfunction, viable myocardial tissue can be identified by low-dose dobutamine infusion as viable segments can be induced to contract with low-dose dobutamine [19].
- Uses of stress echocardiography [32]:
  - Detection and evaluation of coronary artery disease

- Establishment of prognosis following myocardial infarction
- Risk stratification prior to noncardiac surgery
- Establishment of prognosis in patients with high likelihood of coronary artery disease
- Evaluation and follow up of revascularization procedures
- Assessment of myocardial viability

Cardiac MR (CMR)

- Role in assessment of regional and global systolic function, etiology of cardiomyopathy, imaging of myocardial infarction and viability, and the evaluation of pericardial disease and cardiac masses [33].
- Used for perfusion imaging where passage of a contrast agent such as gadolinium through the myocardium can be measured and used for detection of obstructive CAD when performed with pharmacological vasodilation using adenosine or regadenoson. The underlying principle is similar to that in nuclear perfusion imaging, where a vasodilator is used to accentuate regional differences in myocardial blood flow [33].
- MR perfusion imaging has higher spatial resolution (>20-fold) than nuclear techniques and can depict a perfusion defect that is only subendocardial [33].
- CMR is the most sensitive noninvasive imaging test for detection of myocardial infarction. Compared with SPECT, CMR demonstrated 40-fold increase in spatial resolution making it significantly more sensitive for detection of subendocardial infarction, over 40% of which are missed with SPECT [33].
- Dobutamine stress CMR has a higher diagnostic accuracy than dobutamine echo and can be an effective modality for patients with poor acoustic windows.
- Coronary MR angiography (MRA) may be used to directly visualize coronary anatomy and morphology. This is technically demanding resulting in intermediate sensitivity and specificity values for detection of CAD. Currently, coronary MRA is mostly used for evaluation of patients with suspected coronary anomalies.

Cardiac Computed Tomography

- Rapid and accurate imaging of the entire cardiovascular system – coronary arteries, coronary arterial walls, cardiac valves, myocardium, and associated structures.
- Role of cardiac CT in assessment of CAD:
  - CAD detection in symptomatic patients without known heart disease
  - CAD risk assessment in asymptomatic individuals
  - Assessment of severity of CAD in patients with known CAD

- **Coronary artery calcium (CAC) scanning:**
  - CAC detection used in asymptomatic patients to refine their clinically predicted risk of CAD beyond that predicted by standard risk factors.
  - CAC is present in direct proportion to overall extent of atherosclerosis. Its detection indicates an increased risk of incident CAD over that predicted by standard risk factors, ranging from 2-fold for scores up to 100, increasing to 11-fold for scores above 1000 [34]. A calcium score of 0 associated with a very high event-free probability [35].
  - No studies that show whether a strategy of CAC screening improves cardiovascular outcomes. However, studies have demonstrated enhanced risk factor management with CAC information [36].
- **Coronary computed tomography angiography (CTA):**
  - Noninvasive coronary CT angiography in patients with low to intermediate pretest probability of CAD and symptoms suggestive of myocardial ischemia
  - Highly accurate for detection of obstructive CAD in native coronary arteries and bypass grafts
  - Specificity reduced in patients with severe coronary artery calcification and in obesity
- **Detection of noncalcified plaque:** Among symptomatic patients, non-calcified plaque is a common finding. Noninvasive characterization of the plaque morphology and quantification by CT may identify patients with greater vulnerability for subsequent acute coronary syndromes.
- **Coronary blood flow:** Computational FFR, an emerging technique that allows data from resting coronary CT angiographic images to evaluate coronary lesion physiologic significance [37].

Comparison Between Various Imaging Stress Tests: Echo, Stress Nuclear Myocardial Perfusion Imaging, CMR

- Diagnostic performance of both stress echo and stress nuclear myocardial perfusion imaging is quite comparable.
- Several recent reviews have addressed the diagnostic accuracy of SPECT and 2D echocardiography [19]. A meta-analysis by O'Keefe et al. of 12 studies on exercise SPECT, including a total of 2626 patients, showed an overall sensitivity of 90% for SPECT and 81% for exercise echo ($P < 0.0001$), with a specificity of 72% and 89%, respectively ($P = 0.06$) [38].
- In the same meta-analysis by O'Keefe, there were 808 patients in all who had both stress SPECT and stress echo [38]. Comparing the two stress modalities in these patients, the sensitivity was slightly higher for SPECT, but it did not reach statistical significance. Conversely, the specificity was slightly but insignificantly higher by stress echo.

- Stress testing using CMR is not widely available and is restricted to pharmacological stress testing using adenosine, regadenoson, or dobutamine.
- CT angiography is accurate in detection of obstructive CAD, but it is unclear if it adds significantly to evaluation using stress echo or stress nuclear myocardial perfusion imaging in patients with suspected CAD. In the PROMISE trial [39], value of CT angiography was compared to functional imaging (67% SPECT MPI) for assessment of outcomes. Despite initial report of non-inferiority of CTA, critical review of the paper identified CTA was associated with substantially greater downstream invasive testing and revascularization without improvement in cardiac outcomes.

Augmented Stress Test of Choice

- Sensitivity and specificity of stress echo and stress nuclear myocardial perfusion imaging are comparable with slightly better sensitivity of SPECT and slightly better specificity of echo.
- Substantially greater incremental prognostic value is associated with SPECT and PET MPI.
- Compared to ECG using the Duke treadmill test (−10 to +4, 2.5% HCE) in intermediate-risk groups, prognostic value of radionuclide SPECT MPI is reported to be substantially greater than exercise ECG (23×) and stress echocardiography (8×), [40].
- Decision about the use of these two comparable diagnostic methods should be made based on local availability and expertise in each medical center and the importance of assessing prognosis and response of ischemic heart disease to lifestyle, medical, and revascularization therapies.
- In the institutions where expertise is high in both technologies, one test may be chosen over the other depending on whether the clinical goal is optimizing risk stratification, assessment of medical, lifestyle and revascularization therapies, and decisions regarding treatment thresholds for medical and revascularization interventions rather than diagnosis.
- SPECT may be preferred over stress echo in patients with conditions that make establishment of an echocardiographic window technically difficulty, for example, patients who are very obese, have chest wall deformities, or have lung disease (e.g., COPD).
- Pharmacologic vasodilator stress SPECT or PET MPI with regadenoson is the most widely used pharmacologic stress agent and may be preferred over dobutamine stress echocardiography to enhance efficiency, comfort, and safety in patients with prior history of atrial fibrillation, ventricular tachycardia, or other history of arrhythmia.
- High-efficiency cadmium zinc telluride SPECT myocardial perfudion imaging (HE CZT SPECT MPI) has been demonstrated to optimize diagnostic assessment of CAD in morbidly obese patients, a special population which may not be suitable to assess by other modalities.

- Estimates of quantitative MPR (myocardial perfusion reserve) is now FDA approved (June 2016) with HE CZT SPECT MPI as well as PET MPI can help select patients with multivessel CAD in whom CABG provides better hard event outcomes compared to medical therapy and PCI.
- Stress-only HE CZT SPECT imaging provides ultra-low-dose radiation exposure (as low as 1–2 mSv) at a cost comparable to exercise echocardiography with contrast.
- Radiation is often considered to be a disadvantage; but no clinical adverse consequence of diagnostic low-level radiation has ever been reported in BEIR VII* reports on radiation hormesis (improved survival) of very low-level radiation [20].
- No DNA damage response markers have been identified at <7.5 mSv exposure with SPECT MPI [21, 22].

Invasive Coronary Angiography and Heart Catheterization

- Selective catheterization of the coronary arteries with angiographic assessment of the lumen remains the "gold standard" for the detection of obstructive coronary artery disease.
- Left and right heart catheterization in conjunction with coronary angiography gives very useful additional information for evaluation of patients with coronary artery disease, valvular heart disease, pulmonary hypertension, cardiomyopathy, and other illnesses. Figure 8.2 shows commonly used angiographic views.

Indications for Coronary Angiography [40]

- Symptomatic patients with high pretest probability of coronary artery disease.
- Suspected acute coronary syndrome, especially high-risk patients based on TIMI risk score.
- ST elevation MI for possible primary percutaneous coronary intervention (PCI).
- Intermediate- or high-risk findings on noninvasive diagnostic testing.
- Evaluation of valvular heart disease, pulmonary hypertension, and unexplained cardiomyopathy – usually done in combination with hemodynamic measurements obtained during right and left heart catheterization.
- Generally, it should not be performed as an initial evaluation for asymptomatic, low-risk patients, as part of preop evaluation before noncardiac surgery in patients with good exercise capacity, or prior to low risk noncardiac surgery.
- A consensus document of Appropriate Use Criteria (AUC) reviews all indications for cardiac catheterization [40].

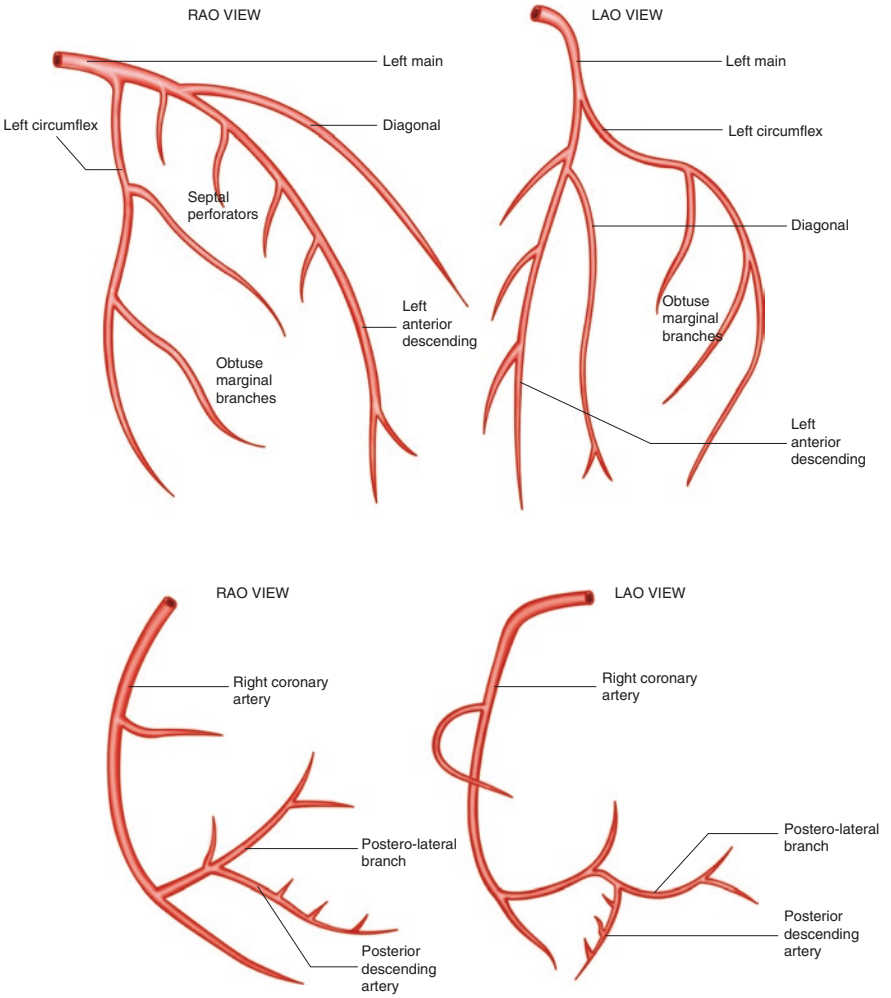

Fig. 8.2 Cath projections and angiographic views

Contraindications for Coronary Angiography

- No definite contraindications.
- Assess benefits versus risks from the procedure before referring the patient for this procedure.

Complications of Coronary Angiography [41]

- Major complications uncommon after coronary angiography (less than 1%):
  - Death (0.10–0.14%)
  - Myocardial infarction (0.06–0.07%)
  - Stroke (0.07–0.14%)
- Procedural complications (1–3%) include access site-related retroperitoneal and anterior hematomas, pseudoaneurysms, and other bleeding events.
- Radial access results in lower rate of vascular complications.
- Contrast-induced nephropathy (CIN)—limit amount of contrast in patient with CKD.
- A consensus document from the American College of Cardiology and Society for Cardiac Angiography and Intervention addresses best practices for minimizing the risk but adequate patient preparation before cardiac catheterization [41].

Patient Preparation for Coronary Angiography [42]

- NPO for 2 h (liquids) and 6 h (solids).
- Stop warfarin 3–5 days before procedure—INR goal <1.8 (<2.2 for radial access).
- Stop novel oral anticoagulants 1–2 days before.
- Adjust insulin and oral hypoglycemic agent dose for NPO status.
- Hold metformin 24 h before the procedure and 48 h after the procedure; restart after checking Cr.
- Consider holding ACE inhibitor and ARB if abnormal GFR.
- Hydrate patients at risk of contrast-induced nephropathy (CIN) with normal saline (1–1.5 ml/kg/h for 3–12 h before procedure and 6–24 h after procedure). N-Acetyl cysteine is no longer recommended.
- If contrast-induced allergy, premedicate with 50 mg prednisone 13, 7, and 1 h before procedure and 50 mg diphenhydramine 1 h before the procedure. Shellfish allergy does not predict contrast reaction and need not be premedicated.
- Baseline ECG.
- Labs – CBC, BMP, and PT/INR if on warfarin and β-hCG for women of childbearing age.
- Bridging with low-molecular-weight heparin is necessary in patients with mechanical prosthetic mitral valves.

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Chapter 9
Preoperative Evaluation and Management of the Patient Prior to Non-cardiac Surgery

Peter A. Bleszynski, Heather Shenkman, and Hanna Z. Mieszczanska

Introduction

- We are frequently asked to "clear the patient" for the surgery.
- The purpose of preoperative evaluation is not to clear patients for a surgery but to perform an individualized assessment of current medical status, cardiac risk posed by the planned operation, and recommend strategies to minimize adverse events in a rational manner.
- The lack of adequately controlled or randomized clinical trials to define the optimal evaluation strategy has led to the proposed algorithm based on collected observational data and expert opinion.
- The aging patient population and advances in surgical techniques have resulted in the performance of an increasing number of complex surgeries in patients with higher likelihood of significant cardiovascular disease.
- Our goal is to identify the risk and determine how the risk can be reduced or eliminated.

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H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7_9

Statistics

- 200 million adults undergo major non-cardiac surgery each year [1].
- >10 million adults worldwide have a major cardiac complication within 30 days after non-cardiac surgery [1].
- More than 40 million people undergo non-cardiac surgical procedures in the United States annually; ~1/3 have prior CAD [2].
- 0.5–1% (200,000–400,000) people have perioperative cardiac complications [2].
- Patients who survive postop MI are twice as likely to die in the following 2 years compared to patients with uneventful surgical procedures [3].

Approach to Perioperative Cardiac Assessment

- Current guidelines propose a stepwise approach to perioperative cardiac assessment (Fig. 9.1).

Step 1: How Urgent Is the Surgery?

- If surgery is emergent or urgent, proceed with surgery [4].
- If not emergent or urgent, evaluate further.

Definitions of Urgency and Risk of Surgery [5]

- **Emergency procedure:** When life or limb is threatened if not in the operating room (OR) within 6 h. When there is time for no or very limited or minimal clinical evaluation.

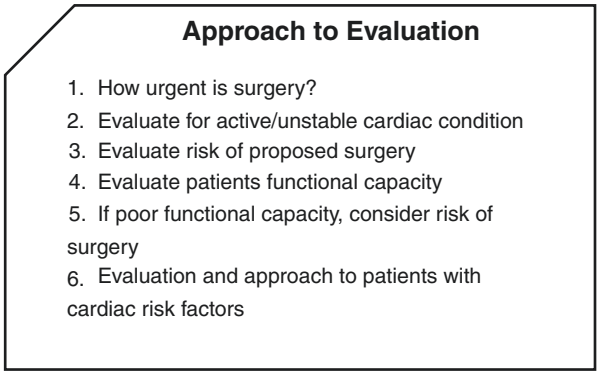

Fig. 9.1 Approach to preoperative evaluation. Adapted from ESC/ESA [4]

- **Urgent procedure:** When life or limb is threatened if not in the OR between 6 and 24 h. There may be time for a limited clinical evaluation.
- **Time-sensitive procedure:** A delay of >1 to 6 weeks to allow for an evaluation and significant changes in management will negatively affect outcome. Most oncologic procedures would fall into this category.
- **Elective procedure:** Could be delayed for up to 1 year allowing for full clinical evaluation and intervention if needed.
- **Low-risk procedure:** When the combined surgical and patient characteristics predict a risk of a major adverse cardiac event (MACE) of death or myocardial infarction (MI) of <1%.

Step 2: Evaluate for Active or Unstable Cardiac Conditions

- The following conditions place patients at high risk for surgery and should be treated prior to surgery:
  - Myocardial infarction (MI) within 30 days or unstable angina
  - Acute heart failure
  - Symptomatic or hemodynamically significant valvular disease
  - Significant arrhythmias (SVT or VT, third-degree AV block, Mobitz II, high-degree AV block, symptomatic bradycardia)

Step 3: Evaluate Surgical Risk According to Type of Surgery or Intervention

- If intermediate- or high-risk surgery, proceed to evaluate functional capacity [4, 5].
- High-risk surgery (>5% risk of MACE):
  - Aortic
  - Major or peripheral vascular
  - Intraperitoneal/intrathoracic with large fluid shifts (i.e., liver transplant, Whipple)
- Intermediate-risk surgery (1–5% risk of MACE):
  - Intraperitoneal
  - Intrathoracic
  - Orthopedic
- Low-risk surgery (<5% risk of MACE):
  - Superficial
  - Breast
  - Eye
  - Endoscopy

Functional Capacity
Excellent (>7 METS)
Outdoor work (shovel snow etc.)
Recreation (ski, basketball, jog/walk)
Moderate (4-7METS)
Walk at 4 mph without stopping
Recreation (dance, roller-skate)
Outdoor work (garden, rake, weed)
Poor (<4 METS)
Wash dishes, dust, make bed
Shower/dress without stopping

A functional capacity >4 METs can generally proceed to surgery without further evaluation and acceptable risk. If the surgery is deemed high-risk, and the functional capacity is <4 METs, additional testing may be warranted if it would modify management [8].

Fig. 9.2 Functional capacity [4]

Step 4: Evaluating Patient Functional Capacity

Functional Status Assessment/Functional Capacity

- Functional status, example in Fig. 9.2, is a good predictor of perioperative and long-term cardiac events.
- Expressed in metabolic equivalents (1 MET = 3.5 mL O_2 uptake/kg per min, which is the resting oxygen uptake in a sitting position).
- Poor functional capacity (<4 METs) is a maker for increased perioperative and long-term cardiac events, and patients with poor functional capacity may need to be considered for noninvasive cardiac risk assessment before elective surgery.
- In general, patients with minor or no clinical predictors of risk and with moderate or excellent functional capacity (4–6 METS) can safely undergo most types of non-cardiac surgery with low risk of cardiac complications.

Step 5: Evaluating Surgical Procedure Risk If Functional Capacity <4 METS

- If it is determined that additional testing will modify perioperative care, assess clinical risk factors when functional capacity is <4 METS [4].

Step 6: Evaluation and Approach to Patients with Clinical Risk Factors

Initial Evaluation

- Clinical risk factors [4]:
  - Ischemic heart disease

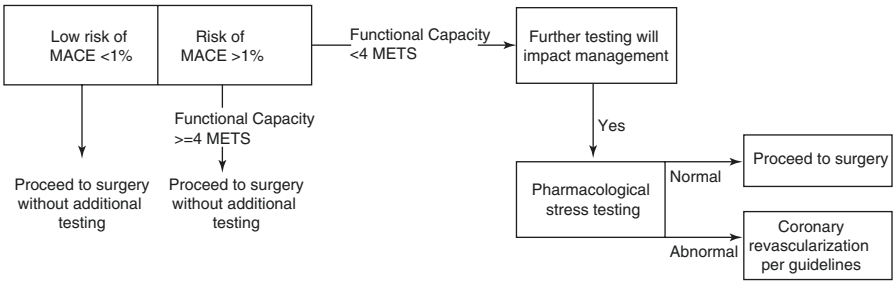

Fig. 9.3 Approach to patients with clinical risk factors. Adapted from the ACC [5]

  - Heart failure
  - Stroke or TIA
  - Renal dysfunction (Cr >2 mg/dL or Cr clearance <80 mL/min/1.73 m^2)
  - Diabetes mellitus requiring insulin therapy
- Figure 9.3 shows how to proceed with evaluation based on risk of MACE.

Cardiac Risk with Surgery

Different non-cardiac operations are associated with different risks of MACE:

- The lowest-risk operations are generally those without significant fluid shifts and stress.
- Some operations can have their risk lowered by taking a less invasive approach.
- It is difficult to assign a specific risk of a MACE to each specific surgery.
- An operation in an emergency situation is understood to increase risk.

Surgical Risk Estimate According to Type of Surgery or Intervention [4]

Risk % is an estimate of 30-day risk of cardiovascular death and myocardial infarction that considers only the specific surgical intervention, without considering the patients' comorbidities.

Calculating Risk

Revised Cardiac Risk Index (RCRI) [6, 7]

- Easier to use and more accurate than the Original Cardiac Risk Index/Goldman Index

- Identifies six independent variables that predict an increased risk for cardiac complications
- Calculates a patient's risk for perioperative cardiac complications with number of variables that are present

1. History of ischemic heart disease
2. History of congestive heart failure
3. History of cerebrovascular disease (stroke or transient ischemic attack)
4. History of diabetes requiring preoperative insulin use
5. Chronic kidney disease (creatinine >2 mg/dL)
6. Undergoing suprainguinal vascular, intraperitoneal, or intrathoracic surgery (high-risk surgery)

Risk for cardiac death, nonfatal myocardial infarction, and nonfatal cardiac arrest: 0 predictors = 0.4%, 1 predictor = 0.9%, 2 predictors = 6.6%, ≥3 predictors = >11%

NSQIP MICA Risk Calculator [7, 8]

- The NSQIP database was used to determine risk factors associated with intraoperative/postoperative myocardial infarction or cardiac arrest (MICA).
- Five factors were identified as predictors of MICA:
  - Type of surgery
  - Dependent functional status
  - Abnormal creatinine
  - American Society of Anesthesiologists' class
  - Increased age

NSQIP Surgical Risk Calculator [7]

- The calculator includes 20 patient-specific variables (i.e., age, sex, body mass index, dyspnea, previous MI, functional status) plus the surgical procedure [9].
- It calculates the percentage risk of a MACE, death, and eight other outcomes. This risk calculator may offer the best estimation of surgery-specific risk of MACE and death.

RCRI vs. NSQIP

- RCRI study systematically monitored perioperative troponin measurements; NSQIP did not.
- NSQIP study defined MI based on EKG changes alone [3].
- Without cardiac biomarker screening, more than half of perioperative MIs are undetected.
- NSQIP may underestimate cardiac risk compared to RCRI [10].

MACE Risk [8]

- Perioperative cardiac events are secondary to thrombosis or oxygen/demand mismatch.
- Most events are demand-mediated ischemia in the setting of a surgical stress response and anesthesia (i.e., tachycardia, bleeding, hypotension, severe HTN, and hypoxia).
- The increased stress during surgery also increases the risk of plaque rupture and thrombus formation [4].
- If perioperative risk for MACE is <1%, generally no further testing is required.
- If perioperative risk for MACE is >1%, determine functional capacity.

Beta Blockers and Biomarkers

Perioperative Beta Blockade

- Perioperative beta blocker therapy can reduce cardiovascular events but may be offset by an increased risk of perioperative stroke and no evidence of mortality benefit [11].
- The effectiveness of perioperative beta blockade in patients undergoing cardiac surgery remains controversial.
- Beta blockers should be continued perioperatively in those patients already on beta blockers.
- Initiation of beta blocker therapy in the following situations may be reasonable:
  - For patients with intermediate- or high-risk ischemia on stress testing
  - In patients with three or more RCRI risk factors [12]
- If beta blockers are to be initiated before surgery, they should be initiated more than 1 day before the operative procedure, as initiation less than 1 day before surgery may be harmful.

Brain Natriuretic Peptide (BNP)

- Preoperative measurement of NT-proBNP or BNP can improve risk estimation [3].
- Elective surgery: Order NT-proBNP or BNP before surgery if age >65 or 18–64 with history of CAD, CVD, PVD, CHF, severe PHTN, or severe valve disease [10].

Troponin

- Most perioperative MIs occur within 48 h after non-cardiac surgery.
- Analgesic medications can mask ischemic symptoms [3].

- Asymptomatic MIs similarly increase 30-day postoperative mortality.
- Asymptomatic troponin elevations not defined as MIs increase 30-day postoperative mortality [3].
- Emergency, urgent, or semi-urgent surgery: Order troponin postop (48–72 h) for age ≥65 or 18–64 with history of CAD, CVD, PVD, CHF, severe PHTN, or severe valve disease [10].
- Elective surgery and NT-proBNP ≥300 mg/L or BNP ≥92 mg/L or BNP unavailable: Order troponin postoperatively (48–72 h) [10].

Noninvasive Cardiac Testing (EKG/ECHO/Stress Test)

EKG

- Obtain in symptomatic patients or those with known coronary heart disease, significant arrhythmia, peripheral arterial disease, cerebrovascular disease, or other significant structural heart diseases, undergoing intermediate- and high-risk surgery [5].
- A routine EKG is not useful for asymptomatic patients undergoing low-risk surgery.
- EKG should be performed within 3 months of the surgical procedure. The EKG provides important prognostic information (i.e., arrhythmias, pathological Q waves, LV hypertrophy, ST depressions, QTc interval prolongation, and bundle branch blocks) [5].
- A baseline EKG is an important resource which can be used as a comparison in case potential cardiac complications occur perioperatively.

Echocardiogram

- An echocardiogram is not indicated as part of the routine preoperative evaluation.
- Perform an echocardiogram in those patients who independent of the surgical procedure have indications for an echocardiogram [4]:
  - Assessment of a new murmur
  - Dyspnea or heart failure of unknown cause
  - Evaluation of known valvular heart disease
- Reduced left ventricular systolic function or severe valvular heart disease correlates with worse postoperative outcomes.

Stress Testing

- A stress test is not part of the routine preoperative evaluation.
- Stress testing (stress echocardiography or radionuclide MPI) is reasonable to perform if:

  - There is otherwise a reason independent of the surgical procedure to perform the test (i.e., new exertional chest pain).
  - A patient is undergoing a high-risk procedure with unknown or poor functional capacity, and the results will change management [5]

Invasive Cardiac Testing

- There is not enough data to suggest use of cardiac catheterization to screen patients prior to non-cardiac surgery.
- There are no randomized controlled trials to support percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) to reduce perioperative cardiovascular events.
- Patients in the CARP trial that underwent coronary revascularization prior to elective vascular surgery had no short-term benefit or significant effect on long-term survival [13].
- Prophylactic coronary revascularization exclusively to reduce perioperative cardiac events is not recommended, even in patients undergoing elective elevated-risk surgery [8].
- Cardiac catheterization should be performed if there is an indication independent of the upcoming surgical procedure (i.e., patient with symptoms of ACS).
- If revascularization is indicated clinically, then consideration should be made to place a BMS versus a DES, as a shorter amount of time of DAPT is required, as a BMS will form endothelium faster.
- Revascularization will delay non-cardiac surgery, based on need for dual antiplatelet therapy after PCI.

Clinical Risk Factors

Coronary Artery Disease (CAD)

- The prevalence of cardiovascular disease, cerebrovascular disease, and diabetes mellitus is higher in patients aged ≥55, which increases the risk of MACE for non-cardiac surgery [5].
- MACE after non-cardiac surgery is often associated with prior CAD events.
- Patients who have been evaluated in the past 2 years with either invasive or non-invasive techniques with favorable findings → need no further ischemic workup if they have been free of cardiac symptoms.
- Patients who are functionally active and asymptomatic post CABG within 6 months have a low likelihood of perioperative cardiac events [4].
- After an MI, patients should wait at least 60 days before undergoing elective surgery [5].

Heart Failure

- Patients with clinical heart failure (HF) are at high risk for perioperative MACE [8].
- Active HF is included in many cardiac risk stratification indexes.
- HF is a greater risk factor than CAD for perioperative MACE [14].
- Thirty-day post-mortality rates: nonischemic HF (9.3%), ischemic HF (9.2%), and stable CAD (2.9%) [8].
- Survival after surgery with a LVEF ≤29% is significantly worse than for those with a LVEF >29% [5].
- One study showed a 63% increased risk of mortality in those aged ≥65 with HF.
- Diastolic dysfunction with and without systolic dysfunction is associated with significantly higher rates of MACE, prolonged hospital length of stay, and higher rates of postoperative HF [8].
- Similar perioperative management is recommended with preserved ejection fraction as those with reduced ejection fraction, with emphasis on general clinical status, volume overload, and increased levels of natriuretic peptides [4].
- Preoperative natriuretic peptide levels independently predict cardiovascular events in the first 30 days after vascular surgery [5]; therefore the assessment of natriuretic peptides should form part of a routine preoperative evaluation when cardiac dysfunction is known or suspected [4].
- With newly diagnosed severe systolic heart failure, it is recommended that non-urgent surgery be deferred >3 months to improve left ventricular (LV) function and LV remodeling [4].

Valvular Heart Disease

- Significant valvular heart disease increases cardiac risk for patients undergoing non-cardiac surgery.
- Patients with clinically suspected moderate or greater degrees of valvular stenosis or regurgitation should undergo preoperative echocardiography if:
  - No prior echo within 1 year, or a there is a significant change in clinical status or physical examination since last evaluation [5].
  - Evaluation of concurrent CAD is also warranted.
  - Valvular intervention before elective non-cardiac surgery is effective in reducing perioperative risk when patients meet standard indications for valvular intervention [5].

Aortic Stenosis (AS)

- AS is the most common valvular disease.
- Non-cardiac surgery can be safely performed in asymptomatic patients with even severe aortic stenosis, with appropriate hemodynamic monitoring [5].

- Severe AS (valve area <1.0 cm^2) increases perioperative mortality from 1.6 to 13% [5].
- Postoperative MI was almost three times as frequent in patients with aortic stenosis than in those without (3.0% vs. 1.1%) in one study [8].
- Hypotension and tachycardia can result in decreased coronary perfusion pressure, development of arrhythmias or ischemia, myocardial injury, and cardiac failure [5].
- In symptomatic patients, surgical or transcatheter aortic valve replacement (AVR) should be considered prior to elective surgery if time permits.
- Consider balloon aortic valvuloplasty in patients that are high risk, have contraindications for AVR, or have severe symptomatic aortic stenosis and require urgent major non-cardiac surgery [4, 15].

Mitral Stenosis

- Patients with nonsignificant mitral stenosis (valve area >1.5 cm^2) and asymptomatic patients with significant mitral stenosis (valve area >1.5 cm^2) and systolic pulmonary artery pressure <50 mmHg are low risk for perioperative MACE [4].
- Risk of MACE is elevated in asymptomatic patients with significant mitral stenosis and systolic pulmonary artery pressure >50 mmHg and in symptomatic patients. If time permits, consider valvular intervention [4].
- Perioperatively, it is important to maintain intravascular volume to ensure adequate cardiac output without excessive rises in left atrial pressure and pulmonary capillary wedge pressure that could precipitate acute pulmonary edema [5].

Aortic and Mitral Regurgitation

- Left-sided valvular regurgitation is better tolerated than stenotic valvular disease [5].
- Consider a pulmonary artery catheter to monitor afterload and prevent hypotension.

Arrhythmias and Conduction Disorders

- Clinically stable patients with a history of atrial fibrillation generally do not require modification of medical management or special evaluation other than adjustment of anticoagulation [5].
- High-grade cardiac conduction abnormalities (e.g., complete AV block) may increase operative risk and necessitate temporary or permanent transvenous pacing [5] and may require additional evaluation with possible device placement.

Additional Risk Modification

Comorbidities

Hypertrophic Obstructive Cardiomyopathy (HOCM)

- Avoid overdiuresis since HOCM is a preload-dependent condition.
- Inotropic agents should not be used in these patients because of increased LV outflow gradient [5].

Peripheral Artery Disease

- Patients with PAD should be clinically assessed for ischemic heart disease and, if more than two RCRI risk factors are present, they should be considered for preoperative stress or imaging testing [4].

Pulmonary Vascular Disease

- Significantly increased risk of complications, mortality and morbidity, most notably cardiac and/or respiratory failure [5].
- Continue targeted therapy (i.e., phosphodiesterase type 5 inhibitors, soluble guanylate cyclase stimulators, endothelin receptor antagonists, and prostanoids) unless contraindicated or not tolerated in patients with pulmonary hypertension [5].

Renal Disease

- Identify patients who might experience perioperative worsening of renal function in order to initiate supportive measures such as maintenance of adequate intravascular volume for renal perfusion and vasopressor use [4].

Cerebrovascular Disease

- Preoperative carotid artery and cerebral imaging are recommended in patients with a history of TIA or stroke in the preceding 6 months [4].

COPD

- Optimize pulmonary function and minimize postoperative respiratory complications:
  - Smoking cessation of smoking
  - Chest physiotherapy and lung expansion maneuvers
  - Continue beta-adrenergic agonists and anticholinergic agents until the day of surgery in symptomatic COPD patients with bronchial hyperreactivity [4].

Obesity Hypoventilation Syndrome (OHS)

- Those at high risk of OHS should receive evaluation for sleep-disordered breathing and pulmonary hypertension.
- Possible preoperative use of positive airway pressure therapy, planning of perioperative techniques (anesthetic and surgical), and postoperative positive airway pressure management [4].

Medications

Statin Therapy

- Statins should be continued if a patient is already taking one.
- Perioperative initiation of statins should be undertaken for patients who would benefit from primary or secondary prevention of CVD for their long-term health.
- There is some evidence that statins reduce perioperative cardiovascular events [16].

Alpha Agonists

- Do not initiate alpha-2 agonists prior to non-cardiac surgery [5].
- POISE-2 trial:
  - Clonidine did not reduce rates of perioperative death or nonfatal MI.
  - Did increase rates of nonfatal cardiac arrest and hypotension [8].

Angiotensin-Converting Enzyme (ACE) Inhibitors/Angiotensin II Receptor Blockers

- There are no randomized controlled studies regarding ACE inhibitors on perioperative cardiac risk.
- Current American and European guidelines state that continuation is reasonable, and if held before surgery, it is reasonable to restart postoperatively when clinically feasible [5, 8].
- Canadian guidelines strongly recommend with low-quality evidence to hold ACE inhibitors/ARBs 24 h before non-cardiac surgery [10].

Antiplatelet Therapy

- Continue DAPT with recent BMS or DES on DAPT, unless the relative risk of bleeding outweighs the benefit of prevention of stent thrombosis [8].
- Those that discontinue DAPT prior to non-cardiac surgery are at higher risk for MACE (7.5%) vs. those who continue DAPT (0.3%) [17].

- Discontinuation of DAPT does not offer significant protection from hemorrhage that "is actionable" and requires diagnostic studies, hospitalization, or treatment by a healthcare professional [17].
- If DAPT is discontinued, clopidogrel should be restarted at a loading dose as soon as possible, even on the day of surgery or if postoperative bleeding has stopped.
- Reasonable to continue aspirin perioperatively in high-risk CAD or cerebrovascular disease patients without prior stent, who are already taking daily aspirin, unless the procedure has a higher bleeding risk.
- Do not initiate aspirin in patients if they have not already been taking it [8].
- The majority of perioperative MIs are secondary to demand-mediated ischemia [4].
  - Perioperative MIs need to be evaluated on a case by case basis to determine if a thrombotic event occurred and if antiplatelet therapy should be initiated.
  - Do not start antiplatelet therapy in patients without CAD and a known perioperative stress event (i.e., hypotension, tachycardia, hypoxia) consistent with demand-mediated ischemia.

Anticoagulants

- First, determine the initial indication for oral anticoagulation (OAC): for example, a patient on warfarin for a provoked deep vein thrombosis on warfarin for >6 months may no longer need OAC [18].
- If there is minimal to no risk of bleeding (cataract surgery, dermatological procedure, pacemaker/AICD placement), OAC should be continued [8, 18, 19].
- The risk of bleeding vs thromboembolism (TE) must be assessed; these rates vary by OAC indication.
- Bridging OAC increases bleeding risk:
  - Data shows a periprocedural bleeding-to-thrombosis ratio of 13:1 with bridging and 5:1 without bridging [18].
- A review of 23,000 OAC interruptions showed:
  - Periprocedural TE is low (0.53%) for unbridged OAC interruptions [18].
  - The rate of TE is 0.92% when OAC is bridged [18].
- Bridging anticoagulation:
  - When the risk of surgical bleeding is more than minimal, it may be appropriate to bridge with unfractionated heparin in patients with a mechanical aortic or mitral valve and one additional risk factor (AF, previous venous thromboembolism, LV dysfunction, hypercoagulable state) [8].
  - Timing of bridging depends on duration of action of OAC and possibility of reversing OAC [20].
  - Warfarin should be held 1–8 days prior to surgery depending on INR [20].
  - Novel oral anticoagulants, such as factor Xa inhibitors and direct thrombin inhibitors, should be held based on creatinine clearance, typically, 1–2 days prior to surgery when creatinine clearance is normal and discontinued earlier with decreased creatinine clearance.

- Atrial fibrillation:
  - Daily stroke risk is generally low off OAC.
  - Bridging therapy is recommended in nonvalvular AF with a prior stroke, embolic event, cardiac thrombus, or $CHADS_2$ score ≥4 [20].
- Mechanical valves:
  - Have a TE perioperative risk of 1% off OAC [18].
  - Low annual risk of TE (<5%) with a bileaflet aortic valve prosthesis without AF or history of TE, intracardiac thrombus, or stroke [20].
  - Moderate annual risk of TE (5–10%) with bileaflet aortic valve prosthesis with AF [20].
  - High annual risk of TE (>10%) with any mitral valve prosthesis, caged-ball, or tilting disk prosthesis, >1 mechanical valve, cardioembolic event, stroke, or TIA [20].
  - Bridging therapy is recommended with mitral valve replacement, >1 mechanical valves, non-bileaflet aortic valve replacement, or aortic valve replacement with other risk factors [20].

Non-cardiac Surgery After PCI

- 5–10% of patients with stents undergo non-cardiac surgery within 1 year of stent implantation [21, 22].
- Need to consider risk of stent thrombosis, consequences of delaying surgery, and risk of intra- and periprocedural bleeding if DAPT is continued [23].
- When coronary PCI is performed, elective non-cardiac surgery should be delayed [8]:
  - 14 days after balloon angioplasty
  - 30 days after bare-metal stent implantation
  - 180 days (at least optimally) after drug-eluting stent (DES) implantation and can be considered after 90 days for elective non-cardiac surgery [23]
- The risk of perioperative adverse cardiac events (stent thrombosis, MI, death, stent thrombosis) is largely secondary to premature cessation of DAPT and the prothrombotic state created by the surgery.
- Patients who are already receiving DAPT therapy and who are undergoing surgery that require cessation of $P2Y_{12}$ inhibitor therapy should continue aspirin if possible and restart $P2Y_{12}$ inhibitor therapy as soon as possible [23].

Cardiovascular Implantable Electronic Devices (CIEDs) [4]

- Electromagnetic interference with the patient's device may reprogram or damage CIEDs.
- The pacing function of the CIED should be changed to asynchronous pacing mode in pacemaker-dependent patients.

- Turn off implantable cardioverter defibrillators before surgery; turn back on after surgery.
- Temporary pacing and defibrillation should be available before, during, and after the surgery.
- Postoperatively, CIEDs should be interrogated and reprogrammed to the appropriate settings.

Anesthesia for Non-cardiac Surgery

Anesthetic Goals

- Prevent ischemia with:
  - Low to normal heart rate (50–80 bpm)
  - Normal to high blood pressure
  - Normal left ventricular end-diastolic volume
  - Adequate arterial oxygen content
  - Normothermia

Monitoring

- Pulmonary artery catheter may be used in select patients who are at high risk for hemodynamic compromise such as those with severe cardiomyopathy, CAD, valvular disease, shunts, or congenital heart disease.

Neuraxial Anesthesia

- In patients who are eligible for an intraoperative neuraxial anesthetic (epidural or spinal anesthesia), there is no evidence to suggest a cardioprotective benefit from the use or addition of neuraxial anesthesia for intraoperative anesthetic management [5].
- Neuraxial anesthesia for postoperative pain relief of abdominal aortic surgeries may decrease the incidence of perioperative MI [5].
- Patients receiving perioperative epidural analgesia for hip fracture may decrease the incidence of preoperative cardiac events [5].

Volatile General Anesthesia and Total IV Anesthesia

- There is no evidence to suggest a difference in MI rates for non-cardiac surgery [5].

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Chapter 10
Diagnosis and Management of Valvular Heart Disease

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Aortic Stenosis (AS)

Epidemiology

- Degenerative, calcific AS is the most common valvular heart disease in the developed world [1].
- About 7% of the population over age 65 years is affected.

Etiology [2]

- Degenerative/calcific (most common): risk factors include hypertension, hyperlipidemia, and end-stage renal disease.
- Congenital: bicuspid aortic valve.
- Rheumatic: usually accompanied by aortic regurgitation and mitral valve disease.

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© Springer International Publishing AG, part of Springer Nature 2018

H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7_10

Pathophysiology [3, 4]

- Very significant aortic leaflet calcification develops prior to outflow obstruction.
- AS causes left ventricular (LV) pressure overload, which results in concentric LV hypertrophy (LVH), a compensatory mechanism to normalize LV wall stress.
- LVH leads to increased LV end-diastolic pressure, diastolic dysfunction, and fibrosis.
- Coronary perfusion pressure diminishes due to decreased aortic pressure and LVH, causing ischemia due to demand-supply mismatch.
- Left atrial (LA) pressure rises as a result of diastolic dysfunction caused by a combination of reduced coronary perfusion, increased myocardial muscle mass, and increased extracellular myocardial collagen.
- Once compensatory mechanisms are overcome, heart failure develops.

Clinical Presentation

- While slow reduction in aortic valve area until symptoms develop is most common (0.1 cm^2/year), some patients progress at much more rapid pace [2, 5].
- Once symptoms develop, survival decreases substantially: angina (5 years), syncope (3 years), and heart failure (HF) (2 years) [2, 6] (Fig. 10.1).
- The prognosis of severe, symptomatic AS if left untreated has a worse prognosis than many metastatic malignancies (50% mortality rate at 2 years) [4].
- AS can be also occasionally associated with acquired von Willebrand disease. Specifically, Heyde's syndrome is characterized by gastrointestinal bleeding from angiodysplasia due to decreased circulating von Willebrand factor in severe aortic stenosis. Aortic valve replacement (AVR) resolves the symptoms in almost all the cases [7, 8].

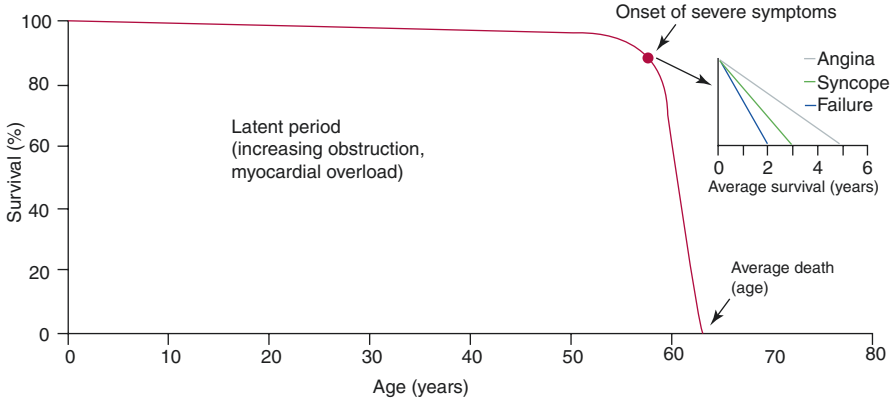

Fig. 10.1 The natural history of aortic stenosis. Reproduced with permission from Ross and Braunwald [6]

Physical Exam [2]

- Midsystolic crescendo-decrescendo murmur at the right upper sternal border that radiates to the carotid arteries, harsh and high-pitched, that increases with leg raise and squatting and decreases with Valsalva maneuver and standing. Apical murmur without radiation to the axilla is sometimes heard, known as Gallavardin phenomenon.
- Severe aortic stenosis: late-peaking murmur or diminished or absent A2 (soft S2) suggests severe AS (a normally split S2 reliably excludes severe AS), S4, LV heave.
- Pulsus parvus et tardus: delayed and diminished carotid upstroke.
- An ejection click is suggestive of bicuspid AV.

Diagnostic Studies

- Electrocardiogram (EKG): LVH, LA enlargement, left bundle branch block, and atrial fibrillation [2].
- Chest X-ray (CXR): cardiomegaly, aortic valve calcification, and pulmonary congestion [2].
- Echocardiogram: valve anatomy, pressure gradient, jet velocity, aortic valve area (AVA), ejection fraction (EF). LVH, LA enlargement, thickened aortic valve with reduced mobility, elevated aortic valve flow velocities, and reduced calculated aortic valve area. Often abnormal diastolic function with mildly elevated pulmonary artery pressure and mitral annular calcification is also present. Repeat if symptoms or signs change, also with noncardiac surgery, pregnancy, infection (infectious endocarditis), anemia, and gastrointestinal bleeding (Heyde's syndrome). Routine follow-up of asymptomatic patients with AS, normal LV systolic function, and no changes in signs or symptoms should be performed according to jet velocity [9] (Table 10.1):
- Exercise stress test: reasonable in patients with asymptomatic severe AS to confirm absence of symptoms (some patients have unconsciously reduced their physical activity to compensate for dyspnea and therefore with limited physical activity report having no symptoms), assess for blood pressure (BP) response (hypotension and <20 mmHg increase in BP predict short-term symptom development), and identify arrhythmias. Exercise stress testing is contraindicated in patients with severe, symptomatic aortic stenosis [9].

Table 10.1 Routine follow-up of asymptomatic AS

Jet velocity (m/s)	Follow-up
≥4	6 months–1 year
3–3.9	1–2 years
2–2.9	3–5 years

Adapted from 2014 ACC guidelines [9]

- Computed tomography (CT) [for transcatheter AVR (TAVR) planning]: annulus area, leaflet length, and annulus to coronary ostium distance.
- Cardiac catheterization:
  - When there is discrepancy between echo and clinical data. Transaortic pressure gradients are obtained using simultaneous LV and aortic pressure measurements and cardiac output measured by Fick or thermodilution technique. AVA is calculated using the Gorlin formula [10] (Fig. 10.2).
  - Also performed prior to AVR to evaluate coronary anatomy.
- Low-dose dobutamine stress testing: some patients with AS have lower than expected calculated aortic valve area relative to the measured transvalvular gradients. This mismatch is due to relatively low LV systolic ejection volume, typically due to either LV systolic dysfunction with a low EF or due to a small hypertrophied LV with a low stroke volume despite a normal or even hyperdynamic EF. In patients with low EF, obtaining low-dose dobutamine stress test during echocardiography (DSE) or catheterization will help differentiate fixed "anatomical" stenosis (afterload mismatch), functional stenosis (pseudostenosis), and lack of contractile reserve (Table 10.2).

Staging of aortic stenosis [9, 12] (Table 10.3):

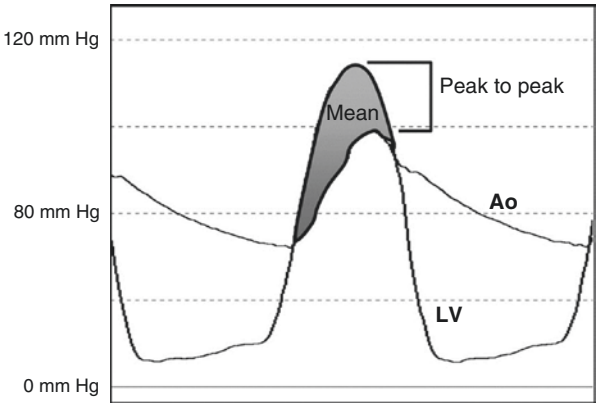

Fig. 10.2 Simultaneous LV and central aortic (Ao) pressures in a patient with aortic stenosis (by cardiac catheterization). The peak-to-peak gradient is a nonphysiological measurement because the peak pressures occur at different points in time. The mean pressure gradient (the integrated gradient between the LV and Ao pressure throughout the entire systolic ejection period) should be used to determine the severity of the aortic stenosis. Reproduced with permission from Nishimura and Carabello [10]

Table 10.2 Effects of low-dose dobutamine stress test on stroke volume, mean gradient, and AVA [9]

	Low-dose dobutamine (5 → 10 → 20 μg/kg/min)			
	Stroke volume	Mean gradient	AVA	Interpretation
Fixed "anatomical" stenosis	↑↑ (20%)	↑↑	=	Good contractile reserve, will benefit from AVR
Functional stenosis	↑↑ (20%)	=	↑	Baseline low AVA due to lack of momentum from dysfunctional LV that fails to open mild-moderately stenotic AV, does not require AVR
Lack of contractile reserve	= (or ↑ <20%)	=	=	Poor prognosis, high surgical mortality risk (~20%); however, if AVR is successful, then survival is better compared to those receiving only medical therapy [11]

Table 10.3 Classification of AS according to echocardiographic parameters

	Mean gradient (mmHg)	Jet velocity (m/s)	AVA (cm^2)
Normal	0	1	3–4
Mild AS	<20	2–2.9	>1.5
Moderate AS	20–39	3–3.9	1–1.5
Severe AS	≥40	≥4	≤1
Very severe AS	≥60	≥5	

Adapted from 2014 ACC guidelines [9]

Treatment

- Medical treatment:
  - There is currently no medical treatment proven to reduce mortality in severe symptomatic AS.
  - Treat hypertension to avoid worsening LV overload. Avoid diuretics if LV volumes are small. Prefer ACE inhibitors/ARBs [9].
  - Statins do not slow AS progression [13].
  - Vasodilatory therapy could be used with strict hemodynamic monitoring in acute management of severe decompensated AS [9].
- Aortic valve replacement (AVR) [9] (Fig. 10.3):
  - AVR is the only treatment which can improve survival of AS patients [1].
  - Symptomatic severe high-gradient AS (Class I).
  - Asymptomatic severe AS with reduced LVEF <50% (Class I).
  - Severe AS undergoing other cardiac surgery (Class I).

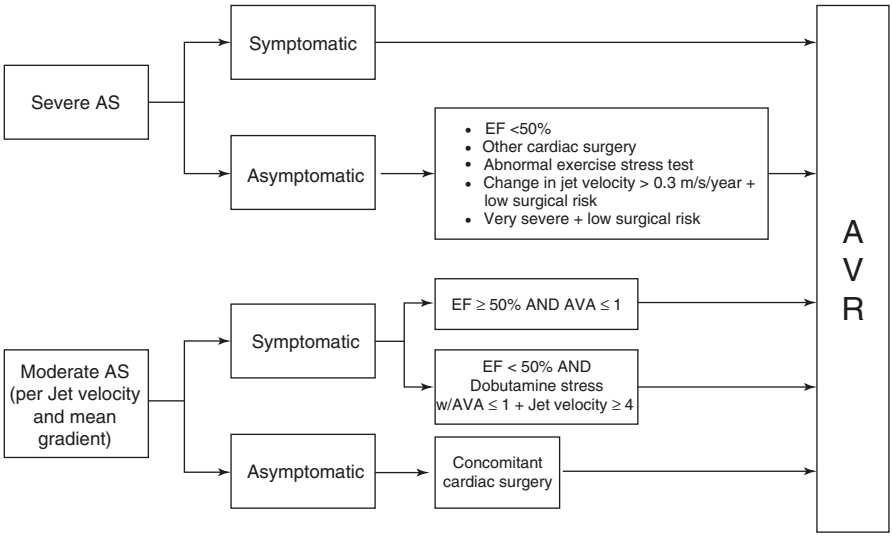

Fig. 10.3 AVR recommendations in patients with moderate and severe AS. Adapted from 2014 ACC guidelines [9]

- Asymptomatic, very severe AS and low surgical risk (Class IIa).
- Asymptomatic, severe AS and decreased exercise tolerance or an exercise fall in blood pressure (Class IIa).
- Symptomatic low-flow/low-gradient severe AS with reduced LVEF with a DSE that shows an aortic velocity ≥4.0 m/s (or mean pressure gradient ≥40 mmHg) with a valve area ≤1.0 cm^2 at any dobutamine dose (Class IIa).
- Symptomatic low-flow/low-gradient severe AS (stage D3) who are normotensive and have an LVEF ≥50% if clinical, hemodynamic, and anatomic data support valve obstruction as the most likely cause of symptoms (Class IIa).
- Moderate AS (aortic velocity 3.0–3.9 m/s) who are undergoing other cardiac surgery (Class IIa).
- Asymptomatic patients with severe AS and rapid disease progression and low surgical risk (Class IIb).

- Choice of intervention [14]:
  - The decision between surgical AVR (SAVR) versus transcatheter AVR (TAVR) depends on multiple factors, including the surgical risk, LV dysfunction, other comorbidities, patient's frailty, advanced age, and patient preferences [15] (Fig. 10.4).
  - SAVR: for symptomatic and asymptomatic severe AS with low [Society of Thoracic Surgeons (STS) predicted risk of mortality with isolated surgical AVR score <4%] or intermediate (STS risk score 4–8%) surgical risk (Class I).
  - SAVR or TAVR: for symptomatic severe AS with high risk (STS risk score >8%) for SAVR, depending on patient-specific procedural risks, values, and preferences (Class I).

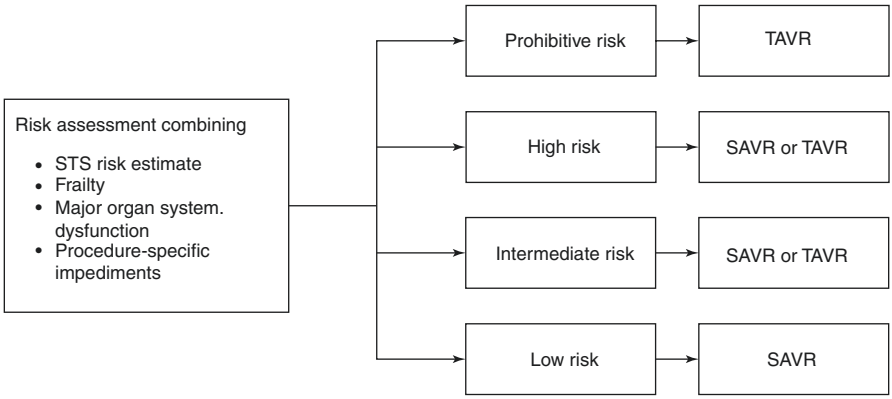

Fig. 10.4 SAVR or TAVR decision-making process in patients with severe symptomatic AS. Adapted from 2017 ACC guidelines [14]

  - TAVR: for symptomatic severe AS with prohibitive risk for SAVR who have a predicted post-TAVR survival greater than 12 months (Class I).
  - TAVR: reasonable alternative to SAVR in symptomatic severe AS with intermediate surgical risk, depending on patient-specific procedural risks, values, and preferences (Class IIa).

- Transcatheter aortic valve replacement (TAVR) [1, 5, 16, 17]:
  - Catheter-based technique is gaining more popularity for the treatment for patients with severe symptomatic AS who are considered intermediate or high risk for standard surgical valve repair.
  - Successful in 92% of the cases [16].
  - Procedure is performed by interventional cardiologists or cardiac surgeons either using transfemoral, transapical, transaxillary/subclavian, or direct transaortic approach.
  - Valve types (bioprosthetic valves with excellent flow profile): (a) self-expanding (e.g., Medtronic CoreValve Evolut series) which is re-capturable and extends from LV outflow tract (LVOT) to just above the sinotubular junction and (b) balloon-expandable (e.g., Edwards-Sapien series) which is not re-capturable and covers only the aortic valve.
  - Post-procedural management includes chronic antiplatelet therapy and prophylactic antimicrobial therapy for high-risk procedures including dental procedures that involve gingival manipulation as patients who underwent TAVR are considered "high risk" for endocarditis.
  - Absolute contraindications to TAVR include [18, 19]:
    Estimated life expectancy <12 months.
    Improvement of quality of life unlikely due to comorbidities (e.g., advanced malignancy).
    Other valvular illnesses that could be contributing to current symptoms and can only be managed surgically.

Inadequate annulus size (<18 mm).
LV thrombus or plaques with mobile thrombus involving the ascending aorta or arch.
Active endocarditis.
Elevated risk of coronary ostium obstruction.

- Balloon valvuloplasty [9]:
  - Has a limited role in the management of AS (as restenosis occurs within weeks to months).
  - Can be used as a bridge to TAVR in patients with decompensated heart failure or as a palliative procedure if patient is not a candidate for SAVR or TAVR.

Aortic Regurgitation

Epidemiology

- The prevalence of aortic regurgitation increases with age, and severe clinical regurgitation is more often observed in men than women.
- Approximately 13% of men and 8.5% of women who participated in the Framingham Heart Study were diagnosed with aortic regurgitation [20].
- It is crucial that aortic regurgitation is identified in a timely manner as these patients are at increased risk of developing heart failure and carry a higher mortality rate than the general population [21].
- Mortality rate of symptomatic patients is 10% per year [22].
- Average survival after the onset of HF is less than 2 years.
- Marked LV enlargement is associated with an increased risk of sudden death [23].

Etiology

- Valvular causes:
  - Most common cause in developing countries is rheumatic disease.
  - Most common causes in western countries are congenital (bicuspid valve) and degenerative causes (calcific degeneration).
  - Infective endocarditis.
  - Less common: systemic illnesses such as Crohn's disease, collagen vascular diseases (rheumatoid arthritis, ankylosing spondylitis, giant-cell arteritis), SLE, and anorectic drugs (fenfluramine/phentermine).
- Aortic root disease:
  - Aortic root dilation (HTN), Marfan syndrome, and syphilitic aortitis.

- Causes of acute severe AR:
  - Most frequently caused by infective endocarditis, or aortic dissection (type A).
  - May also result from procedural complications of percutaneous valve procedures.
  - Blunt trauma may result in leaflet rupture.
  - Prosthetic valve dysfunction.
  - Paravalvular regurgitation can result from complications associated with TAVR procedures [24, 25]. Moderate to severe paravalvular AR has been shown to be an independent predictor of mortality [26].

Pathophysiology

- Acute AR:
  - Pathophysiology of acute aortic regurgitation differs from chronic aortic regurgitation [9].
  - In acute aortic valve regurgitation, there is lack of time for adaptation of the LV to additional blood volume.
  - Normal ventricular size results in a marked increase in end-diastolic pressure relative to the regurgitant volume.
  - The left ventricle is not able to adequately compensate for the regurgitant volume, and excessive backward blood flow impairs forward stroke volume, which yields a decreased systolic pressure and a narrow pulse pressure.
  - Compensatory tachycardia may preserve cardiac output initially, but eventually hypotension, organ failure, and other evidence of cardiogenic shock will develop.
  - The acute volume overload on the left ventricle usually results in abrupt severe pulmonary congestion as well as a low forward cardiac output.
  - Decreased myocardial perfusion may lead to myocardial ischemia.
- Chronic AR:
  - Chronic aortic regurgitation causes both volume overload and pressure overload on the left ventricle which leads to marked ventricular dilation [25].
  - The end-diastolic volume increases, enabling an increase in the stroke volume to maintain cardiac output despite the regurgitant volume. Initially there is no significant increase in end-diastolic pressure due to the adaptation of the left ventricle to an increase in diastolic volume.
  - Eccentric LVH develops to counteract the increased wall tension and stress that result from LV dilatation (Laplace law: the wall tension is the product of the pressure inside the chamber times the radius of the chamber and the tension is inversely related to the thickness of the wall).
  - Eventually chronic volume overload leads to impairment of the LV emptying, with an increase in LV end-systolic volume and end-diastolic pressure. This

leads to further dilation of the LV and decrease of forward cardiac output (CO) and LVEF.
  - The LV volume overload is indicated by an enlarged left ventricle on echocardiography or angiography, and pressure overload is indicated by increased end-diastolic pressure [21].

Clinical Presentation

- Acute AR [27]:
  - Dyspnea due to pulmonary edema.
  - Cardiogenic shock: hypotension, diaphoresis, weakness, dizziness, and encephalopathy.
  - Chest pain.
  - Fever.
- Chronic AR:
  - Most patients are asymptomatic for a lengthy period of time.
  - Exertional dyspnea and heart failure.
  - Angina.
  - Palpitations.

Physical Exam

- Acute AR:
  - Findings such as hypotension, tachycardia, diaphoresis, pallor, and cooling of extremities that are associated with cardiogenic shock.
  - Soft early diastolic murmur; in acute AR, the diastolic murmur may be absent because of rapid equilibration of aortic and LV diastolic pressures.
  - Narrow pulse pressure.
  - Pulmonary edema can be present.
- Chronic AR:
  - Diastolic decrescendo murmur best heard at the left upper sternal border, best heard in the sitting forward position. Severity of AR correlates with duration of the murmur, not the intensity.
  - In some patients, low-pitched mid to late diastolic apical rumble (Austin-Flint murmur) is heard, possibly because of vibration of the anterior mitral leaflet as it is struck by a posteriorly directed AR jet.
  - Bounding arterial pulses.
  - The wide pulse pressure (the difference in systolic and diastolic blood pressure with a low diastolic pressure) caused by the runoff into the ventricle.

- There are many clinical signs related to wide pulse pressure: De Musset sign (head bob with every cardiac cycle), Corrigan pulse (bounding carotid pulse with rapid carotid upstroke followed by arterial collapse), Muller sign (pulsations of the uvula), Quincke pulsations (systolic flashes of capillary perfusion in the nailbeds), Duroziez sign (to-and-fro murmur over the femoral artery when partially compressed), Traube sign (pistol-shot murmur heard over the femoral artery), and LV heave.
- Soft S1 (early closure of mitral valve).
- S3 (as a manifestation of volume overload).
- Point of maximal impulse is displaced laterally and inferiorly (hyperdynamic LV apex).

Diagnostic Studies

- EKG: LVH, repolarization abnormalities, and LAD.
- Echocardiogram: first test to establish diagnosis of AR, evaluates morphology of the valve, ventricular size, LVEF, and evaluates for staging. Echocardiographic parameters [EF and LV end-systolic dimension (LVESD)] are strong predictors of outcome. Best signs of severe aortic regurgitation are large AR color Doppler vena contracta width, large LV stroke volume, significant diastolic flow reversal in the descending thoracic aorta, mitral valve preclosure, high AR CW Doppler deceleration rate, and large LV end-diastolic volume/diameter. Routine follow-up of asymptomatic patients with AR and no changes in signs or symptoms should be performed according to AR severity. If LV dilatation is noted, then follow-up should be more frequent (Table 10.4).
- CTA: to evaluate aorta size.
- Cardiac MR: can be obtained if echocardiogram results are inconclusive or suboptimal. Cardiac MR provides high accuracy measurements of LV measurements [28].
- Angiography: helps assess the severity of aortic root disease when echocardiogram is inconclusive. To evaluate coronary anatomy prior to valve surgery.

Staging of aortic regurgitation [9] (Table 10.5):

Table 10.4 Routine follow-up of asymptomatic AR

AR severity	Follow-up
Severe	Every 6–12 months
Moderate	Every 1–2 years
Mild	Every 3–5 years

Adapted from 2014 ACC guidelines [9]

Table 10.5 Classification of AR according to echocardiographic parameters

	Jet width (% LVOT)	Vena contracta (cm)	Regurgitant fraction (%)	Regurgitant volume (mL/beat)
Normal	0	0	0	0
Mild AR	<25	<0.3	<30	<30
Moderate AR	25–64	0.3–0.6	30–49	30–59
Severe AR	≥65	>0.6	≥50	≥60

Adapted from 2017 ASE guidelines [29]

Treatment

- Medical treatment:
  - Acute AR:
    Acute severe aortic regurgitation is a surgical emergency, but accurate and timely diagnosis can be difficult. Rapid diagnosis is very important, because the mortality of acute severe regurgitation is high if untreated.
    Intra-aortic balloon pump (IABP) is contraindicated in acute aortic regurgitation, because balloon inflation during diastole would worsen the severity of the acute regurgitant volume and would be detrimental to LV hemodynamics [27].
  - Chronic AR:
    In asymptomatic patients with chronic severe aortic regurgitation, monitoring for symptoms, LV size, and function is mandatory.
    There are limited data on benefits of medical management.
    Mild or moderate aortic regurgitation is usually managed conservatively, unless dilatation of the ascending aorta is an indication for surgery.
    Vasodilator therapy is not recommended routinely in patients with chronic asymptomatic AR and normal LV systolic function.
    Treatment of hypertension (systolic BP >140 mmHg) is recommended in patients with chronic AR (stages B and C), preferably with dihydropyridine calcium channel blockers or ACE inhibitors/ARBs (Class I).
    Adequate medical support for patients with concurrent heart failure or presenting with acute congestive heart failure (salt restriction, diuretics, ACE inhibitors).
- Surgical management [9] (Fig. 10.5):
  - Symptomatic patients with severe AR (Class I).
  - Asymptomatic with severe AR and impaired LV function (LVEF <50%) (Class I).
  - Asymptomatic with severe AR undergoing other cardiac surgery (Class I).
  - AVR can be considered in patients with severe AR and severe LV dilation (LVESD >50 mm, stage C2) in the setting of normal LV systolic function (Class IIa).

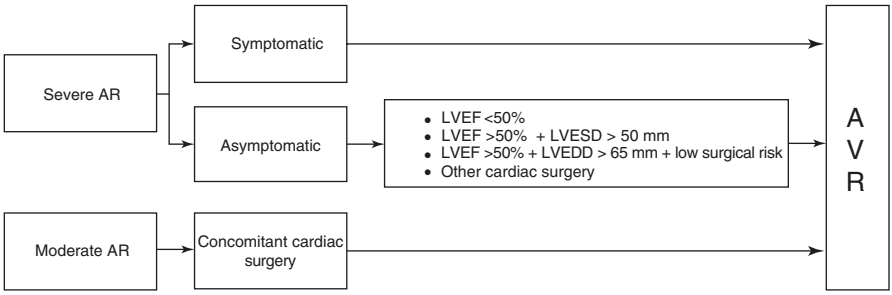

Fig. 10.5 AV replacement (AVR) recommendations in patients with progressive (moderate) and severe AR. Adapted from 2014 ACC guidelines [9]

  - AVR can be considered for asymptomatic patients with a low surgical risk in the setting of severe AR with normal systolic function and severe LV dilation (LVEDD >65 mm) (Class IIb).
  - ESC/EACTS Guidelines [30] additionally recommend surgery with significant enlargement of ascending aorta. Aortic root or tubular ascending aortic aneurysm (irrespective of the severity of aortic regurgitation).
  - Surgery is recommended, whatever the severity of AR, above certain thresholds especially in patients with Marfan syndrome (maximal aortic diameter >50 mm) or those with bicuspid valves (maximal aortic diameter >50 mm in the presence of bicuspid valve with additional risk factors [FH of aortic dissection or coarctation) or >55 mm for all other patients [30].

- Transcatheter aortic valve replacement (TAVR):
  - Currently under investigation for patients with pure AR. A recent study reported device success of 71 and 72% in patients with pure native severe AR and failing bioprosthetic surgical valve presenting with pure AR, respectively [31].

Mitral Stenosis (MS)

Epidemiology

- Isolated MS is twice as common in women as in men [2].
- The vast majority of cases of MS are rheumatic, which is largely seen in developing countries.
- Rheumatic changes are present in 99% of stenotic mitral valves excised at the time of mitral valve replacement [32].
- In developed countries, the most common cause of MS is rheumatic, distantly followed by calcific (in the elderly).

Etiology [2, 3, 33, 34]

- Rheumatic:
  - Approximately 10–40% of patients with rheumatic fever have cardiac involvement.
  - Up to 25% of patients with rheumatic heart disease have MS.
  - Time between initial episode of rheumatic fever and clinical evidence of mitral stenosis is variable, ranging from few years to two decades.
  - Leaflet tips are thickened, and commissures are fused and calcified, and there is and chordal fusion resulting in MS.
- Calcific: mitral annular calcification that does not involve leaflet tips.
- Congenital.
- Carcinoid disease.
- Systemic lupus erythematosus and rheumatoid arthritis.
- Mucopolysaccharidoses.

Pathophysiology [2, 3, 33]

- Repeated rheumatic fever episodes result in valvulitis with thickening at the level of leaflet tips, commissural fusion, and chordal shortening and fusion.
- Once MS develops the transvalvular pressure gradient increases. LV filling is dependent on diastole duration (tachycardia markedly elevates transvalvular gradients) and LA augmentation (the latter contributes up to 20% of the cardiac output).
- LA pressure rises and leads to increased pulmonary venous and capillary pressures. Venous stasis in the LA may lead to thrombus formation and systemic embolism.
- Pregnancy, tachycardia, anemia, infection, or the development of atrial fibrillation can precipitate the onset of symptoms.
- Right ventricular (RV) failure (that occurs due to longstanding pulmonary hypertension) causes improvement of dyspnea since it unloads the LA; however, this is a sign of end-stage and usually inoperable disease.

Clinical Presentation

- Mitral stenosis is a disease of plateaus. It can be asymptomatic for many years [3, 33].
- Progression is usually slow, with a decrease in mitral valve area (MVA) around 0.01 cm^2/year, but it is extremely variable between individuals [33–35].
- Usually early symptoms include dyspnea, fatigue, and decreased exercise tolerance [2, 32].

- Marked LA enlargement can predispose to atrial fibrillation and LA thrombus with resultant embolic events [3, 33, 34].
- Chest pain: 15% of patients. Usually indistinguishable from angina. May be caused by severe RV hypertension due to pulmonary vascular disease or concomitant coronary atherosclerosis [2].
- Hemoptysis: rupture of dilated bronchial veins due to increased LA pressure [2].
- Ortner syndrome: hoarseness can result from left recurrent laryngeal nerve compression due to (a) LA dilatation, (b) pulmonary artery (PA) dilatation, and/or (c) tracheobronchial lymph node enlargement [2].

Physical Exam [2]

- Loud S1 (unless calcific MS), opening snap (late in diastole), diastolic low-pitched, and rumbling murmur best heard at the apex.
- Severe mitral stenosis: soft S1, early opening snap (almost immediately after S2), diastolic murmur persists until end-diastole (longer murmur since it takes more time to pass though stenotic valve), and single S2. Pansystolic murmur of TR (increases with inspiration) and S3 coming from RV could be noted as well.
- A high-pitched decrescendo diastolic murmur along the left sternal border in patients with MS and pulmonary hypertension may be audible pulmonic regurgitation (Graham Steell murmur) but more often is caused by concomitant AR.
- Irregularly irregular pulse caused by atrial fibrillation.

Diagnostic Studies

- EKG: Atrial fibrillation, LA enlargement (P mitrale), right atrial enlargement, and right bundle branch block. RV hypertrophy can be present in patients with pulmonary hypertension [2].
- CXR: dilated LA and pulmonary congestion.
- Echocardiogram: valve anatomy (rheumatic mitral valves show a characteristic diastolic ballooning often referred to as "doming," "hockey stick," or "fish mouth" appearance, all of which refer to the fact that the restriction in mitral valve opening is at the commissure margin level, rather than restriction that starts at the annular leaflet attachment and progresses toward the commissure margin, as in calcific stenosis), elevated flow velocities with no "diastasis" indicating persistent LA-LV pressure gradient throughout diastole, sub-mitral thickening/fusion/foreshortening in rheumatic etiology, reduced calculated MVA, elevated PA pressure, and elevated Wilkins' score in rheumatic valves. Transesophageal echocardiogram should be done to investigate if there is a LA appendage thrombus prior to percutaneous mitral valve balloon valvuloplasty and to evaluate severity of concomitant mitral regurgitation.

- Routine follow-up of asymptomatic patients with MS, normal systolic function, and no changes in signs or symptoms should be performed according to MVA [9] (Table 10.6).
- Exercise stress assessment with Doppler or invasive hemodynamics: to evaluate the response of the mean mitral gradient and PA pressure when there is a discrepancy between resting Doppler echocardiographic findings and clinical symptoms or signs [10].
- Cardiac catheterization (Fig. 10.6): simultaneous LV and pulmonary capillary wedge pressures are measured in patients with severe symptoms and discrepant transmitral gradient and pulmonary pressure. MVA can be calculated after measuring mitral valve gradient. This method tends to overestimate transmitral gradient; however, it can be corrected if transeptal puncture is performed (allowing to measure LA pressure directly) [10]. It is also performed to evaluate for coronary artery disease in patients scheduled for valve surgery [9].

Staging of mitral stenosis [9] (Table 10.7):

Table 10.6 Routine follow-up of asymptomatic MS

MVA (cm^2)	Follow-up
<1	Every year
1–1.5	Every 1–2 years
≥1.5	Every 3–5 years

Adapted from 2014 ACC guidelines [9]

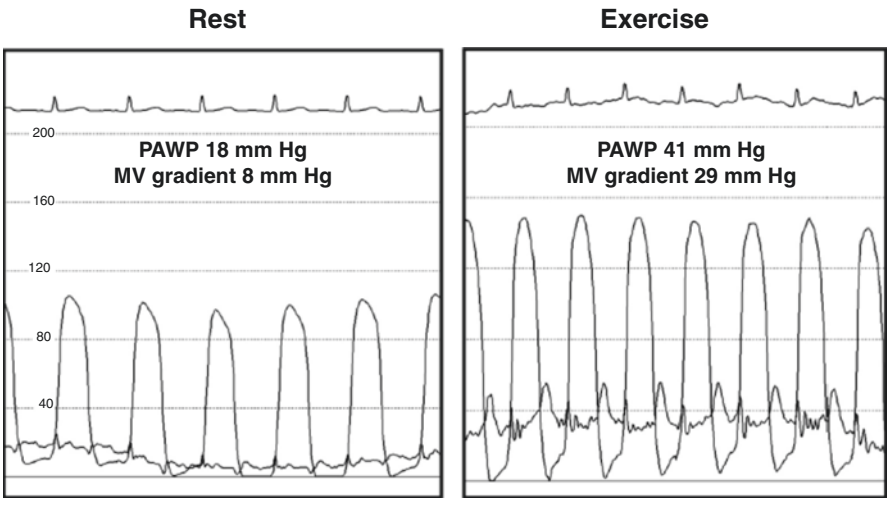

Fig. 10.6 Hemodynamic assessment of transmitral gradient at rest and after exercise. Reproduced with permission from Nishimura and Carabello [10]

Table 10.7 Classification of MS according to echocardiographic parameters

	Valve anatomy/hemodynamic consequences	Diastolic pressure half-time (ms)	MVA (cm^2)
At risk	Mild valve diastolic doming	Normal transmitral flow velocity	3–4
Progressive MS	Commissural fusion and diastolic Doming of leaflets Mild to moderate LAE	<150 ms	>1.5
Severe MS	Commissural fusion and diastolic Doming of leaflets Severe LA enlargement Elevated PA systolic pressure >30 mmHg	150–<220	1–1.5
Very severe MS		≥220	≤1

Adapted from 2014 ACC guidelines [9]

Treatment

- Medical therapy:
  - In cases of rheumatic MS, secondary prophylaxis to prevent recurrent acute rheumatic fever episode is mandatory [9, 30].
  - Patients with mitral stenosis and (a) atrial fibrillation, (b) prior embolic event, or (c) LA thrombus should be anticoagulated with vitamin K antagonists (Class I) [9, 14].
  - Novel oral anticoagulants are not approved in patients with atrial fibrillation and mitral stenosis [14, 30].
  - Heart rate control with beta-blockers or digoxin can be beneficial in patients with mitral stenosis and atrial fibrillation with rapid ventricular response to allow adequate LV diastolic filling [9].
  - Nitrates and diuretics can transiently improve symptoms [30].
- Percutaneous mitral balloon valvuloplasty (PMV):
  - Transcatheter-based procedure that separates commissural fusion. It is the procedure of choice in rheumatic MS (calcific MS does not have commissural fusion; therefore, it is not indicated) [9, 30].
  - Wilkins score predicts PMV success. It is based on four echocardiographic variables (leaflet mobility, thickening, calcification, subvalvular apparatus thickening). Each variable is assessed and scored (1–4 points, maximum total 16 points). The sum of ≤8 is associated with optimal outcomes ("pliable valve"). Scores ≥12 associated with poor outcomes [36].
  - Indications for balloon valvuloplasty [9, 30] (Fig. 10.7):
    Symptomatic severe MS and favorable valve morphology (Class I).
    Asymptomatic very severe MS and favorable morphology (Class IIa).
    Asymptomatic severe MS patients and favorable morphology who have new onset atrial fibrillation (Class IIb).

Symptomatic progressive MS if there are significant hemodynamic changes (PCWP >25 mmHg or mean mitral valve gradient >15 mmHg) during exercise (Class IIb).
Symptomatic (NYHA III–IV) severe MS patients who have a suboptimal valve anatomy and are not candidates for surgery or at high risk for surgery (Class IIb).

– Contraindications to balloon valvuloplasty [9, 30]:
Moderate to severe MR, LA appendage thrombus, concomitant coronary, or valvular disease requiring surgical repair.

- Mitral valve surgery:
  – Repair, commissurotomy, and valve replacement [9] (Fig. 10.7):
  Symptomatic (NYHA III–IV) severe MS who are not at high risk for surgery and who are not candidates for or who have failed previous PMBC (Class I).
  Severe MS who undergo cardiac surgery for other indications (Class I).
  Symptomatic (NYHA III–IV) severe MS who undergo cardiac surgery for other indications (Class IIa).
  Progressive MS who undergo cardiac surgery for other indications (Class IIb).

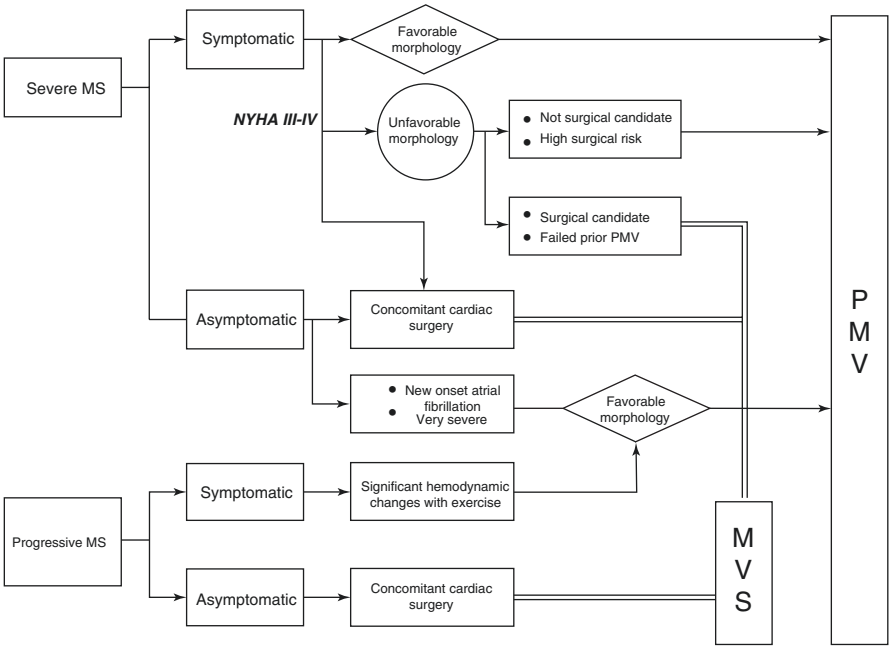

Fig. 10.7 MV valvuloplasty (PMV) or surgery (MVS) recommendations in patients with progressive and severe MS. Adapted from 2014 ACC guidelines [9]

Severe MS with recurrent embolic events despite adequate anticoagulation—with excision of the LA appendage (Class IIb).
Patient with atrial fibrillation may undergo surgical Maze procedure during the operation (Class IIa).

Mitral Regurgitation

Epidemiology

- Mitral regurgitation is the second most common valve lesion (next to aortic stenosis) in the USA and seen in approximately 2% of the population [37].
- Mitral regurgitation affects more than two million people in the USA [38].

Etiology [2, 3]

- Most common causes of MR in western countries are degenerative (primary myxomatous disease, primary flail leaflets, annular calcification), representing 60–70% of cases, followed by ischemic mitral regurgitation (20%) [38].
- Most common cause in the developing world is rheumatic heart disease.
- According to the Carpentier classification (Table 10.8) in type II lesions, the MR jet is directed in opposite direction the pathologic leaflet (anterior MVP-posterior jet; posterior MVP-anterior jet).

Table 10.8 Mechanisms of MR according to the Carpentier classification

	Primary (organic)			Secondary (functional)	
	Type I	Type II	Type IIIa	Type I	Type IIIb
	Normal valve movement	Excessive movement	Restrictive movement (in diastole)	Normal valve movement	Restrictive movement (in systole)
Non-ischemic	Endocarditis (perforation) Degenerative (annular calcification) Congenital (cleft leaflet)	Degenerative (billowing/flail leaflets) Endocarditis (ruptured chordae) Traumatic Rheumatic	Rheumatic Iatrogenic (radiation, drugs) Inflammatory (lupus, eosinophilic endocardial disease, endomyocardial fibrosis)	Cardiomyopathy (annular dilatation) Myocarditis LV dysfunction	
Ischemic	–	Ruptured papillary muscle	–	Functional ischemia	

Adapted from Enriquez-Sarano et al. [38]

Pathophysiology

- Acute MR:
  - The acute presentation of the mitral regurgitation is related to the timing and degree of regurgitant volume.
  - The increased atrial volume from the back-flow results in sudden increase in preload to the left ventricle, decreased afterload, and increased stroke volume and EF.
  - However, due to the severity and acute development of mitral regurgitation, there is diminished forward flow from the left ventricle and decreased LA compliance resulting in hemodynamic compromise and conditions such as pulmonary edema and cardiogenic shock [39].
- Chronic MR:
  - Patients with chronic mitral regurgitation are usually asymptomatic, especially during the early stages of this condition. The increasing preload is accommodated by increased LV volumes and correspondingly increased stroke volume allows for a normal or near normal forward LVOT stroke volume, despite a high regurgitant volume. LVEF is usually maintained or even elevated until end stages. Eventually, the increased stress on the ventricle results in progressive remodeling of myocardium that at some point becomes irreversible. Left ventricular decompensation is suggested if there is depressed LV function (EF <50%) and increased LV diastolic pressure [39].

Clinical Presentation [2]

- Acute MR:
  - Acute dyspnea, orthopnea associated with tachycardia, hypotension, and pulmonary edema. High index of suspicion is needed to recognize it.
- Chronic MR:
  - Can remain asymptomatic until patients present with exertional dyspnea, reduced exercise tolerance [33], or decompensated heart failure (pulmonary edema).
  - Orthopnea and paroxysmal nocturnal dyspnea may develop as MR progresses.
  - Long-standing severe MR may cause pulmonary hypertension, with symptoms of RV failure.
  - Atrial fibrillation can occur as a consequence of LA enlargement.
  - Thromboembolism, hemoptysis, and right heart failure are less common.

Physical Exam [2]

- Acute MR:
  - Tachycardia, hypotension, and pulmonary edema.
  - Early systolic murmurs are typical of acute MR (decrescendo murmur). However, the murmur may not be heard (in 50% of patients) with acute severe MR (due to equalization of pressures between LV and LA).
- Chronic MR
  - PMI is large, hyperdynamic, and displaced laterally.
  - Brisk carotid upstroke.
  - Holosystolic, blowing high-pitched murmur heard best in the apex in the left lateral decubitus position. It radiates to the left axilla.
  - Systolic thrill.

Diagnostic Studies [2]

- EKG: LA enlargement, LV hypertrophy, and atrial fibrillation.
- Echocardiogram is the gold standard for diagnosis and determining severity of MR (Class I). Usually transthoracic echocardiogram correctly grades MR severity; however, when there are discordant echocardiographic and/or clinical findings, transesophageal echocardiogram should be considered.
- Routine follow-up of asymptomatic patients with MR, with no changes in signs or symptoms, should be performed according to MR severity (Table 10.9). If LV dilatation is noted, then follow-up should be more frequent.
- Cardiac MRI: generally more accurate and reproducible for quantitating EF, regurgitant volume, and regurgitant fraction [29].

Staging of mitral regurgitation (Table 10.10):

Table 10.9 Routine follow-up of asymptomatic MR

MR severity	Follow-up
Severe	Every 6–12 months
Moderate	Every 1–2 years
Mild	Every 3–5 years

Adapted from 2014 ACC guidelines [9]

Table 10.10 Classification of MR according to echocardiographic parameters

	Vena contracta (cm)	Regurgitant fraction (%)	Regurgitant volume (mL/beat)	Effective regurgitant orifice area (cm^2)
Normal	0	0	0	0
Mild MR	<0.3	<30	<30	<0.2
Moderate MR	0.3–0.69	30–49	30–59	0.2–0.39
Severe MR	≥0.7	≥50	≥60	≥0.4

Adapted from 2017 ASE guidelines [29]

Treatment [9, 14]

1. Acute MR Treatment
   (a) Acute MR can present with findings of heart failure such as cardiogenic shock and pulmonary edema.
   (b) Treatment consists of symptomatic management while awaiting surgical intervention (such as nitroprusside).
   (c) Avoid treating tachycardia as it is a physiologic response to improve cardiac output (CO = SVR × HR).
   (d) Contrary to acute aortic regurgitation, IABP can be placed in patients presenting with acute MR prior to surgery.
   (e) Emergency MV surgery is indicated (repair is preferred).
2. Chronic MR Treatment
   (a) Medical therapy:
      - Mild asymptomatic MR can be followed clinically.
      - Medical treatment consists of managing symptoms associated with heart failure.
      - There is no therapeutic benefit of vasodilators in asymptomatic patients who are normotensive.
      - There is no evidence that medical therapy reduced the progression for need of valve surgery.

   (b) Mitral valve surgery (MVS) (Fig. 10.8):
      - Mitral valve repair is the treatment of choice for severe mitral regurgitation and offers superior long-term survival compared with mitral valve replacement [33].
      - Moderate to severe asymptomatic MR with preserved LVEF (>60%) should have surgical consultation for valvular repair/replacement (Class IIa).

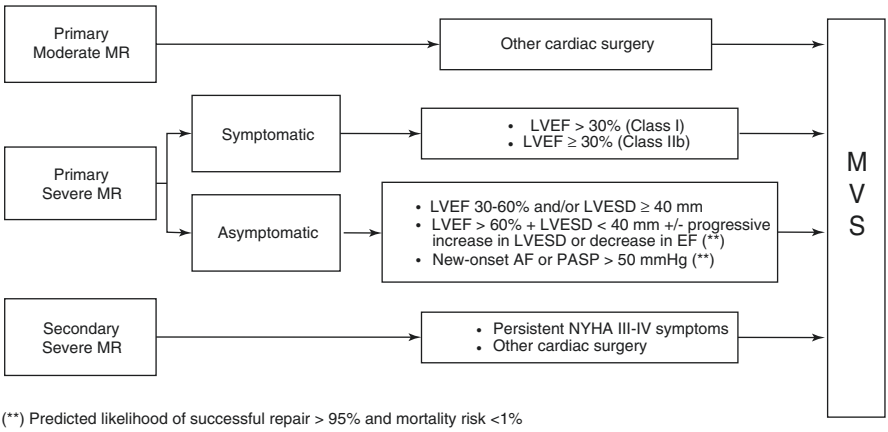

Fig. 10.8 MV surgery recommendations in patients with moderate and severe MR. Adapted from 2017 ACC guidelines [14]

- Asymptomatic patients with severe primary mitral regurgitation and pulmonary hypertension (PA systolic pressure >50 mmHg at rest) undergoing surgical evaluation should have confirmatory invasive measurements [30].
- Operative mortality in experiences centers for isolated degenerative MR is <1% prior to onset of HF or LV dysfunction [40].
- Selected patients can benefit from Cox Maze procedure for mitral regurgitation and atrial fibrillation [41].
- Surgery in the setting of moderate-severe MR and severe LV dysfunction provides improvement in symptoms; however, it is not associated with benefits in long-term survival, hospitalization rate, or LV reverse remodeling [42–44].
- Indications for surgery [14]:
  - Symptomatic chronic severe primary MR and LVEF >30% (Class I).
  - Consider surgery if symptomatic chronic severe primary MR and LVEF ≤30% (Class IIb).
  - Consider MVR in patients without prior rheumatic heart disease and have primary MR with preserved LV function with either new diagnosis of atrial fibrillation and/or pulmonary hypertension [PA systolic arterial pressure >50 mmHg (Class IIa)].
  - Asymptomatic chronic severe primary MR and LV dysfunction [LVEF 30–60% and/or LVESD ≥40 mm (Class I)].
  - Chronic severe primary MR undergoing other cardiac surgery (Class I).
  - Consider MVR for chronic severe secondary MR undergoing AVR or CABG (Class IIa).
  - Chronic moderate primary MR undergoing other cardiac surgery (Class IIa).
- Choice of intervention:
  - Repair over replacement:
    Chronic severe primary MR limited to posterior leaflet (Class I)
    Chronic severe primary MR that involves anterior leaflets or both leaflets when a successful and durable repair can be achieved (Class I).
    Asymptomatic chronic severe primary MR with preserved LV function (LVEF >60% and LVESD <40 mm) when the likelihood of a successful repair without residual MR >95% with an expected mortality <1% (Class IIa).
  - Replacement over repair:
    Chordal-sparing MVR over downsized annuloplasty repair if operation is considered for severely symptomatic patients (NYHA Class III–IV) with chronic severe ischemic MR (stage D) and persistent symptoms despite guideline-directed medical therapy for HF.

(c) Transcatheter mitral valve repair:

- The MitraClip (transcatheter mitral valve repair) is a new technology, which offers an alternative to open surgical repair or replacement via a minimally invasive route [40, 45].

- May be considered if severely symptomatic (NYHA Class III or IV) with chronic severe secondary MR (stage D) who have persistent symptoms despite receiving maximum medical therapy for HF and not candidate for surgical repair (Class IIb).
- Symptom improvement is achieved in both ischemic and non-ischemic etiologies; however, long-term effects over hospitalization or mortality rates have not been demonstrated [46–48].

Prosthetic Valves

Types of Prosthetic Valves [2, 49]

- Bioprosthetic valves: transcatheter (Edwards-Sapien or CoreValve), stented porcine xenografts (Hancock II, Mosaic), stented bovine pericardial xenografts (Carpentier-Edwards), stentless xenografts (Freestyle), stentless cadaveric homografts, and stentless autografts.
- Mechanical valves: bileaflet (On-X, St. Jude Medical Regent) or single-tilting disc (Hall) and ball-and-cage (Starr-Edwards).

Selection of Prosthetic Valves

- Shared decision between the patient and valve team, taking into account patient's values and preferences, valve durability, indications for and risks of anticoagulant therapy, age as well as potential need for future reintervention (Class I) [14].
- Valve durability: shorter in bioprosthetic valves, especially in younger patients, with the following 15-year risk of reoperation due to valve structural deterioration [50]:
  - 22% in patients 50 years old
  - 30% in patients 40 years old
  - 50% in patients 20 years old
- Risk of long-term anticoagulation [14]:
  - In patients of any age for whom anticoagulation is contraindicated, cannot be managed appropriately, or is not desired, a bioprosthesis is recommended (Class I).
  - In young patients for whom anticoagulation is contraindicated or not desired, replacement of aortic valve by a pulmonary autograft (Ross procedure) may be considered (Class IIb).
- Age considerations [14]:
  - Patients younger than 50 years: if no contraindications for anticoagulation are present, a mechanical prosthesis (AVR or MVR) is reasonable (Class IIa).

  - Patients older than 70 years: a bioprosthesis is reasonable (Class IIa).
  - Age between 50 and 70 years: either a bioprosthetic or mechanical valve is reasonable (Class IIa).

- Potential future reintervention:
  - A mechanical prosthesis may be considered in patients for whom future redo valve surgery would be at high risk (e.g., porcelain aorta or prior radiation therapy) [14, 30].
  - Patients with small aortic root size may not be candidates for future valve-in-valve interventions; therefore consider mechanical prosthesis [14].

- Other considerations:
  - A bioprosthesis should be considered in young women contemplating pregnancy [30].
  - In patients who develop mechanical valve thrombosis and require reoperation, consider using a bioprosthesis, regardless of good long-term anticoagulation control [30].

Antithrombotic therapy for prosthetic valves [14] (Table 10.11):

- Mechanical prosthesis:
  - Oral anticoagulation with vitamin K antagonists (VKA) is recommended lifelong for all patients (Class I).

Table 10.11 Antithrombotic therapy for prosthetic valves

Type of valve	INR goal	Treatment
On-X mechanical valve (AVR or MVR)	1.5–2	VKA antagonist + Aspirin (75–100 mg daily)
Mechanical AVR (bileaflet or current-generation single-tilting disc) + no risk for thromboembolism	2.5	VKA antagonist + Aspirin (75–100 mg daily)
Mechanical AVR + risk for thromboembolism (AF, previous thrombus, hypercoagulable state)	3.0	VKA antagonist + Aspirin (75–100 mg daily)
Mechanical MVR	3.0	VKA antagonist + Aspirin (75–100 mg daily)
Bioprosthetic AVR	2.5 for 3–6 months	VKA antagonist + Long-term aspirin (75–100 mg daily)
Bioprosthetic MVR	2.5 for 3–6 months	VKA antagonist + Long-term aspirin (75–100 mg daily)
TAVR	2.5 for 3 months	VKA antagonist: first 3 months Clopidogrel + aspirin: first 6 months Long-term aspirin

Adapted from 2017 ACC guidelines [14]

  - Oral direct thrombin inhibitors (dabigatran) or anti X-a agents (apixaban, rivaroxaban, edoxaban) are contraindicated (Class III).
  - Aspirin 75–100 mg daily is recommended in addition to anticoagulation with VKA antagonists (Class I).
  - Patients should achieve INR 2.5 if they have a bileaflet or current-generation single-tilting disc AVR (Class I).
  - Patients should achieve INR 3 if they have (a) a mechanical AVR and additional thromboembolic risk factors (atrial fibrillation, prior thromboembolism, LV dysfunction, hypercoagulable conditions), (b) an older-generation mechanical AVR (ball-in-cage), or (c) a mechanical MVR (Class I).
  - It is reasonable to achieve INR 1.5–2 in patients with mechanical On-X AVR with no thromboembolic risk factors who are also receiving ASA (Class IIb) [51].

- Bioprosthesis:
  - Aspirin 75–100 mg daily is reasonable in all patients with bioprosthetic AVR or MVR (Class IIa).
  - It is reasonable for patients with surgical bioprosthetic MVR or AVR at low risk of bleeding to receive anticoagulation with VKA antagonists to achieve INR 2.5 for at least 3 months and for as long as 6 months after implantation (Class IIb).
  - It is reasonable to anticoagulate with VKA antagonists (goal INR 2.5) post-TAVR patients at low risk of bleeding, at least for 3 months after implantation (Class IIb).
  - It is reasonable to use clopidogrel 75 mg daily for the first 6 months after TAVR implantation in addition to life-long aspirin 75–100 mg daily (Class IIb).

Bridging Therapy for Prosthetic Valves [14]

- Continuation of VKA with a therapeutic INR: in patients with mechanical valves undergoing minor procedures where bleeding is easily controlled (dental extraction or cataract removal) (Class I).
- Temporary interruption of VKA without bridging while INR is subtherapeutic: in patients with a bileaflet mechanical AVR and no other risk factors for thrombosis who are undergoing invasive or surgical procedures (Class I).
- Bridging anticoagulation while INR is subtherapeutic: reasonable on an individualized basis, with the risks of bleeding weighed against the benefits of thromboembolism prevention, for patients who are undergoing invasive or surgical procedures with a (1) mechanical AVR and any thromboembolic risk factor, (2) older-generation mechanical AVR, or (3) mechanical MVR (Class IIa).
- Anticoagulation reversal (fresh frozen plasma or prothrombin complex concentrate use): reasonable in patients with mechanical valves receiving VKA who require emergency noncardiac surgery or invasive procedures (Class IIa).

Evaluation and Follow-Up [9, 30, 52]

- In asymptomatic and uncomplicated patients, yearly follow-up including cardiac history and physical examination is appropriate.
- Blood tests for hemolysis should be part of routine follow-up after valve replacement, including lactate dehydrogenase, which is related to hemolysis severity.
- INR monitoring in an anticoagulant clinic is of critical importance since high INR variability is a strong independent predictor of reduced survival after valve replacement.
- An initial transthoracic echocardiogram (reporting transvalvular velocities, pressure gradients, and quantitation of valvular and paravalvular regurgitation) performed 2–4 weeks after valve implantation should be reviewed in the first postoperative visit since it will allow for an assessment of the results of surgery/intervention and will become the new baseline for comparison should complications arise.
- Repeat transthoracic echocardiogram should be obtained when there is a change in clinical symptoms or signs concerning for valve dysfunction. If acoustic shadowing does not allow proper valve evaluation, a transesophageal echocardiogram should be performed.
- In asymptomatic patients with bioprosthetic valves, it is reasonable to perform annual transthoracic echocardiogram after the first 10 years.
- Endocarditis prophylaxis is recommended for all patients with prosthetic valves before dental procedures that involve manipulation of gingival tissue, manipulation of the periapical region of teeth, or perforation of the oral mucosa.

Complications of Prosthetic Valves

- Acute prosthetic valve thrombosis [14, 30]:
  - Occurs mainly in patients with mechanical prosthesis, but there are reported cases in patients with bioprosthesis (either surgical or TAVR).
  - Prompt suspicion is required if patients present with recent dyspnea or an embolic event.
  - Urgent evaluation with transthoracic/transesophageal echocardiogram, cinefluoroscopy, or CT scan should be used to confirm the diagnosis (Class I).
  - In patients with a thrombosed left-sided mechanical prosthetic valve presenting with symptoms of valve obstruction, initial treatment with either slow-infusion low-dose fibrinolytic therapy or emergency surgery is recommended (Class I).
- Prosthetic valve stenosis [9, 14, 30]:
  - Prosthetic valves can slowly develop progressive stenosis months to years after implantation.
    In mechanical valve, stenosis could be due to chronic thrombus or pannus formation that impedes normal leaflet occluder motion.

In bioprosthetic valves, stenosis is a result of fibrosis and calcification.
Some patients have patient-prosthesis mismatch, where the implanted valve results in inadequate blood flow to meet the patient's metabolic demands, even when the valve function is normal.

  - Initial treatment with VKA: bioprosthetic valve stenosis who are hemodynamically stable and have no contraindications to anticoagulation (Class IIa).
  - Repeat valve replacement: in severely symptomatic (Class I).
  - Transcatheter valve-in-valve procedure: in patients with severe symptomatic bioprosthetic aortic valve stenosis with high or prohibitive risk of reoperation (Class IIa).

- Prosthetic valve regurgitation [14, 30]:
  - Mechanical valves:
    Surgery is indicated in patients with intractable hemolysis or HF due to severe prosthetic or paraprosthetic regurgitation (Class I).
    Medical therapy (iron supplementation, beta-blockers, and erythropoietin) is indicated in patients with severe anemia when contraindications for surgery exist.
  - Bioprosthetic valves:
    Surgery: reasonable in asymptomatic patients with severe regurgitation if operative risk is acceptable (Class IIa).
    Percutaneous repair of paravalvular regurgitation: reasonable in patients with intractable hemolysis or NYHA Class III–IV HF at high risk for surgery and have suitable anatomy for catheter-based therapy (Class IIa).
    Transcatheter valve-in-valve procedure: reasonable in patients with bioprosthetic aortic valve regurgitation at high or prohibitive risk for surgical therapy if improvement in hemodynamics is foreseen (Class IIa).

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Chapter 11
Common Adult Congenital Heart Disease Issues

Erica O. Miller and James P. Eichelberger

Epidemiology

- Advances in diagnosis, surgical techniques, and medical management have dramatically altered the survival of children born with CHD and consequently the demographics of the CHD population.
- Over the last several decades, survival to adulthood for babies born with CHD has improved to greater than 85% [1].
- Heart failure, sudden death, arrhythmias, and vascular complications account for approximately 80% of deaths in all ACHD patients [2].
- Since 1990 myocardial infarction has been the leading cause of death in patients with acyanotic CHD, emphasizing the importance of prevention and management of atherosclerotic cardiovascular disease in patients with CHD [3].
- There are more adults living with congenital heart disease than children. In 2010, there were an estimated 1.4 million adults and 1 million children with CHD in the United States [4].
- The adult CHD population is growing more quickly than the pediatric CHD population. Data from the United States are unavailable, but in Canada between 1985 and 2005, the number of children living with CHD increased by 22%, while the number of adults living with severe CHD increased by 85% [5].
- In 2004, there were 46,500 hospitalizations for cardiac and circulatory congenital anomalies, with an aggregate cost of $1.4 million [6].

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H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7_11

Access to Healthcare

- One of the most important tasks of the adult cardiology consultant providing care for patients with CHD is improving access to care (Table 11.1). For a variety of psychosocial, financial, and infrastructural reasons, many young adults with congenital heart disease become disconnected with cardiology care and often with the healthcare system.
- According to 2008 American College of Cardiology (ACC) and American Heart Association (AHA) guidelines on the management of ACHD patients, all ACHD patients, even those with simple CHD such as isolated aortic valve disease or a small atrial septal defect, should be seen at least once in an ACHD center (Class I Recommendation). However, fewer than 30% of adults with CHD are seen in a specialized ACHD center [7, 8].

Transition from Pediatric to Adult Approach to Care

- Medical transition is the process of patients moving from a pediatric system of healthcare to an adult one.
- Transition involves both the process of pediatric patients becoming adults responsible for their healthcare decisions, depending on their capacity, and transferring care to adult healthcare providers.
- Goals of the transition process include optimizing health, minimizing disruptions in care, and helping youths reach their full potential [9].
- Transition planning has demonstration improvements in medical complications, cost, quality of life, functional status, perceived health status, adherence,

Table 11.1 Summary of consultant's role in improving access to care for ACHD patients [8]

ACC/AHA guideline	Role of cardiology consultant
Academic adult cardiology and cardiac surgery centers should have access to a regional ACHD center for consultation and referral	• Be aware of regional ACHD center • Contact ACHD center for consultation • Refer patients to ACHD center
All ACHD patients should be seen at least once in an ACHD center	• Document need for follow-up with an ACHD specialist in each patient's chart • Discuss the need for follow-up with an ACHD specialist with each patient
Diagnostic and interventional procedures for adults with complex and moderate CHD should be performed at a regional ACHD center	• Refer patients to ACHD center for diagnostic and interventional procedures
Surgical procedures requiring general anesthesia or conscious sedation should be performed at a regional ACHD center by an anesthesiologist familiar with ACHD	• Refer patients to ACHD center when general anesthesia or conscious sedation is required
Patients with complex or high-risk CHD should be transferred to an ACHD center for urgent or acute noncardiac problems	• Assist primary team in transfer of patients with complex or high-risk CHD to regional ACHD center when appropriate

continuity, and patient experience in chronic illnesses such as diabetes, cystic fibrosis, and juvenile idiopathic arthritis [9].
- In 2004, it was estimated that only 48% of adolescents with CHD underwent successful transition [10].
- Cardiology consultants can improve the transition process by recommending follow-up with an ACHD specialist to the patient and healthcare team. One series demonstrated that documentation in the chart recommending follow-up with an ACHD specialist was associated with a successful transition process (odds ratio 8, 95% confidence interval 4.72–16.41) as well as patient belief that follow-up should be with an ACHD specialist [10].

Hypertension

- ACHD patients may be particularly vulnerable to the effects of hypertension due to underlying altered hemodynamics.
- Blood pressure should be monitored and hypertension treated with a similar approach as for those without CHD, with special considerations listed in Table 11.2.

Dyslipidemia

- Lipids should be monitored and dyslipidemia treated for primary and secondary prevention of atherosclerotic cardiovascular disease in patients with ACHD similar to the general population, with special considerations listed in Table 11.3.

Table 11.2 Special considerations for the management of hypertension in patients with ACHD

ACHD population	Special hypertension considerations
Single ventricle Systemic right ventricle	Particularly sensitive to increased afterload Focus on afterload reduction Consider lower blood pressure goal [11]
Marfan syndrome with aortopathy	Use beta-blockers to reduce the rate of aortic dilation [12] Add angiotensin receptor blocker as tolerated
Coarctation of the aorta	Angiotensin-converting enzyme (ACE) inhibitors can precipitate renal failure in the setting of severe coarctation of the aorta due to restricted renal artery flow mimicking renal artery stenosis [11] Intervention (surgical or percutaneous) is recommended for coarctation with peak-to-peak gradient greater than or equal to 20 mmHg or at lower gradients with radiological evidence of significant collaterals [8]
Cyanotic heart disease	Risk for nephropathy Use caution with ACE inhibitors, angiotensin receptor blockers, and diuretics (Class I, Level of Evidence C) [11]
Eisenmenger physiology	Risk for increased right-to-left shunting with systemic vasodilators Use hydralazine with caution [11]

Table 11.3 Special considerations for the management of dyslipidemia in patients with ACHD [11]

ACHD population	Special dyslipidemia considerations
Transposition of the great arteries with a history of arterial switch operation	Coronary arteries have been translocated Translocated coronary arteries have abnormal vasoreactivity and increased intimal thickness Consider earlier and aggressive lipid management due to higher risk for coronary events (Class IIa, Level of Evidence: C)
Coarctation of the aorta	Increased risk for coronary events through unclear mechanisms, potentially hypertension or primary vasculopathy Consider earlier and more aggressive lipid management

Table 11.4 Indications for cardiac transplantation in patients with CHD [13]

New York Heart Association functional class IV HF not amenable to palliative or corrective surgery
Severe symptomatic cyanotic heart disease not amenable to palliation
Post-Fontan procedure with refractory HF, persistent protein-losing enteropathy, and/or plastic bronchitis despite optimal medical and surgical therapy
Pulmonary hypertension with the potential risk of developing fixed, irreversible elevation of pulmonary vascular resistance (PVR) that could preclude heart transplantation in the future

Heart Failure and Transplantation

- Unfortunately, medications demonstrating improved outcomes in non-ACHD patients with heart failure have not shown the same benefits in ACHD patients.
- Patients with moderate to complex CHD and heart failure should be managed by ACHD specialists (Class I, Level of Evidence: C) [11].
- Indications for cardiac transplantation in CHD patients are listed in Table 11.4.
- ACHD patients have longer transplant waitlist times than patients without CHD [14].
- When compared with non-ACHD heart transplant patients, ACHD heart transplant patients have higher 1-year mortality but lower 5- and 10-year mortality when adjusted for 1-year mortality [14].

Arrhythmias

- Arrhythmias are a major cause of morbidity and mortality in the ACHD population.
- ACHD patients may have arrhythmias related to their underlying anatomy, procedures, or both.
- Intra-atrial reentrant tachycardia (IART), including typical atrial flutter and often unusual circuits, is the most common arrhythmia in adults over the age of 40 years with CHD. Since atypical flutter is common and can have different flutter rates and flutter wave morphologies, it may be mistaken for sinus rhythm, so a high index of suspicion is needed [11].

- The more common arrhythmias and associated native and surgical anatomy are reviewed in Table 11.5.
- The most important step in management of arrhythmias in patients with ACHD is referral to an ACHD center for expert consultation in necessary further evaluation, medical management, and catheter and surgical interventions.
- Patients with ACHD are generally considered to be at higher risk for thromboembolic complications of atrial fibrillation, so anticoagulation is recommended even in the absence of traditional stroke risk factors such as those represented in the CHADS2VASC scoring algorithm. Warfarin is generally used since direct acting oral anticoagulants have not been well studied in patients with ACHD.
- Other guidelines for management of arrhythmias in ACHD patients are listed in Table 11.6.

Table 11.5 Trends in arrhythmia occurrence among patients with CHD [11]

Arrhythmia	At-risk population
Intra-atrial reentrant tachycardia (IART) or atrial flutter	Mustard or Senning repair for D-transposition of the great arteries (TGA) Fontan procedure for single ventricle physiology Atriotomy for atrial septal defect (ASD) or tetralogy of Fallot (TOF)
Atrial fibrillation	Mitral valve disease Congenital aortic stenosis (AS) Palliation procedure for single ventricle physiology
Ventricular tachycardia (VT)	TOF Ventriculotomy Ventricular septal defect (VSD) patch Congenital AS D-TGA or L-TGA Severe Ebstein's anomaly Single ventricle physiology Pulmonary arterial hypertension
Atrioventricular (AV) block	L-TGA Atrioventricular septal defect

Table 11.6 ACC/AHA guidelines for the management of arrhythmias in patients with ACHD [8, 11]

Class I
1. Effective anticoagulation (generally with warfarin) is recommended in older ACHD patients with sustained atrial fibrillation, whether or not those patients meet the usual criteria for anticoagulation of patients with atrial fibrillation in acquired heart disease (e.g., CHADS2VASC score) (Level of Evidence: C) [11]
Class IIa
1. It is reasonable to recommend the use of an implantable cardioverter defibrillator for any patient who has had a cardiac arrest or experienced an episode of hemodynamically significant or sustained VT (Level of Evidence: C) 2. Pacemaker implantation can be beneficial in ACHD patients with bradyarrhythmias and may be helpful in overdrive pacing in patients with difficult-to-control tachyarrhythmias (Level of Evidence: B) [8]
Class IIb
1. Pacemaker implantation may be beneficial for asymptomatic adult patients with resting heart rates of less than 40 beats per minute or abrupt pauses in excess of 3 s (Level of Evidence: C) [8]

Table 11.7 ACC/AHA guidelines for the evaluation and management of liver disease [11]

Class I
1. Serial evaluation of liver function should be performed for all patients with a history of previous palliation with the Fontan procedure (Level of Evidence: B)
2. All ACHD patients with a history of previous surgical palliation of CHD before 1992 should undergo screening for hepatitis C (Level of Evidence: B)
3. There is an increased frequency of gallstones and need for cholecystectomy in ACHD, especially in the cyanotic and Fontan populations. Vigilance should be high for diagnosis (Level of Evidence: B)

Liver Disease

- Patients with right-sided heart failure are at risk for congestive hepatopathy.
- Patients with a history of Fontan palliation procedure are at risk for liver disease including cirrhosis. The mechanism for this is not clearly defined but may include hypoxia, low cardiac output, perioperative insults, and elevated central venous pressures [11].
- Additional guidelines for liver disease are listed in Table 11.7.

Hyperviscosity

- Patients with cyanosis develop secondary erythrocytosis as a physiologic compensation mediated by erythropoietin to improve tissue oxygenation.
- Typically, patients with cyanosis develop a new equilibrium with a higher hematocrit and are considered compensated, especially if they are iron replete. Other patients have decompensated erythrocytosis with rapidly increasing hematocrit and symptoms of hyperviscosity (Table 11.8) [15].
- Symptoms of hyperviscosity include headache, fatigue, dizziness, visual disturbances, paresthesias, irritability, myalgias, anorexia, loss of concentration, and muscle weakness.
- Volume depletion can mimic and worsen symptoms of hyperviscosity and must be ruled out and treated.
- The symptoms of iron deficiency are also similar to those of hyperviscosity, and iron deficiency also worsens hyperviscosity due to decreased oxygen carrying capacity and increased rigidity of iron-deficient microspherocytes [15].
- ACC/AHA guidelines for the use of phlebotomy are listed in Table 11.9.
- Phlebotomy is only recommended for symptomatic hyperviscosity as frequent phlebotomy increases the risk of stroke for reasons that are poorly understood, as well as iron deficiency.
- Phlebotomy may also be considered in select patients undergoing noncardiac surgery who are at significantly increased risk of bleeding, as phlebotomy may decrease perioperative bleeding risk.
- Phlebotomy is performed by withdrawing blood and replacing the removed volume with isotonic saline [16].

Table 11.8 Compensated and decompensated erythrocytosis

Compensated erythrocytosis	Decompensated erythrocytosis
Stable hematocrit	Unstable, increasing hematocrit
Iron replete	Iron deficiency may be present
Absent or mild hyperviscosity symptoms	Hyperviscosity symptoms present

Table 11.9 ACC/AHA guidelines for the use of phlebotomy in patients with cyanotic CHD [8]

Class I
Therapeutic phlebotomy is indicated for: • Hemoglobin >20 g/dL and hematocrit >65% • Symptoms of hyperviscosity: headache, increasing fatigue, or others • Absence of dehydration or anemia/iron deficiency (Level of Evidence: C)
Class III
Repeated routine phlebotomies are not recommended due to the risk of iron depletion, decreased oxygen carrying capacity, and stroke (Level of Evidence: C)

Preoperative Risk Assessment

- While patients with CHD were not excluded from the major perioperative risk assessment studies from which the revised cardiac risk index (RCRI) and the National Surgical Quality Improvement Program (NSQIP) were derived, CHD is not specifically addressed in either model [17, 18]. One series demonstrated increased risk of death, perioperative cardiac arrest, myocardial infarction, stroke, respiratory complications, renal failure, sepsis, venous thromboembolism, perioperative transfusion, and reoperation in young adults aged 18–39 years with a history of prior heart surgery who were then undergoing noncardiac surgery, as compared with those without a history of prior heart surgery [19].
- Overall rates of complications are likely relatively low with one series including both children and adults up to age 50 years with a history of congenital heart disease reporting an overall event rate of perioperative morbidity and mortality of 5.4%. Factors associated with perioperative events in this series included cyanosis, current treatment for congestive heart failure, poor general health, and procedures performed on the respiratory or nervous systems [20]. Other features associated with increased perioperative risk are included in Table 11.10.
- In addition to consideration of these risk features, preoperative risk assessment for the ACHD patient should include the basic diagnostic tests listed in Table 11.11.
- Consultation with an ACHD expert regarding assessment of perioperative risk is also recommended [8].
- In the absence of an emergency, surgeries should be performed at an ACHD center with an anesthesiologist familiar with ACHD.

Table 11.10 CHD lesions and features associated with increased perioperative risk [8]

High risk	• Prior Fontan procedure • Primary or secondary pulmonary hypertension, especially if severe • Cyanotic CHD • Complex CHD with residual valvular dysfunction or the need for anticoagulation • New York Heart Association (NYHA) functional class III or IV • Severe systemic ventricular dysfunction (ejection fraction <35%) • Malignant arrhythmias • Severe left-sided obstructive lesions
Moderate risk	• Prosthetic valve or conduit • Intracardiac shunt • Moderate left-sided obstruction • Moderate systemic ventricular dysfunction

Table 11.11 Components of preoperative evaluation for ACHD patients [8]

• Systemic arterial oximetry
• ECG
• Chest X-ray
• Transthoracic echocardiogram
• Complete blood count
• Coagulation screen

Imaging

- Noninvasive imaging modalities for patients with ACHD include transthoracic and transesophageal echocardiography, cardiac magnetic resonance imaging (MRI), and cardiac computed tomography (CT). The benefits and limitations of each of these imaging modalities are described in Table 11.12.
- Transthoracic echocardiography is the primary imaging technique.

Pregnancy

- The recommendations for care of pregnant women with CHD are outlined in Table 11.13 [8].
- CHD is the most common type of heart disease encountered in pregnant women, and among women with CHD who become pregnant, 11% of pregnancies are affected by cardiac complications, most commonly heart failure and arrhythmias [22].
- Heart failure is related to the 30–50% increase in plasma volume that occurs in pregnancy, which is typically less well tolerated in the setting of myocardial dysfunction or obstructive lesions such as a stenotic valve.
- Arrhythmias during pregnancy are likely a result of multiple factors, including chamber dilation in the setting of volume overload and adrenergic receptor hyperexcitability related to estrogen and progesterone [23].

Table 11.12 Imaging modalities for patients with ACHD

Imaging modality	Benefits	Limitations
Transthoracic echocardiography (TTE)	• Define anatomy • Quantify ventricular function • Assess severity of valvular lesions • Quantify right ventricular and pulmonary artery pressure • Identify arterial and venous vascular anomalies • Assess volume status • Contrast agents help with assessment of left ventricular size and function • Agitated saline can be used to identify intracardiac or transpulmonary right-to-left shunts (ASD, patent foramen ovale, baffle leak), anomalous venous connections (e.g., persistent left-sided superior vena cava), and acquired intrapulmonary shunts (e.g., arteriovenous malformations) • Strain imaging may be helpful in identifying ventricular dysfunction	• Image quality affected by prior surgeries, obesity, and lung disease • Limited assessment of the right ventricle due to geometric shape and location • Interpretation requires expertise in both congenital and acquired heart diseases • Ultrasound contrast agents aside from agitated saline are not approved for use in patients with right-to-left shunts or bidirectional shunts • Strain imaging not uniformly available
Transesophageal echocardiography (TEE)	• Overcome some imaging limitations of TTE (e.g., obesity, lung disease) • Excellent imaging of the thoracic aorta, bioprosthetic valves, intra-atrial septum, and potential right and left atrial thrombi • Superior image resolution than TTE for identification of vegetations in the workup of endocarditis	• Invasive procedure requiring sedation • Performance and interpretation require expertise in both congenital and acquired heart diseases
Cardiac MRI	• Three-dimensional real-time imaging with high spatial and temporal resolution • Unparalleled visualization of the right ventricle • Excellent visualization of myocardium for tissue characterization (e.g., scar and fibrosis) • Can be used to quantify severity of regurgitant lesions and shunt fractions	• Local and regional expertise varies • Unable to reliably assess coronary arteries • Longer image acquisition times • Patient tolerance may be limited by claustrophobia and difficulty with breath holding • Arrhythmias affect gating and limit image quality • Patients may have metallic implants (pacemakers, surgically placed epicardial pacing leads, mechanical heart valves) making MRI contraindicated • Gadolinium contraindicated in the setting of significant renal dysfunction due to the risk of nephrogenic systemic fibrosis
Cardiac CT	• Noninvasive imaging of the coronary arteries • Qualitative LV and RV assessments for patients with inability to tolerate MRI • Faster image acquisition time	• Radiation exposure [11, 21]

Table 11.13 ACC/AHA guidelines for pregnancy management in patients with ACHD [8]

Class I
1. Patients with CHD should have consultation with an ACHD expert before they plan to become pregnant to develop a plan for management of labor and the postpartum period that includes consideration of the appropriate response to potential complications. This care plan should be made available to all providers (Level of Evidence: C)
2. Patients with intracardiac right-to-left shunting should have fastidious care of intravenous lines to avoid paradoxical air embolus (Level of Evidence: C)
3. Prepregnancy counseling is recommended for women receiving chronic anticoagulation with warfarin to enable them to make an informed decision about maternal and fetal risks (Level of Evidence: B)
Class IIa
1. Meticulous prophylaxis for deep venous thrombosis, including early ambulation and compression stockings, can be useful for all patients with intracardiac right-to-left shunt. Subcutaneous heparin or low-molecular-weight heparin is reasonable for prolonged bed rest. Full anticoagulation can be useful for the high-risk patient (Level of Evidence: C)
2. It is reasonable to consider antibiotic prophylaxis against endocarditis before vaginal delivery at the time of membrane rupture in select patients with the highest risk of adverse outcomes: prosthetic cardiac valve or prosthetic material used for cardiac valve repair and unrepaired and palliated cyanotic CHD, including surgically constructed palliative shunts and conduits (Level of Evidence: C)

Table 11.14 CARPREG risk factors for cardiac complications in pregnancy [24]

1. Prior cardiac event, including heart failure, transient ischemic attack, or stroke or arrhythmia preceding pregnancy
2. New York Heart Association Class III (marked limitation of physical activity) or IV (symptoms of heart failure at rest) or cyanosis
3. Significant obstructive lesions including mitral or aortic stenosis
4. Left ventricular systolic dysfunction with ejection fraction <40%

- Cardiac risk in pregnancy can be estimated using the CARPREG score, in which four risk factors are assessed (Table 11.14) [24].
- If no risk factors are present, the risk for adverse cardiac events during pregnancy including pulmonary edema, arrhythmia, embolic stroke, or cardiac death in a woman with known cardiac disease (CHD or acquired) is 5%. If one risk factor is present, the risk increases to 25%, and if two risk factors are present, the risk increases to 75% [24].
- The World Health Organization (WHO) has developed a well-validated strategy to quantify risk during pregnancy according to type of CHD, as described in Table 11.15 [23].
- Thromboembolism is another important risk for women with CHD during pregnancy. Two percent of pregnancies of women with CHD are affected by thromboembolic events, while these occur in only 0.5–0.1% of uncomplicated pregnancies [22]. Pregnancy is a hypercoagulable state due to decreased free protein S and increased vitamin K-dependent clotting factors. Women with CHD at particularly high risk for arterial and venous thrombosis are those with grafts, mechanical heart valves, arrhythmias, and cardiac chamber dilatation [23].

- Guidelines recommend prepregnancy counseling for women receiving warfarin to enable them to make an informed decision regarding maternal and fetal risks [8]. Continuation of warfarin during pregnancy is controversial, with some advocating avoidance since it crosses the placenta and, at doses higher than 5 mg per day and during weeks 6–12 of gestation, is associated with central nervous system teratogenicity. If used during pregnancy and vaginal delivery is planned, warfarin should be discontinued at around 36 weeks of gestation due to risk of fetal intracranial hemorrhage [25]. If enoxaparin is used in place of warfarin during pregnancy, anti-Xa levels must be followed carefully, drawn 4–6 h after injection with a goal level of 0.8–1.2 U/mL [26].
- Common cardiac medications that are generally avoided in pregnancy are angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins, and amiodarone [23].

Contraception

- Many women with congenital heart disease are not offered appropriate contraception, likely due to a combination of cardiologists' lack of familiarity with contraception and patients' incorrect perception that they may not be candidates for hormonal contraception [27]. Cardiologists as well as patients should understand that the risk for complications from pregnancy is significantly higher than the risk of contraception-related adverse events.
- Contraception should especially be emphasized for patients whose pregnancy would be very high risk, including those with Eisenmenger's syndrome, cyanotic congenital heart disease with resting oxygen saturation less than 85%, severe coarctation of the aorta, and Marfan syndrome with aortic dilation (Table 11.15).
- Other important considerations are the risk for hypertension and thrombosis with estrogen-containing contraceptives and potential drug interactions between hormonal contraceptives and cardiac medications [28].

Exercise

- Patients with CHD have lower exercise tolerance than those without CHD, but CHD patients tend to be less aware of exercise limitations [29].
- Many noncardiac factors may contribute to exercise intolerance, including deconditioning, exercise limitations during childhood, and misperceptions about exercise limitations [8].
- Given the physical and psychosocial benefits of exercise, the importance of exercise should be emphasized to all CHD patients. Patients should have an individualized exercise prescription that is updated regularly by their ACHD provider. Evidence to support specific exercise recommendations in patients with CHD is limited.

Table 11.15 WHO categories of risk for cardiac complications during pregnancy in patients with ACHD [23]

WHO Class	Risk for cardiac complications in pregnancy	Type of CHD
I	Low: risk of maternal morbidity or mortality no higher than in general population	• Uncomplicated, small, or mild: pulmonary stenosis, ventricular septal defect, patent ductus arteriosus • Successfully repaired simple lesions: atrial septal defect, ventricular septal defect, patent ductus arteriosus, total anomalous pulmonary venous return
II	Moderate: small increase in risk of maternal morbidity or mortality	• Unrepaired atrial septal defect • Repaired tetralogy of Fallot
II or III		• Hypertrophic obstructive cardiomyopathy • Marfan syndrome without aortic root dilatation
III	High: significant increase in risk of severe maternal morbidity or mortality	• Unrepaired cyanotic heart disease • Complex congenital heart disease • Marfan syndrome with bicuspid aortic valve
IV	Very high: pregnancy contraindicated due to very high risk of severe maternal morbidity or mortality	• Eisenmenger's syndrome • Cyanotic congenital heart disease with resting oxygen saturation <85% • Severe coarctation of the aorta • Marfan syndrome with aortic dilation

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- Patients with cyanosis should be advised to avoid dehydration due to risk for hyperviscosity (see "Hyperviscosity" section above).
- Patients with Marfan syndrome should be counseled to avoid high-impact activity due to the risk of aortic injury.
- Patients on therapeutic anticoagulation should also be counseled to avoid high-impact activity due to the risk of bleeding.
- Vigorous exercise should also be avoided in those at risk for sudden death, for example, patients with hypertrophic obstructive cardiomyopathy [29].

Infective Endocarditis Prevention and Evaluation

- Patients with congenital heart disease are at increased risk for endocarditis due to native valvular abnormalities and shunts including ventricular septal defect and patent ductus arteriosus, as well as surgical implantation of prosthetic material. The risk for endocarditis must be discussed with patients.
- Administration of antibiotics for endocarditis prophylaxis is reasonable for dental procedures in CHD patients with the conditions listed in Table 11.16, because these patients are at highest risk for infective endocarditis.

Table 11.16 Cardiac conditions and types of CHD with significantly increased risk for endocarditis for which administration of antibiotics for endocarditis prophylaxis with dental procedures is reasonable [8]

ACC/AHA Class IIa recommendations (Level of Evidence: B)
Previous infective endocarditis
Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
Unrepaired cyanotic CHD including palliative shunts and conduits
CHD completely repaired with prosthetic material or device, during the first 6 months after the procedure
Repaired CHD with residual defects at or adjacent to the site of repair inhibiting endothelialization

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Table 11.17 ACC/AHA guidelines for the evaluation of infective endocarditis [8]

Class I
When patients with ACHD present with an unexplained febrile illness, blood cultures should be drawn before antibiotics are administered to avoid delay in diagnosis of potential infective endocarditis (Level of Evidence: B)
Transthoracic echocardiography should be performed when the diagnosis of native valve infective endocarditis is suspected (Level of Evidence: B)
Transesophageal echocardiography should be performed if transthoracic echocardiography images or inadequate or equivocal, in the presence of a prosthetic valve or material or surgically corrected shunt or complex CHD anatomy, or to define possible endocarditis complications (abscess, valvular destruction or dehiscence, embolism, or hemodynamic instability) (Level of Evidence: B)
ACHD patients with evidence of infective endocarditis should have early consultation with a surgeon with expertise in ACHD due to potential for rapid deterioration and possible infection of prosthetic material (Level of Evidence: C)

- Endocarditis prophylaxis is not indicated for nondental procedures such as gastrointestinal endoscopy or sterile urologic procedures [8].
- In patients with CHD and fever without another clear source, clinicians must maintain a high index of suspicion for infective endocarditis. The ACC/AHA guidelines for the evaluation of infective endocarditis are listed in Table 11.17 [8].

Anatomy of CHD Lesions

- More commonly encountered acyanotic and cyanotic CHD lesions are listed in Table 11.18.
- Cyanosis is defined as concentration of deoxygenated hemoglobin greater than 5 gm/dL, which correlates with a peripheral oxygen saturation less than 85% [21].

Table 11.18 Acyanotic and cyanotic CHD lesions

Acyanotic	Cyanotic
Atrial septal defect	Tetralogy of Fallot
Patent foramen ovale	Ebstein's anomaly
Ventricular septal defect	Transposition of the great arteries
Patent ductus arteriosus	Eisenmenger's syndrome [30]
Pulmonary stenosis	
Aortic coarctation	

Atrial Septal Defect (ASD)

- An ASD allows blood to pass from the left atrium to the right atrium resulting in right ventricular volume overload and pulmonary overcirculation.
- Small defects (less than 0.5 cm in diameter) generally are not associated with significant shunting. Large defects (greater than 2 cm in diameter) often have associated large shunts [30].
- Types: ostium secundum (75%) near the fossa ovalis, ostium primum (15–20%) near the crux of the heart, sinus venosus (5–10%) near the superior or inferior vena cava, and rarely coronary sinus (less than 1%) near the ostium of the coronary sinus.
- Symptoms: dyspnea, palpitations, fatigue, exercise intolerance, and frequent pulmonary infections.
- Signs:
  - Physical examination: fixed splitting of the second heart sound on auscultation and relative pulmonic stenosis murmur secondary to increased blood flow across the pulmonic valve. Flow across the atrial septal defect does not create a murmur.
  - ECG: right axis deviation and incomplete right bundle branch block for ostium secundum ASDs and left axis deviation for ostium primum ASDs.
  - Chest X-ray: cardiomegaly secondary to right ventricular and right atrial enlargement, enlarged pulmonary artery, and increased pulmonary vascularity.
- Diagnosis is with echocardiography. Sinus venosus ASDs may be missed on transthoracic echocardiography. Agitated saline contrast echocardiography increases sensitivity for detection of ASDs. Transesophageal echocardiography may be needed.
- Cardiac catheterization may be necessary to quantify the shunt fraction.
- Indications for interventional or surgical treatment of ASDs are listed in Table 11.19.
- All types of ASDs may be repaired surgically; percutaneous repair is for ostium secundum ASDs only.
- Complications: atrial arrhythmias (atrial flutter, atrial fibrillation, sick sinus syndrome) and paradoxical embolism from venous thromboses or intravenous infusions [8, 21, 30].

Table 11.19 ACC/AHA guidelines for interventional or surgical treatment of ASDs [8]

Class I recommendation
Closure of an ASD either percutaneously or surgically is indicated for right atrial and right ventricular enlargement with or without symptoms (Level of Evidence: B)
Class IIa recommendation
Closure of ASD, either percutaneously or surgically, is reasonable in the presence of paradoxical embolism (Level of Evidence C) or documented platypnea-orthodeoxia (Level of Evidence: B)
Class IIb recommendation
Closure of an ASD, either percutaneously or surgically, may be considered in the presence of net left-to-right shunting, pulmonary artery pressure less than two thirds systemic levels, pulmonary vascular resistance less than two thirds systemic vascular resistance, or when responsive to either pulmonary vasodilator therapy or test occlusion of the defect (patients should be treated in conjunction with providers who have expertise in the management of pulmonary hypertensive syndromes) (Level of Evidence: C)
Class III recommendation
Patients with severe irreversible PAH and no evidence of a left-to-right shunt should not undergo ASD closure (Level of Evidence: B)

Patent Foramen Ovale (PFO)

- A PFO is a flap-like communication between the right and left atria and may have associated fenestrations or aneurysmal changes in the septum primum or secundum.
- Many do not consider PFO an atrial septal defect since no tissue is missing from the atrial septum but it can result in a shunt, hemodynamic consequences, symptoms, some signs, and complications similar to those of atrial septal defects.
- Found in 27% of normal hearts on autopsy [31].
- Valsalva maneuver greatly increases sensitivity of echocardiography in diagnosis of PFO. PFO is found in 5% of general population with saline contrast at rest and 25% with Valsalva (similar to prevalence in autopsy study) [32].
- Data are mixed on association between PFO and cryptogenic stroke. Risk of paradoxical embolism (RoPE) score can be used to estimate the probability that a PFO discovered in a patient with a cryptogenic stroke is incidental or pathogenic and the PFO-attributable fraction of stroke [33].
- Antiplatelet therapy is recommended for patients with stroke or transient ischemic attack (TIA) and PFO. Anticoagulation is recommended for patients with stroke, PFO, and venous thrombosis. Additional recommendations from the AHA and American Stroke Association (ASA) are listed in Table 11.20 [34].
- Invasive management such as PFO closure for patients with stroke and PFO is controversial, with recent studies showing reduction in the risk of recurrent stroke in patients treated with percutaneous PFO closure devices but an increased risk of atrial fibrillation and procedure and device-related complications [35, 36].
- The most recent American Academy of Neurology practice update recommends counseling all patients with PFO and stroke or TIA that having a PFO is common and it is uncertain if their PFO contributed to their stroke or TIA. The practice

Table 11.20 AHA and American Stroke Association (ASA) guidelines for the management of PFO in the setting of stroke [34]

Class I recommendations
For patients with an ischemic stroke or transient ischemic attack (TIA) and both a PFO and a venous source of embolism, anticoagulation is indicated, depending on stroke characteristics (Level of Evidence: A)
For patients with an ischemic stroke or TIA and a PFO who are not undergoing anticoagulation therapy, antiplatelet therapy is recommended (Level of Evidence B)
Class IIa recommendation
For patients with an ischemic stroke or TIA and both a PFO and a venous source of embolism in whom anticoagulation is contraindicated, an inferior vena cava filter is reasonable (Level of Evidence: C)
Class IIb recommendations
There are insufficient data to establish whether anticoagulation is equivalent or superior to aspirin for secondary stroke prevention in patients with PFO (Level of Evidence: B)

update also recommends against routinely offering percutaneous PFO closure to patients with cryptogenic stroke and in rare circumstances such as patients having recurrent strokes despite medical therapy, considering closure with the Amplatzer PFO Occluder [37].

Ventricular Septal Defect (VSD)

- VSD is the most common congenital heart defect in children, with many (especially muscular VSDs) closing spontaneously in childhood.
- Nomenclature has been complicated by multiple synonyms used to describe different types of VSDs, with perimembranous VSDs being the most common (80%). Muscular VSDs are next most common (20%), followed by VSDs just below the aortic valve (5%) and near the junction of the mitral and tricuspid valves (5%).
- Symptoms and signs depend on the type and size of VSD.
- Signs:
  - Physical examination: systolic murmur loudest over the left lower sternal border. Holosystolic in the setting of low right ventricular pressures and can be early systolic as RV pressure increases or with very small defects that close with muscular contraction
  - ECG: right and left or isolated right ventricular hypertrophy
  - Chest X-ray: left atrial and left ventricular enlargement with increased pulmonary vascular markings, which will all resolve if significant pulmonary arterial hypertension develops
- Complications: infective endocarditis, aortic regurgitation, and pulmonary vascular disease.
- Diagnosis is by echocardiography; typically transthoracic echocardiography is sufficient.

Table 11.21 ACC/AHA guidelines for the management of VSDs [8]

Class I recommendations
Closure of a VSD is indicated when there is a Qp/Qs (pulmonary-to-systemic blood flow ratio) of 2.0 or more and clinical evidence of LV volume overload (Level of Evidence: B)
Closure of a VSD is indicated when the patient has a history of IE (Level of Evidence C)
Class IIa recommendations
Closure of a VSD is reasonable when net left-to-right shunting is present at a Qp/Qs greater than 1.5 with pulmonary artery pressure less than two thirds of systemic pressure and PVR less than two thirds of systemic vascular resistance (Level of Evidence: B)
Closure of a VSD is reasonable when net left-to-right shunting is present at a Qp/Qs greater than 1.5 in the presence of LV systolic or diastolic failure (Level of Evidence: B)
Class IIb recommendation
Device closure of a muscular VSD may be considered, especially if the VSD is remote from the tricuspid valve and the aorta, if the VSD is associated with severe left-sided heart chamber enlargement, or if there is PAH (Level of Evidence: C)
Class III recommendation
VSD closure is not recommended in patients with severe irreversible pulmonary arterial hypertension. (Level of Evidence: B)

- Cardiac catheterization may be helpful to quantify shunting, to assess for pulmonary arterial hypertension including response to vasodilators, and to look for other lesions [8, 21, 30].
- Recommendations for VSD closure are included in Table 11.21 [8].

Patent Ductus Arteriosus (PDA)

- The ductus arteriosus is a communication between the left pulmonary artery and the descending aorta just distal to the left subclavian artery, which allows blood to bypass the lungs in the fetal circulation. It typically closes in the days following birth.
- If the ductus arteriosus remains open, there is a left-to-right shunt.
- Symptoms and signs depend on size and degree of shunting.
- Symptoms may include fatigue, dyspnea, palpitations, and those of infective endocarditis, endarteritis, and congestive heart failure.
- Signs:
  - Physical examination: widened pulse pressure, lower oxygen saturation with cyanosis or clubbing in the lower extremities, bounding peripheral pulses, continuous “machine-like” murmur loudest in the left infraclavicular area
  - ECG: left atrial and left ventricular hypertrophy
  - Chest X-ray: left atrial and left ventricular enlargement, enlarged proximal pulmonary artery, prominent ascending aorta, PDA which may be visible as an opacity at where the descending aorta and aortic knob meet
- Complications: infective endocarditis and arteritis.

- Diagnosis may be by echocardiography and often in combination with cardiac catheterization to quantify the shunt, evaluate for pulmonary arterial hypertension including response to vasodilators, and angiography to determine the size and shape of the ductus.
- Recommendations for closure of PDAs are listed in Table 11.22. Closure is often percutaneous in the cardiac catheterization laboratory and is safer for calcified PDAs. Larger PDAs or those distorted by aneurysm or prior endarteritis may need to be closed surgically [8, 21, 30].

Pulmonic Stenosis

- Pulmonic stenosis can be valvular, supravalvular, or subvalvular. Valvular is the most common, comprising 80–90% of all congenital causes of right ventricular outflow tract obstruction. There are three types of valvular pulmonic stenosis, including the most common dome-shaped form and less commonly a dysplastic, unicuspid, or bicuspid valve [8].
- Pulmonic stenosis may be associated with other forms of congenital heart disease. Valvular pulmonic stenosis is a part of Noonan syndrome, which demonstrates autosomal dominant inheritance with variable penetrance. Other features of Noonan syndrome include short stature, intellectual disability, low set ears, and webbed neck. Supravalvular pulmonic stenosis is associated with Williams syndrome, with other features including an infantile hypercalcemia, outgoing personality, intellectual disability, and a broad forehead with full cheeks.
- Many patients are asymptomatic. Symptoms, if present, may include dyspnea, presyncope, syncope, and anginal chest pain related to an enlarged pulmonary artery causing left main coronary artery compression.
- Signs:
  - Physical examination: pulmonary ejection sound ("click") that decreases with inspiration, early systolic murmur that increases with inspiration, wide splitting of S2, and signs of right heart failure that occur late

Table 11.22 ACC/AHA guidelines for PDA closure [8]

Class I recommendation
Closure of a PDA either percutaneously or surgically is indicated for left atrial and/or left ventricular enlargement or if pulmonary arterial hypertension is present or in the presence of net left-to-right shunting (Level of Evidence C) or in the setting of prior endarteritis (Level of Evidence: C)
Class IIa recommendations
It is reasonable to close an asymptomatic small PDA by catheter device (Level of Evidence: C)
PDA closure is reasonable for patients with PAH with a net left-to-right shunt (Level of Evidence: C)
Class III recommendation
PDA closure is not indicated for patients with PAH and net right-to-left shunt (Level of Evidence: C)

  - ECG: usually normal, with severe pulmonic stenosis, and may see right axis deviation, right atrial enlargement, and right ventricular hypertrophy
  - Chest X-ray: may see increased vascular fullness in the left lung base as compared with the right (Chen's sign) and dilation of the main pulmonary artery in some forms

- Complications: right ventricular failure
- Diagnosis is by echocardiography. Often transthoracic echocardiography is sufficient. In some cases, transesophageal echocardiography may be helpful to better visualize the right ventricular outflow tract. Cardiac MRI and CT may be helpful to define pulmonary artery anatomy and quantify associated lesions like pulmonic regurgitation and tricuspid regurgitation. Cardiac catheterization is rarely necessary.
- Treatment for pulmonic stenosis may be surgical or percutaneous with balloon valvotomy. ACC/AHA guidelines for management are listed in Table 11.23 [8].

Table 11.23 ACC/AHA guidelines for the management of pulmonic stenosis [8]

Class I recommendations
Balloon valvotomy is recommended for asymptomatic patients with a domed pulmonary valve and a peak instantaneous Doppler gradient greater than 60 mmHg or a mean Doppler gradient greater than 40 mmHg (in association with less than moderate pulmonic valve regurgitation) (Level of Evidence: B)
Balloon valvotomy is recommended for symptomatic patients with a domed pulmonary valve and a peak instantaneous Doppler gradient greater than 50 mmHg or a mean Doppler gradient greater than 30 mmHg (in association with less than moderate pulmonic regurgitation) (Level of Evidence: C)
Surgical therapy is recommended for patients with severe pulmonic stenosis and an associated hypoplastic pulmonary annulus, severe pulmonary regurgitation, subvalvular pulmonic, or supravalvular pulmonic stenosis. Surgery is also preferred for most dysplastic pulmonary valves and when there is associated severe tricuspid regurgitation or the need for a surgical Maze procedure (Level of Evidence: C)
Class IIb recommendations
Balloon valvotomy may be reasonable in asymptomatic patients with a dysplastic pulmonary valve and a peak instantaneous gradient by Doppler greater than 60 mmHg or a mean Doppler gradient greater than 40 mmHg (Level of Evidence: C)
Balloon valvotomy may be reasonable in selected symptomatic patients with a dysplastic pulmonary valve and peak instantaneous gradient by Doppler greater than 50 mmHg or a mean Doppler gradient greater than 30 mmHg (Level of Evidence: C)
Class III recommendations
Balloon valvotomy is not recommended for asymptomatic patients with a peak instantaneous gradient by Doppler less than 50 mmHg in the presence of normal cardiac output (Level of Evidence: C)
Balloon valvotomy is not recommended for symptomatic patients with pulmonic stenosis and severe pulmonary regurgitation (Level of Evidence: C)
Balloon valvotomy is not recommended for symptomatic patients with a peak instantaneous gradient by Doppler less than 30 mmHg (Level of Evidence: C)

Coarctation of the Aorta

- Coarctation of the aorta is a discrete narrowing of the descending aorta at the ligamentum arteriosus, which is near the origin of the left subclavian artery.
- May be associated with other congenital lesions such as bicuspid aortic valve, subvalvular aortic stenosis, VSD, and hypoplasia of the aortic arch.
- Usually asymptomatic, but patients may have headaches and leg fatigue, or with severe coarctation, there may be lower extremity claudication.
- Signs:
  - Physical examination: hypertension in the right arm (and often the left arm as well) with lower blood pressures in the lower extremities, decreased femoral pulses, brachio-femoral delay, hyperdynamic carotid pulses, continuous mammary artery murmurs if significant collaterals have developed
  - ECG: left ventricular hypertrophy
  - Chest X-ray: dilated ascending aorta, "3 sign" due to indentation at the coarctation site, notching on the underside of ribs due to collateral vessels
- Complications: systemic hypertension even after treatment, aortic dissection or rupture (not necessarily at the site of the coarctation) due to associated aortopathy, accelerated coronary artery disease, stroke, congestive heart failure, endocarditis, endarteritis, and intracerebral hemorrhage.
- Diagnosis is by echocardiography in the suprasternal notch view, with turbulent flow in the proximal descending aorta and characteristic forward flow in diastole.
- Additional imaging: every patient with coarctation, including those who have had reparative procedures, should have at least one MRI or CT scan to completely evaluate the thoracic aorta and intracranial vessels (ACC/AHA Class I Recommendation, Level of Evidence: B) [8].
- Medical management: first-line medications for the treatment of hypertension in the setting of coarctation of the aorta include beta-blockers, ACE inhibitors, or angiotensin receptor blockers (with monitoring of renal function).
- ACC/AHA guidelines for the management of coarctation of the aorta are listed in Table 11.24.

Tetralogy of Fallot

- As the name implies, tetralogy of Fallot has four components:
  - Right ventricular outflow tract obstruction
  - Right ventricular hypertrophy
  - VSD
  - Aorta that overrides the right and left ventricles (Fig. 11.1)
- Cyanosis results from right-to-left shunting across the VSD.
- There is a spectrum of severity including very mild cyanosis.

Table 11.24 ACC/AHA guidelines for the management of coarctation of the aorta [8]

Class I recommendations
Intervention for coarctation is recommended for peak-to-peak coarctation gradient greater than or equal to 20 mmHg or peak-to-peak coarctation gradient less than 20 mmHg in the presence of anatomic imaging evidence of significant coarctation with radiological evidence of significant collateral flow (Level of Evidence: C)
Choice of percutaneous catheter intervention versus surgical repair of native discrete coarctation should be determined by consultation with a team of ACHD cardiologists, interventionalists, and surgeons at an ACHD center (Level of Evidence: C)
Percutaneous catheter intervention is indicated for recurrent, discrete coarctation and a peak-to-peak gradient of at least 20 mmHg (Level of Evidence: B)
Surgeons with training and expertise in CHD should perform operations for previously repaired coarctation and long recoarctation segment or concomitant hypoplasia of the aortic arch (Level of Evidence: B)
Class IIb recommendation
Stent placement for long-segment coarctation may be considered, but the usefulness is not well established, and the long-term efficacy and safety are unknown (Level of Evidence: C)

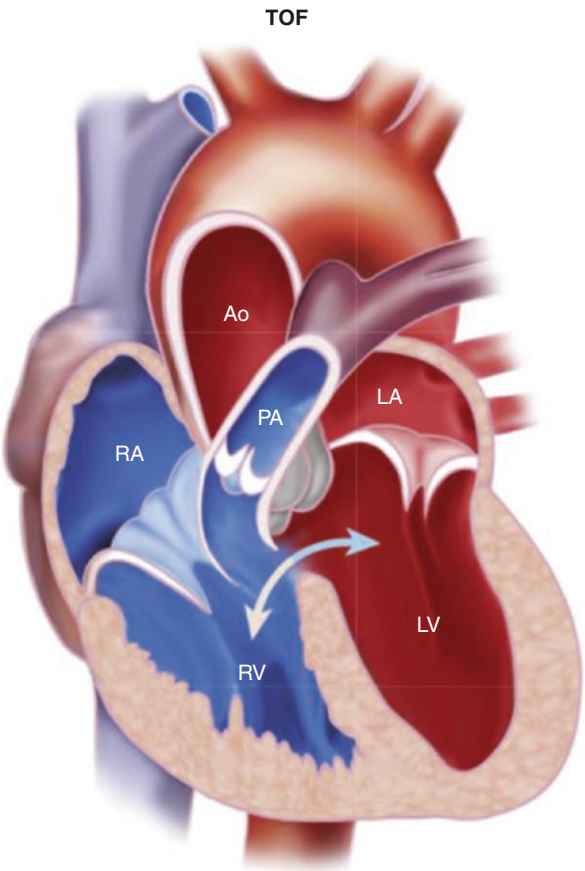

Fig. 11.1 Tetralogy of Fallot. Reproduced with permission from Otto (2013) [32]

- Associated congenital lesions include pulmonary artery hypoplasia and stenosis, ostium secundum ASD, atrioventricular septal defect (more commonly in patients with Down syndrome), right-sided aortic arch, and anomalous coronary arteries (left anterior descending artery arising from the right coronary artery and crossing the right ventricular outflow tract).
- Most patients with tetralogy of Fallot seen as adults in the United States will have had prior surgery.
- Historically, patients underwent palliative procedures to increase pulmonary blood flow, including Blalock-Taussig, Potts, and Waterston shunts (see Table 11.26).
- Currently, patients with tetralogy of Fallot undergo complete repair at a young age, including relief of right ventricular outflow tract obstruction with patch augmentation, pulmonary valve replacement, VSD closure, and surgeries for associated anomalies.
- Symptoms include cyanosis including episodic worsening ("spells") in children, dyspnea, and exercise intolerance.
- Signs:
  - Physical examination: digital clubbing, right ventricular lift or tap, systolic ejection murmur potentially with a thrill due to right ventricular outflow tract obstruction with shorter, softer murmur consistent with more severe obstruction, and a single second heart sound (due to inaudible pulmonic component)
  - ECG: right axis deviation and right ventricular hypertrophy
  - Chest X-ray: "boot-shaped" heart with an upturned right ventricular apex and concave main pulmonary artery segment

Table 11.26 Commonly encountered shunts

Shunt	Purpose	Details	Lesions treated	Years used
Blalock-Taussig	Increase pulmonary blood flow	Connect subclavian artery to pulmonary artery via direct anastomosis or with graft	Tetralogy of Fallot Pulmonary atresia Tricuspid atresia	1945–present
Glenn	Provide pulmonary blood flow without utilizing a ventricle in single ventricle physiology	Connect superior vena cava to right pulmonary artery. Classic: right pulmonary artery is no longer connected to main pulmonary artery. Bidirectional: right pulmonary artery remains connected to main pulmonary artery	Single ventricle anatomy Tricuspid atresia Double-inlet ventricle Hypoplastic left heart syndrome	Classic, 1959–1980s Bidirectional, 1985–present
Potts	Increase pulmonary blood flow	Connect descending aorta to left pulmonary artery	Tetralogy of Fallot Pulmonary atresia Tricuspid atresia	1940s–1960s
Waterston	Increase pulmonary blood flow	Connect ascending aorta to right pulmonary artery	Tetralogy of Fallot Pulmonary atresia Tricuspid atresia	1960s–1980s [32]

- Complications: ventricular tachycardia and fibrillation with increased risk of sudden death, atrial arrhythmias, severe pulmonic insufficiency following reparative surgery with resulting right ventricular failure, endocarditis, and complications of chronic cyanosis.
- Diagnosis is by echocardiography. Cardiac catheterization can provide additional hemodynamic data and define coronary and pulmonary artery anatomy [8, 21, 30].
- Repeat intervention for pulmonary regurgitation is often required, with ACC/AHA guidelines for interventions listed in Table 11.25 [8].
- Patients with tetralogy of Fallot should be followed closely by an ACHD specialist [8].

Ebstein's Anomaly

- Rare form of congenital heart disease.
- Tricuspid valve leaflets displaced into the right ventricle resulting in a dysfunctional tricuspid valve (often regurgitant, may be stenotic) as well as a small functional right ventricle (Fig. 11.2).
- Eighty percent of patients have an associated intra-atrial communication (ASD or PFO), and cyanosis results from right heart and tricuspid valve dysfunction, increased right atrial pressure, and right-to-left shunting across the intra-atrial communication.
- Approximately 25% of patients have one or more accessory conduction pathways (Wolff-Parkinson-White syndrome).

Table 11.25 ACC/AHA guidelines for surgery for adults with previous repair of tetralogy of Fallot [8]

Class I recommendation
Pulmonary valve replacement is indicated for severe pulmonary regurgitation and symptoms or decreased exercise tolerance (Level of Evidence: B)
Class IIa recommendation
Pulmonary valve replacement is reasonable in adults with previous tetralogy of Fallot, severe pulmonary regurgitation, and moderate to severe right ventricular dysfunction (Level of Evidence: B), moderate to severe right ventricular enlargement (Level of Evidence: B), development of symptomatic or sustained atrial and/or ventricular arrhythmias (Level of Evidence: C), or moderate to severe tricuspid regurgitation (Level of Evidence: C)
Surgery is reasonable in adults with prior repair of tetralogy of Fallot and residual right ventricular outflow tract (RVOT) obstruction (valvular or subvalvular) with peak instantaneous RVOT echocardiography gradient greater than 50 mmHg (Level of Evidence: C), right ventricle to left ventricle pressure ratio greater than 0.7 (Level of Evidence: C), progressive and/or severe dilatation of the right ventricle with dysfunction (Level of Evidence: C), residual VSD with a left-to-right shunt greater than 1.5:1 (Level of Evidence: B), severe aortic insufficiency with associated symptoms or more than mild left ventricular dysfunction (Level of Evidence: C), or a combination of multiple residual lesions (e.g., VSD and RVOT obstruction) leading to right ventricular enlargement or reduced right ventricular function (Level of Evidence: C)

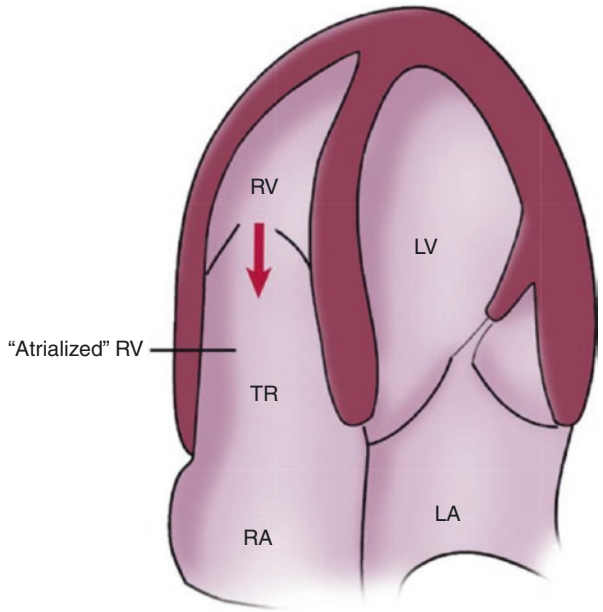

Fig. 11.2 Ebstein's anomaly. Reproduced with permission from Otto (2013) [32]

- Spectrum of severity from severe heart failure and death in the fetus or infant to minimal hemodynamic derangements with a normally functioning tricuspid valve.
- Symptoms include palpitations, syncope, dyspnea, exercise intolerance, fatigue, and right-sided congestive heart failure.
- Signs:
  - Physical examination: jugular venous pressure often normal due to large and compliant right atrium and holosystolic murmur at the left lower sternal border due to tricuspid regurgitation
  - ECG: delta wave due to preexcitation, tall and peaked ("Himalayan") P waves, right bundle branch block
  - Chest X-ray: may be normal in mild cases or demonstrate significant cardiomegaly ("wall-to-wall heart") with right atrial enlargement in severe cases
- Complications include atrial arrhythmias, sudden death, and, if an intra-atrial communication is present, paradoxical embolism and brain abscess.
- Diagnosis is by echocardiography, and transesophageal echocardiography may be required to evaluate for ASD or PFO.
- Management of Ebstein's anomaly in adults is generally aimed at prevention and treatment of complications. Tricuspid valve repair or replacement and ASD closure if present should be performed by congenital heart disease surgeons in the setting of symptoms, decreasing exercise tolerance, oxygen saturation less than 90%, paradoxical embolism, progressive cardiomegaly on chest X-ray, or progressive RV dilation or reduction of RV systolic function (Class I ACC/AHA Recommendation, Level of Evidence: B) [8].

Dextro-transposition of the Great Arteries (D-TGA)

- The aorta arises anteriorly from the right ventricle and the pulmonary artery arises from the left ventricle (see Fig. 11.3).
- Creates parallel circuits of blood flow with deoxygenated blood returning to the right heart and then being pumped into the systemic circulation via the aorta and oxygenated blood returning to the left heart and then being pumped into the pulmonary circulation. For a baby with transposition of the great arteries to survive, there must be a communication between the circuits, via a patent ductus arteriosus, patent foramen ovale, ASD, or VSD.
- Untreated, mortality is 90% by 6 months of age [30].
- Repaired patients will have had an atrial switch procedure (Senning or Mustard procedures) in the 1960s–1990s or an arterial switch procedure performed more recently.

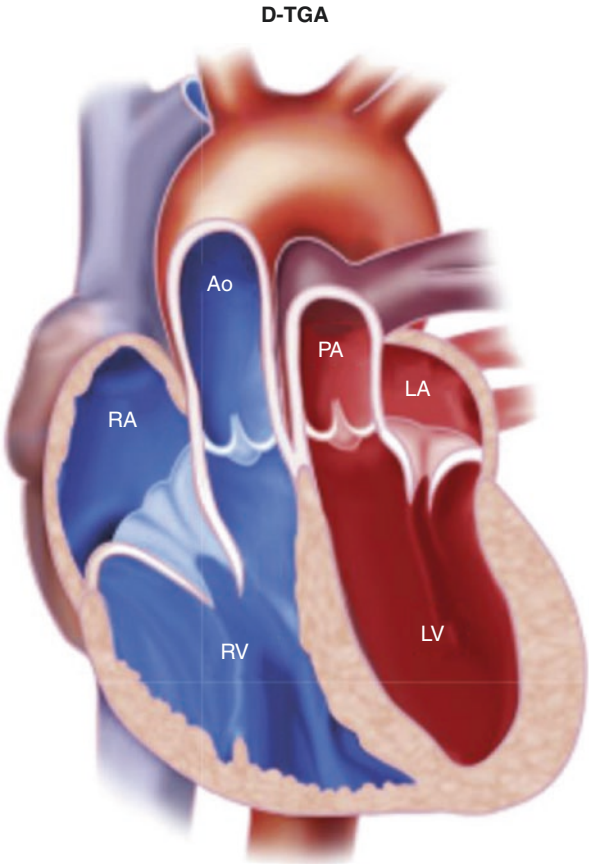

Fig. 11.3 Dextro-transposition of the great arteries. Reproduced with permission from Otto (2013) [32]

- The atrial switch procedure involves construction of intra-atrial baffles from atrial tissue (Senning) or pericardium (Mustard) to redirect systemic venous return to the left ventricle to be oxygenated in the lungs and pulmonary venous return to the right ventricle and onto the systemic arterial circulation (Fig. 11.4). The right ventricle continues to function as the systemic ventricle. Complications include congestive heart failure from systemic right ventricular dysfunction, tricuspid regurgitation, atrial arrhythmias including sinus node dysfunction, baffle leak and stenosis, and sudden death.
- Since the 1990s, patients have undergone the arterial switch procedure, which involves transecting the pulmonary artery and aorta above the semilunar valves, anastomosing the aorta to the native pulmonic valve with reimplantation of coronary arteries, and anastomosing the pulmonary artery to the native aortic valve. The arterial switch is performed in infants and has excellent long-term outcomes. Complications include coronary artery stenosis, valvular regurgitation, and stenosis in the great arteries.
- Coronary angiography is reasonable in all patients following arterial switch operation to rule out obstruction (Class IIa ACC/AHA Recommendation, Level of Evidence: C).
- Patients with D-TGA should be followed closely by an ACHD specialist [8, 21, 30, 32].

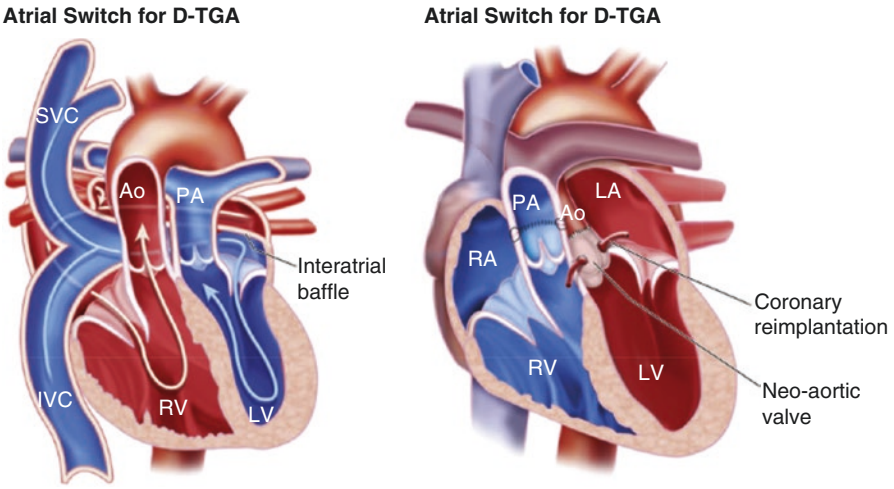

Fig. 11.4 Atrial switch operation and arterial switch operation. Reproduced with permission from Otto (2013) [32]

Eisenmenger's Syndrome

- Occurs in various forms of congenital heart disease with left-to-right shunts that result in severe and eventually irreversible pulmonary vascular disease and pulmonary arterial hypertension with subsequent reversal of shunt direction to create a right-to-left shunt.
- A murmur of childhood may disappear as left-to-right shunting ceases, which be falsely interpreted as the communication closing.
- Symptoms may not appear until late childhood or adulthood and include decreased exercise tolerance, exertional dyspnea, palpitations, hemoptysis, and symptoms of hyperviscosity (see "Hyperviscosity" section).
- Signs:
  - Physical examination: clubbing and cyanosis, palpable right ventricular heave, prominent second heart sound, right-sided fourth heart sound, clear lungs
  - ECG: right ventricular hypertrophy
  - Chest X-ray: prominent central pulmonary arteries with decreased vascular markings ("pruning")
- Complications include atrial arrhythmias, thrombosis as well as bleeding due to abnormal hemostasis, paradoxical embolization, brain abscess, and sudden death.
- Echocardiography is used to define anatomy, but cardiac catheterization is needed to quantify shunt and pulmonary vascular disease and to assess responsiveness to inhaled vasodilators.
- Treatment includes pulmonary vasodilators (due to potential to improve quality of life) and heart or combined heart and lung transplantation.
- The following exposures must be avoided: pregnancy, dehydration, moderate and severe strenuous exercise, excessive heat (hot tub or sauna), chronic high-altitude exposure (especially greater than 5000 ft above sea level), iron deficiency, air bubbles in intravenous tubing, and endocardial pacing.
- Patients with Eisenmenger's syndrome should be followed closely by an ACHD specialist [8, 30].

Prior Surgeries

- History and details or prior surgeries must be obtained.
- Commonly encountered shunts are listed in Table 11.26.

Fontan Palliation

- A palliative surgery performed for children with congenital heart disease that is not amenable to biventricular repair, for example, tricuspid atresia, double-inlet ventricle, and hypoplastic left heart syndrome.
- Goals of the Fontan procedure include providing adequate pulmonary and systemic blood flow, alleviating cyanosis, and decreasing ventricular volume overload.
- A direct connection is created from systemic venous return to the pulmonary artery without a ventricle in between. This may be done via an extra- or intracardiac conduit (see Fig. 11.5).
- Drawbacks of Fontan physiology include chronic systemic venous hypertension and decreased cardiac output and exercise tolerance with passive filling of the pulmonary circulation.
- A 12-year survival is approximately 70% [38].
- Complications include atrial arrhythmias, sudden death, atrial thrombus, hepatic congestion, cirrhosis, hepatocellular carcinoma, protein-losing enteropathy, and plastic bronchitis.
- Management includes regular imaging with echocardiography or cardiac MRI, cardiac catheterization for change in cardiac symptoms, electrophysiology consultation, warfarin for patients with atrial level shunting, atrial thrombus, atrial

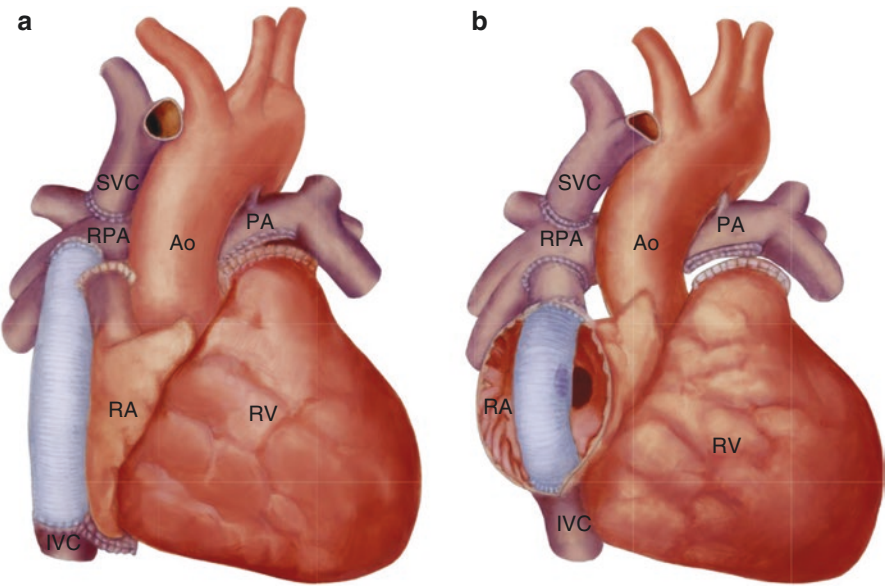

Fig. 11.5 Fontan anatomy with extra-cardiac (**a**) or intracardiac (**b**) conduit. Reproduced with permission from Otto (2013) [32]

arrhythmia, or history of thromboembolic event, ACE inhibitors and diuretics for systemic ventricular dysfunction (Class IIa ACC/AHA Recommendation, Level of Evidence: C), and in some cases reoperation or cardiac transplantation [8].

- Patients who have undergone Fontan should be followed closely by an ACHD specialist [8, 32].

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Chapter 12
Diseases of the Pericardium

Marabel D. Schneider and J. Franklin Richeson

Etiologies of Pericardial Diseases

- Ninety percent of cases of acute pericarditis are idiopathic or viral in etiology.
- Other causes include malignancy, autoimmune disease, uremia (occurs in 5% of CKD patients and up to 13% of dialysis patients), tuberculosis (4%), bacterial (1–2%), trauma, aortic dissection, adverse drug reactions, and acute myocardial infarction (Dressler syndrome occurs with 5–15% of patients with AMIs) [1].
- Bacterial pericarditis is uncommon but generally indicative of infection with an aggressive bacterium with a poor prognosis and is more commonly seen in immunocompromised patients.
- Uremia/renal failure is a common cause of pericarditis and pericardial effusion. It can occur even in patients receiving regularly scheduled dialysis.
- Mixed connective tissue diseases and rheumatologic diseases, including rheumatoid arthritis, scleroderma, and systemic lupus erythematosus, are common etiologies. These causes are often more indolent, and the presenting symptoms are generally associated with more systemic symptoms of these diseases.
- Pericardial effusions and tamponade occur for many of the same reasons as pericarditis. Pericardial effusions are caused by blood (hemopericardium) in the setting of trauma or aortic dissection, transudative fluid (hydropericardium) such as in setting of congestive heart failure or low oncotic states, or exudative fluid (inflammatory, infectious, malignant) [2].

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H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7_12

Pericarditis

Symptoms

- Chest pain is the most common presenting symptom of pericarditis. The pain description is often similar to the pain associated with myocardial ischemia but differs in that it generally has a positional component.
- Pain is generally worse when lying supine or with deep inhalation (pleuritic pain) and improves with leaning forward or bending over.
- Pain often radiates to the left trapezius muscle.
- Pain may be preceded by a prodrome of fever and myalgias.

Evaluation

- **Clinical history**: The diagnosis of pericarditis can often be made based on clinical history, as the ECG and cardiac enzymes may not be abnormal and echocardiography may not reveal fluid (pericardial effusion).
- **ECG**: ECG findings are characteristically diffuse ST segment elevation/PR segment depression (Fig. 12.1). This can appear similar to ST segment elevation

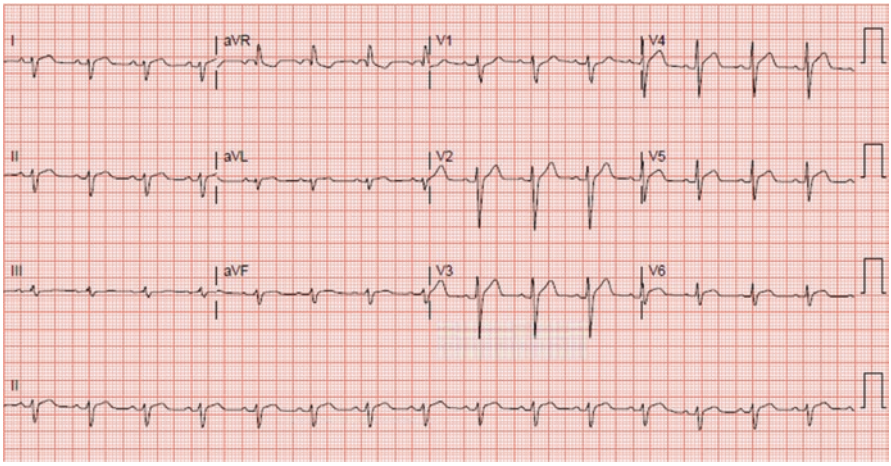

Fig. 12.1 Pericarditis on ECG. Diffuse ST segment elevations, particularly notable in lateral and precordial leads in young patient presenting with positional chest pain and troponin elevation. PR depressions can also be seen but are not notable in this tracing

found in acute myocardial infarction but does not follow a particular vascular distribution and has upward concavity of ST segments.

- **Exam Findings**
  - A pericardial rub is a pathognomonic, while not necessary, sign of pericarditis.
    The pericardial rub, also known as a friction rub, is an extra heart sound with three components (systolic, mid-diastolic, and presystolic) though fewer components may be present. It is generally described as leathery, scratching, raspy, grating, or like the sound of walking on wet snow.
    Best heard at the apex or base of left sternal border but may be widespread.
    Best heard when patient sitting and leaning forward.
    Pericardial rub can be differentiated from a pleural rub if it has three clear components (a pleural rub generally has two components) and by its presence with breath holding, whereas a pleural rub is present during inspiration and/or expiration only.
- **Laboratory studies**: Troponin and CK-MB elevations can be seen and attributed to the involvement of superficial cardiac myocytes (myopericarditis). Inflammatory markers including ESR and CRP are expected to be elevated in the acute setting and usually of little utility. In recurrent pericarditis or in first occurrences with evidence systemic symptoms, evaluating thyroid function with TSH and autoimmune evaluation for rheumatologic diseases is warranted.

Treatment/Prognosis

- Viral and idiopathic causes of pericarditis are often self-limiting and resolve without intervention. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen or ketorolac, for 2 weeks are often effective symptomatic relief and may shorten the disease course. The addition of colchicine to NSAIDs can also be prescribed for up to 3 months in the first episode and may be protective against recurrence. Corticosteroids may also be used in treatment but have been found to be an independent risk factor for recurrence [3, 4].
- NSAID and colchicine combination therapy is also recommended for treating recurrent pericarditis [1, 3–6].
- Recurrent pericarditis is not uncommon. Careful attention should be paid to ensure non-viral/idiopathic causes have been ruled out including malignancy, which carries a poor prognosis, and rheumatologic/autoimmune diseases, which may require additional disease-modifying therapies [2].

Pericardial Effusions and Tamponade

Definition

A pericardial effusion is an increase in amount of fluid within the pericardial sac beyond the normal few milliliters of serous fluid (>50 mL). The rate at which the effusion accumulates is more important in determining its consequences than is the volume of fluid itself.

Assessment

Physical exam is often unremarkable in the setting of pericardial effusion without tamponade. Even in the setting of very large pericardial effusions, there may be no or subtle physical exam findings, including distant heart sounds, bronchial breath sounds, and a triangular area of dullness at the medial tip of the left scapula, known as Ewart's sign [7].

- **ECG**
  - ECG will not typically have any abnormal findings in the setting of pericardial effusion in the absence of cardiac tamponade. Large effusions may show globally reduced amplitude (low voltage with QRS complex ≤5 mm), though this is not a diagnostic or reliable finding.
  - In tamponade, ECG may show sinus tachycardia, electrical alternans, or low voltage (Fig. 12.2).
- **Chest X-ray**: An enlarged cardiac silhouette and, in tamponade, a characteristically "water bottle-shaped" cardiac silhouette caused by the enlarged pericardial sac resting on the diaphragm with clear costophrenic angles.
- **Echocardiogram**
  - Cardiac tamponade is a physiological condition characterized by a pericardial effusion that is large enough to compress the heart to the point ventricular stroke volume is significantly reduced. As such there is a spectrum of clinical presentations from dyspnea to sudden death. The goal of echocardiography is to diagnose the presence of cardiac tamponade physiology before cardiovascular collapse.
  - Cardiac tamponade is diagnosed by echocardiography by documenting (1) the presence of a pericardial effusion (usually large), (2) the reduced cardiac chamber volume, and (3) the presence of characteristic physiological variations in cardiac chamber filling and output with respiration. The most common findings are [9]:
    - Pericardial effusion (usually circumferential and ≥1.5 cm)
    - Small right and left heart as evidenced by free wall invagination (chamber "collapse," mild if only with respiration, moderate to severe if present

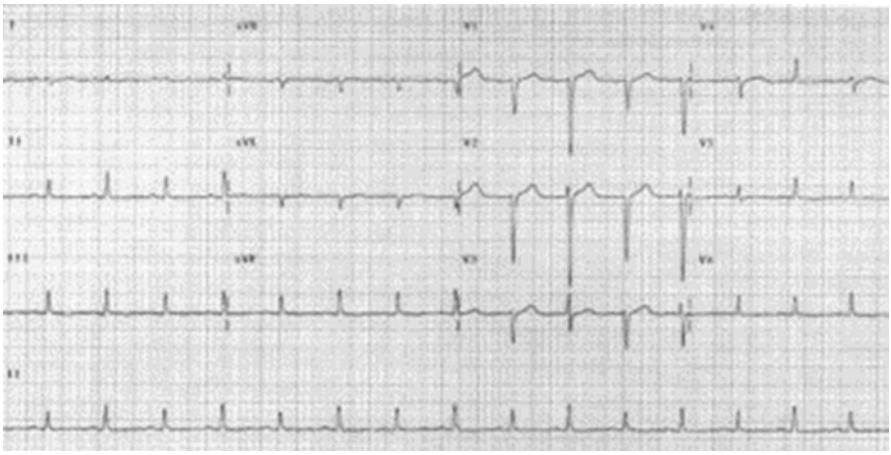

Fig. 12.2 Electrical alternans in cardiac tamponade. Alternating QRS complex amplitudes, most notable in septal leads (V1–V3), and alternating axis seen in V4, which can be representative of a pendulous swinging of the heart within the pericardial sac in the setting of tamponade. Electrical alternans is a specific but not sensitive finding for cardiac tamponade, though it should be noted that it is a non-specific finding in the setting of irregular rate or tachyarrhythmia, such as with atrial fibrillation, SVT, or VT. Electrocardiogram reproduced with permission from [8]

regardless of respiration) and reduced LV stroke volume index with preserved LVEF (SVI < 30 cc/m^2)
  - Physiological variation in left and right heart size and transvalvular flow velocity with respiration and swinging heart (Fig. 12.3)
  - Evidence of elevated filling pressure (plethoric IVC > 2.1 cm with reduced to absent respiratory collapse) [5, 9, 10]

Urgency

- Size does not matter: The size of a pericardial effusion typically has less impact of urgency of treatment than the rate of accumulation.
- A small- or moderate-sized, but rapidly accumulating, effusion may tamponade the heart, whereas a slowly accumulating effusion may grow to be quite large (as much as several liters in volume) before a patient develops symptoms and findings of tamponade.
- The pericardial sac will stretch slowly over time to accommodate the increased volume of a slowly accumulating pericardial effusion, but in the short term, the pericardium does not have the compliance to allow for rapid fluid accumulation, and diastolic filling becomes impaired (tamponade occurs) [9].

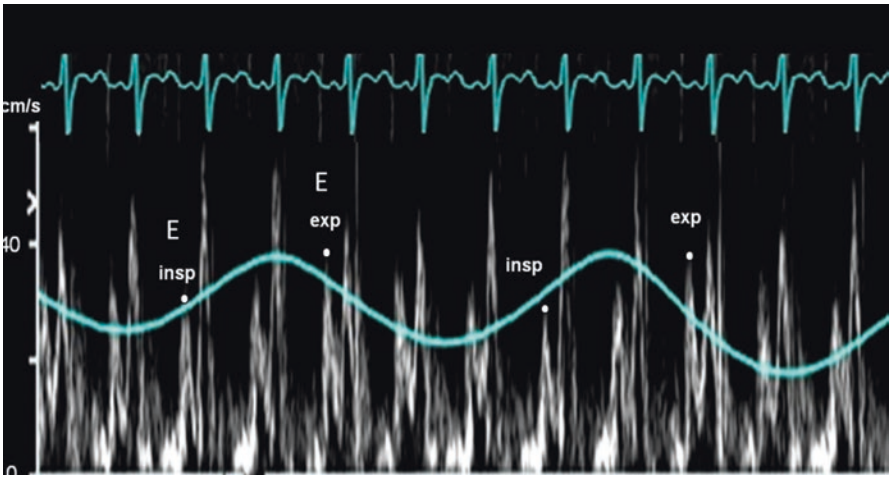

Fig. 12.3 Pulsed-wave Doppler recording of mitral inflow with a respirometer in a patient with cardiac tamponade. There are low peak velocities and velocity-time integrals demonstrating reduced cardiac output. The peak E-wave inflow velocity (**E**) shows increased respiratory variation with the lowest values during the first beat of inspiration (**insp**) and the highest values on the first beat of expiration (**exp**) [% respiratory variation = (exp − insp)/(exp)]. In tamponade, the decrease in peak mitral E-wave velocity between expiration and inspiration is >30%. Reproduced with permission from [5]

Pericardial Tamponade

1. **Pathophysiology**

   (a) The pressure inside the pericardial sac is normally slightly subatmospheric. As fluid accumulates and exhausts the reserve volume of the space, the pressure increases rapidly with any additional volume.

   (b) The heart is contained within the limited space of pericardial sac and must share space with any rapidly accumulating fluid within the pericardial space. The cardiac chambers are more compliant than the pericardium. As volume within the pericardial space expands beyond the critical volume, the right ventricle yields to the pressure in the pericardial space since it is thinner-walled and more compressible than the left ventricle.

   (c) Flow into the right ventricle becomes impeded and its diastolic pressure equals that of the pericardium. As more fluid accumulates, end-diastolic pressures within the pericardium, RV, and LV become equal, at which point tamponade is present and stroke volume begins to decrease. Initially, cardiac output and blood pressure are maintained through sympathetic activation and increased heart rate.

   (d) As tamponade worsens with LV and RV, pressures continue to rise in parallel but without increase in presystolic myocardial stretch, and thus SV does not rise as would typically occur by the Frank-Starling curve.

(e) With progression of tamponade, stroke volume and cardiac output continue to fall. Hypotension is a late occurrence in tamponade and indicates the failure of compensatory mechanisms.

2. **Clinical Exam Findings in Pericardial Tamponade**
   (a) **Symptoms:** Commonly patients report dyspnea or cough, which may be related to compression of surrounding structures. Of note, dyspnea in tamponade usually does not stem from pulmonary congestion, so radiographic findings of congestion/edema are usually lacking.
   - The presence of (1) elevated JVP, (2) attenuated "y" descent of JVP, and (3) pulsus paradoxus is highly suggestive of cardiac tamponade. The absence of these findings collectively also virtually rules out the diagnosis.
     - **Attenuated "y" descent of JVP** represents a decrease in venous pressure that occurs following systole when the tricuspid valve opens allowing blood to flow into the RV from the RA. Since all of the space in the pericardium is "spoken for," the only time blood enters (the RA and RV) is when blood leaves (during ejection). As there is pan-diastolic compression of the cardiac chambers during tamponade, there is increased pressure from the RV impeding blood flow into the RV and thus dampening or eliminating the "y" descent.
     - **Pulsus paradoxus** is an exaggerated decrease (>10 mmHg) in systolic blood pressure during inspiration that was first described by Adolf Kussmaul in his 1873 manuscript [7, 11]:
       - Pulsus paradoxus is not specific to cardiac tamponade and was first described by Kussmaul in asthmatics and now most commonly seen in COPD. It is also not particularly sensitive as it is often absent in the presence of severe LVH and structural defects that impact normal cardiac inflow (septal defects, severe aortic regurgitation) or in the presence of arrhythmias with LV stroke volume variability, such as atrial fibrillation.
       - **Mechanism:** In tamponade, the mechanism of pulsus paradoxus differs from that in COPD (in which the wide swings of pleural pressure act directly as varying afterload on the LV). In tamponade, the inspiratory fall of pleural pressure accelerates the filling of the right heart (as normally occurs); however, there being no "reserve volume" in the pericardial space, the LV becomes compressed, and it descends the Starling curve, causing a less forceful contraction during inspiration [12].
3. **Treatment:** The majority of pericardial effusions are often self-limiting and self-resolving and do not require intervention.

- **When Is Intervention Needed?**
  - Cardiac tamponade (hemodynamic compromise).
  - Patient is symptomatic from compression of adjacent structures (esophagus, trachea, laryngeal or phrenic nerves, lungs).

  - Concern for malignancy or infectious process where diagnostic sampling of the fluid may be necessary.

- **Types of Intervention**
  - **Pericardiocentesis**: drainage or sampling of the fluid from the pericardial space by percutaneous needle. This is now generally performed in the cardiac catheterization lab or operating room under imaging guidance to improve safety of the procedure and reduce adverse outcomes. A temporary indwelling drain may be placed during this procedure.
  - **Pericardial window**: Surgical excision of a small area of pericardium and pleura to allow drainage of fluid from within the pericardial space. This is typically performed by cardiothoracic surgeons in the operating room and is most commonly performed in the case of trauma or recurrent pericardial effusions or when tissue sampling of the pericardium for diagnostic purposes is desired.
  - **Pericardial fluid studies**
    Pericardial fluid that is drained should be sent for cell counts, bacterial cultures, fungal cultures, and AFB stains (and medical cytology, when appropriate) to help determine if further treatment is necessary as in the case of infectious or malignant causes.

Pericardial Constriction

Etiologies

- Idiopathic or viral, post-cardiac surgery/pericardiectomy, postradiation, infectious, mixed connective tissue disorder, or others (malignancy, sarcoidosis, trauma, etc.).

Pathophysiology of Pericardial Constriction

- Pericardial constriction occurs when there is scarring or other causes impacting the elasticity of the fibrous pericardial sac causing increased rigidity. A stiff pericardium prevents satisfactory diastolic filling. It is typically a chronic condition but does have subacute, transient, and occult variants.
- During inspiration, intrathoracic pressure decreases, and a normal compliant pericardium expands to allow for increased venous return to the right heart with a temporary increase in RV volume and size. In pericardial constriction, the pericardium has become rigid and can neither communicate with reduction in intrathoracic pressure to the cardiac chambers nor expand to accommodate increased RV volume.

- The transpulmonary gradient is reduced due to the inability to transmit the reduction in intrathoracic pressure to the cardiac chambers:
  - The pulmonary venous pressure is reduced with the reduction in intrathoracic pressure, but the LV pressure does not decrease as it should leading to low LV volume. This leads to interventricular dependence with RV that is constricted by the rigid pericardium pushing against the interventricular septum to expand into the underfilled LV.

Symptoms and Physical Exam (Table 12.1)

- Symptoms are those of right heart failure (edema, ascites, portal hypertension, elevated JVP) usually more so than left heart failure [pulmonary edema is less common since the pressure threshold for accumulation of pulmonary edema (about 20 mmHg) is higher than the threshold for ascites and peripheral edema formation (about 10 mmHg)]. Stroke volume is low and fixed, so cardiac output is maintained by relative tachycardia.
- Elevated JVP will be present and Kussmaul's sign (absent decrease in JVP with inspiration) may also be present.
- Pericardial knock can be heard in early diastole, and it represents the abrupt cessation of the diastolic filling of the ventricle by the rigid pericardium.

Table 12.1 Comparison of pathophysiology of pericardial tamponade and pericardial constriction

	Tamponade	Constriction
Duration	Acute	Subacute, chronic
Common symptoms	Dyspnea, cough	Edema, ascites
BP	Low or normal	Low–normal
Heart rate	Increased	Increased
Pulsus paradoxus	Present	Usually absent
Jugular venous pressure	Elevated	Elevated
"Y" descent	Absent or attenuated	Accentuated
Kussmaul's sign	Absent	May be present
Impairment of filling	Pan-diastolic	Latter two-thirds of diastole
Equalization of diastolic pressures	Yes	Yes
Heart size—CXR	Markedly increased—water bottle configuration	Mildly increased, often calcified pericardium
Echocardiogram	Echo-free space (black fluid between the pericardium and ventricular wall), RA, RV diastolic collapse	Thickened pericardium, early diastolic septal bounce

Diagnosis

- It is important to differentiate constrictive pericarditis from other causes of heart failure like restrictive cardiomyopathy:
  - There are no specific ECG abnormalities in constriction.
  - Chest X-ray will generally show a normal cardiac size without pulmonary congestion. In chronic constriction, calcification of the pericardium may be evident.
  - Echocardiogram is a helpful imaging modality for diagnosis and will generally show pericardial thickening and may show calcification of the pericardium.
- Restrictive filling pattern of mitral and tricuspid inflow velocities (the ratio of early-to-late mitral inflow velocity [or E/A] is >0.8) due to elevated filling pressure.
- There may also be evidence of hepatoportal congestion with distention of the IVC and hepatic veins without inspiratory collapse (Fig. 12.4). In a 2008–2010 study at the Mayo Clinic, it was found that the presence of interventricular septal shift with respiration combined with either a preserved or increased medial mitral annular flow velocity or hepatic vein expiratory flow reversal corresponded to 87% sensitivity and 91% specificity in diagnosing constrictive pericarditis vs. restrictive cardiomyopathy [13].
- Hepatic vein flow reversal (a diastolic reversal of blood flow from the right atrium to the inferior vena cava (IVC) and hepatic vein during expiration).
- Tissue Doppler measures myocardial tissue velocity. A normal peak early diastolic annular tissue velocity of mitral annulus (peak e') is >8 cm/s, which indi-

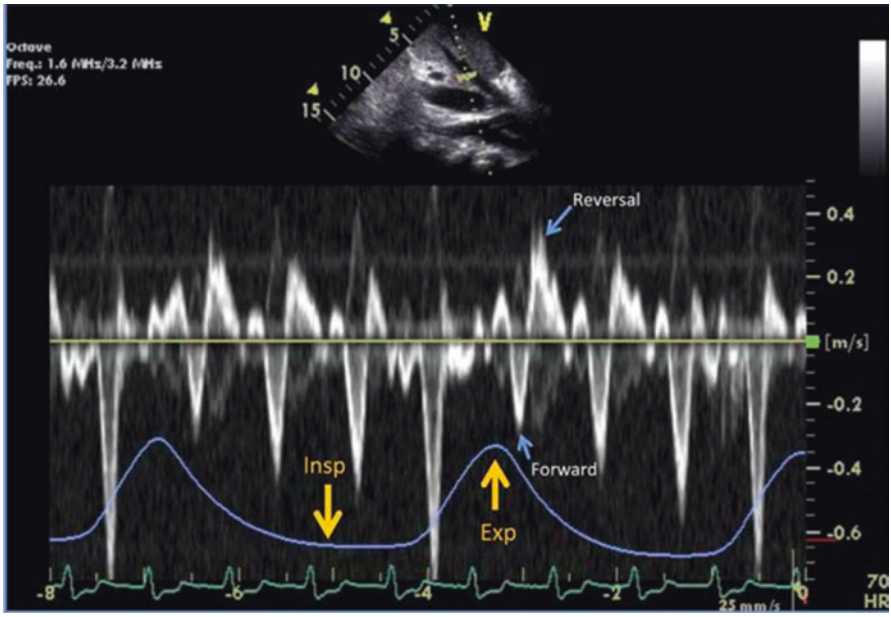

Fig. 12.4 Hepatic vein flow reversal in tamponade. Pulsed-wave Doppler recording (subcostal window) within the hepatic vein with a prominent diastolic flow reversal in expiration. Reproduced with permission from [13]

cates normal LV relaxation. Normally, e' of the lateral mitral annulus is higher than e' of the medial mitral annulus. In pericardial constriction, the relationship between the lateral and medial mitral annuli is reversed ("annulus reversus") with e' of the lateral mitral annulus lower than e' of the medial mitral annulus since the lateral motion of the heart is limited by the constrictive pericardium (Fig. 12.5).

- In constriction, there is an exaggerated early diastolic myocardial velocity (e' is increased) (see d, Fig. 12.6 below), whereas, in restrictive cardiomyopathies, there is characteristic low, early diastolic annular velocity (e') (<8 cm/s) (Fig. 12.6).

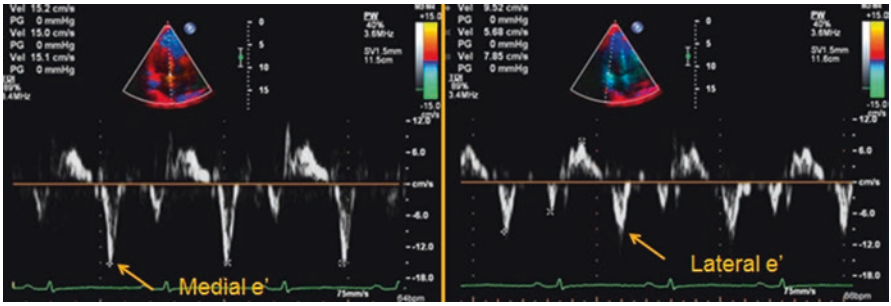

Fig. 12.5 Annulus reversus in constrictive pericarditis. Medial (left) and lateral (right) mitral annular tissue Doppler recording (apical window) in a patient with constrictive pericarditis. There is normal to increased early relaxation velocity (e'), with medial velocity (e' 12 cm/s) greater than lateral (e' 6 cm/s). Reproduced with permission from [13]

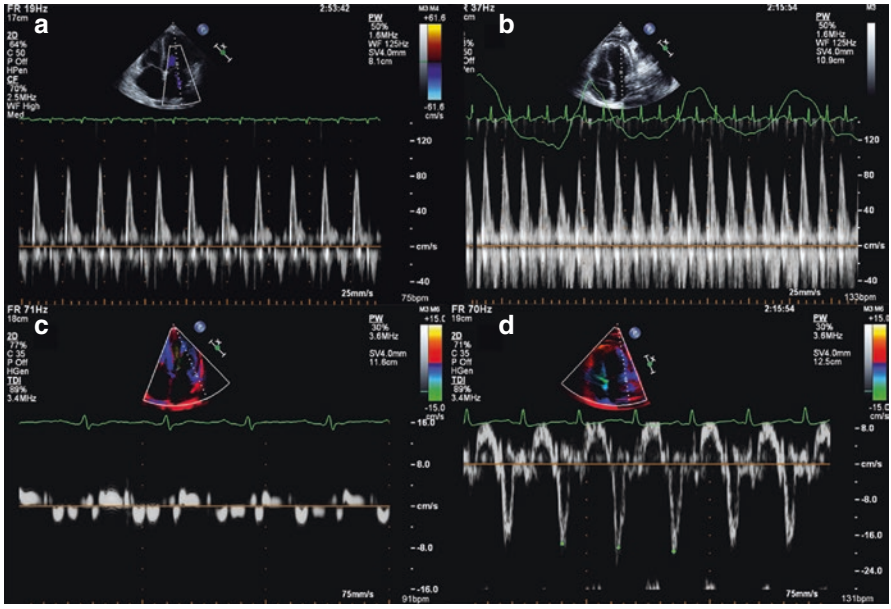

Fig. 12.6 Differences in pericardial constriction compared to restrictive cardiomyopathy. Pulsed Doppler recordings of LV inflow (**a**, **b**) and tissue Doppler myocardial velocities of the basal lateral wall (**c**, **d**) in a patient with restrictive cardiomyopathy (**a**, **c**) and constrictive pericarditis (**b**, **d**). Reproduced with permission from [14]

- Other findings of echocardiography may include:
  - Moderate (usually not severe) biatrial enlargement.
  - Abnormal contour between posterior LV and LA walls.
  - Hypermobile AV valves.
  - The presence of ventricular septal shift (septal "bounce") during the respiratory cycle due to the exaggerated interventricular dependence.
- Right and left heart catheterization to evaluate hemodynamic pressure tracings and evaluate for interventricular dependence (Fig. 12.7).
  - The end-diastolic pressures of both ventricles are elevated and equal (with <5 mmHg difference between LV and RV EDP).
  - The RV systolic pressure is usually <55 mmHg.
  - Rapid early and not restricted diastolic filling of the ventricles with subsequent abrupt cessation of flow due to the stiff pericardium produces the classic "dip-and-plateau pattern" referred to as "square root sign" in the ventricular pressure waveforms (Fig. 12.8). Elevated pressure in late diastole plateaus is in accordance with the pericardial compression.

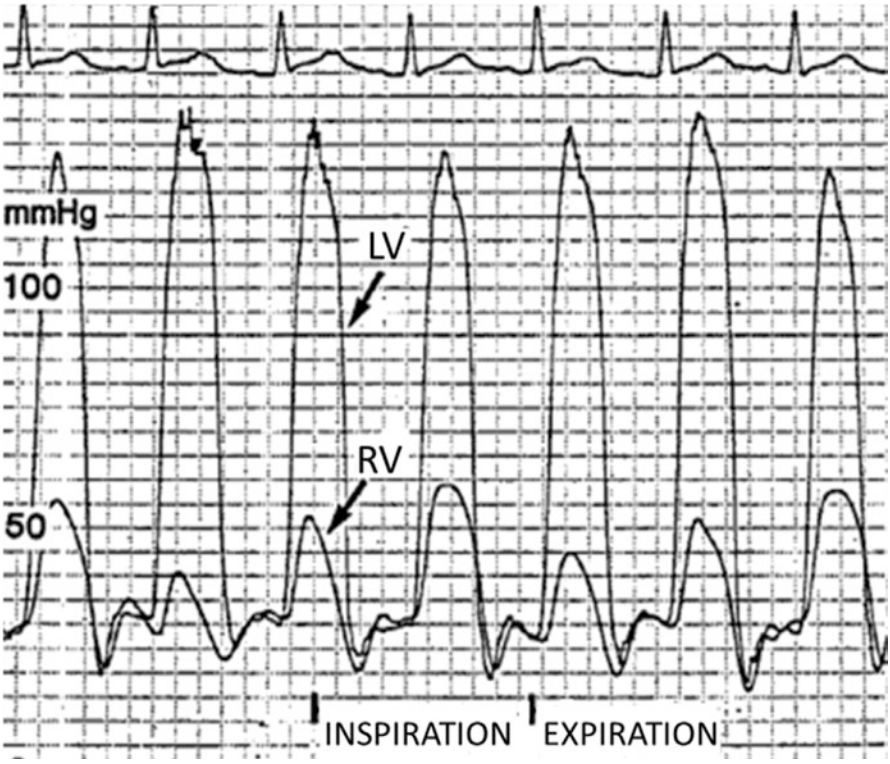

Fig. 12.7 Interventricular dependence demonstrated on discordance in RV and LV diastolic pressures during inspiration on invasive hemodynamic simultaneous pressure tracings. During inspiration, RV pressure increases, while LV pressure decreases in the setting of constrictive pericarditis because the constrictive pericardium does not transmit with normal inspiratory decrease in intrathoracic pressure. Reproduced with permission from [15]

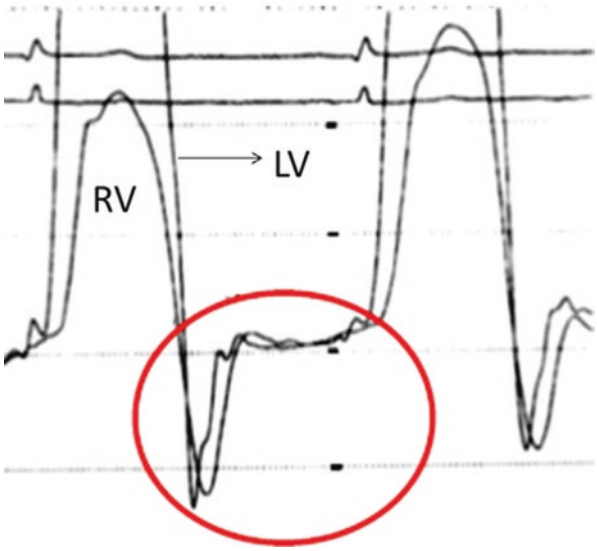

Fig. 12.8 Simultaneous RV and LV tracing from a patient with constrictive pericarditis showing square root sign. Also note that the diastolic pressures in both the ventricles are equal demonstrating interventricular dependence. Reproduced with permission from [15]

- Further imaging with cardiac MR and cardiac CT is also useful in assessing for pericardial thickness vs. effusion, calcification, and hemodynamic signs such as interventricular interdependence in differentiating the diagnosis of constrictive pericardial disease [16, 17].
- Contrast-enhanced cardiac CT can show pericardial thickening and calcifications [5, 13].

Treatment

- The mainstay of medical treatment is diuretic management to manipulate cardiac filling. Though there is the possibility of surgical removal of the pericardium, it carries a high mortality and has mixed results in providing symptomatic relief.

Effusive-Constrictive Pericarditis

- There is the possibility of constrictive pericarditis with a large effusion and often evidence of tamponade. These patients tend to present with both symptoms of right heart failure and criteria for tamponade necessitating drainage.
- If following drainage of effusion, patients continue to have an elevated JVP and have the presence of an accentuated "Y" JVP descent, they may have constrictive physiology.
- This may resolve over time if the constrictive component is merely secondary to fibrin deposition and not calcified scar tissue [10, 13, 18].

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Chapter 13
Acute and Chronic Heart Failure

Alan Brooks and Himabindu Vidula

Definitions

- Systolic HF/HF with reduced ejection fraction (HFrEF)—loss of normal cardiac function in systole such that ventricular ejection fraction is impaired, frequently defined as EF ≤40% [4].
- Diastolic HF/HF with preserved ejection fraction (HFpEF)—Impaired cardiac performance resulting from impaired ventricular filling in diastole and/or altered ventricular geometry in the setting of relatively preserved EF [5].
- The European Society of Cardiology (ESC) has defined a population described as HF with moderately reduced ejection fraction (HFmrEF) who have an EF ranging from 41 to 49% and appear to share characteristics of HFpEF and HFrEF [6].
- Frequently, systolic and diastolic abnormalities occur in the same patient [4].
- Regardless of etiology, HF is a clinical syndrome consisting of symptoms frequently including dyspnea, orthopnea, and peripheral swelling. Clinical findings accompanying these symptoms include venous distension, peripheral edema, and pulmonary congestion. Symptoms and clinical findings in HF are caused by structural abnormalities and/or functional impairment which result in elevated filling pressures and reduced cardiac output [6].
- American College of Cardiology Foundation (ACCF)/AHA Stages of left- and right-sided HF:
  - A: At risk but without structural disease or HF symptoms
  - B: Structural disease but without symptoms
  - C: Structural disease with current symptoms or symptoms at any time in the past
  - D: Refractory HF requiring advanced interventions

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H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7_13

- New York Heart Association (NYHA) functional classes of HF:
  - I: HF in the absence of fatigue/dyspnea or physical activity limitation
  - II: HF resulting in symptoms slightly limiting physical activity
  - III: HF with marked symptoms and significant physical activity limitation but no rest symptoms
  - IV: HF with inability to perform physical activity without discomfort and including rest symptoms

Epidemiology

- There is an estimated 6.5 million people with HF in the United States and more than 23 million people across the world [7, 8].
- The prevalence of HF has been increasing with time and hospitalizations for HF have risen concurrently.
- Over 1 million hospital discharges listed HF as a cause, and nearly 1.8 million primary care visits were associated with HF in 2010 and 2012, respectively [2].
- The incidence of HF increases with age and doubled with each successive decade of life in the Framingham Study [9].
- The lifetime risk for developing HF is 20% for Americans 40 years of age [9].
- One in nine death certificates lists HF as a cause [10].
- It is estimated that approximately 50% of patients diagnosed with HF have preserved EF [11].
- Conflicting data are present in the literature, but a meta-analysis suggests HFpEF is associated with less mortality than HFrEF even when adjusted for age, gender, comorbid states, and etiology [12].
- Confounding the matter, in HFpEF associated with right ventricular dysfunction, worse outcomes have been observed with regard to hospitalization rates and mortality [13].

Etiology and Risk Factors

Etiology of Left Heart Failure

- Myocardial ischemia or infarction is the most common cause in the United States [14].
- Non-ischemic causes are responsible for the remaining HF burden and include the following [15]:
  - Dilated cardiomyopathies—characterized by ventricular dilation and reduced contractility not explained by ischemia, valvular dysfunction, or hypertension
    Idiopathic
    Familial
    Infectious

Cardiotoxicity (e.g., anthracyclines) related to cumulative lifetime dose [16]
Connective tissues disease (autoimmune)
Extreme emotional stress (Takotsubo or stress cardiomyopathy, apical ballooning syndrome) with female predominance [17]

- Restrictive cardiomyopathies—characterized by normal or diminished ventricular volumes with impaired filling in the absence of dilation, valvular disease, or systolic dysfunction [18]
  Amyloidosis
  Sarcoidosis
  Hemochromatosis
  Storage diseases
  Autoimmune
- Hypertrophic cardiomyopathies
- Valvular dysfunction—commonly aortic regurgitation, aortic stenosis, mitral regurgitation, and mitral stenosis [19]
- Peripartum cardiomyopathy
- Hypertensive
- Tachycardia-mediated (with atrial fibrillation being a common cause) [20]
- HIV
- Substance abuse (e.g., EtOH, cocaine)
- Poor diet
- Medication nonadherence

Etiology of Right Heart Failure

- Right heart failure (RHF) commonly results from pulmonary hypertension, right ventricular (RV)/tricuspid valve pathology, and pericardial disease [21].
- Left-sided HF is the most common cause of RHF due to resultant pulmonary hypertension, which if left untreated, causes progression from RV dysfunction to failure [22].
- Other etiologies of pulmonary hypertension which may lead to RHF include pulmonary arterial hypertension (PAH), pulmonary hypertension associated with lung diseases and/or hypoxia (e.g., COPD, interstitial lung disease, or sleep apnea), and chronic thromboembolic pulmonary hypertension (CTEPH) (e.g., with chronic pulmonary embolism).
- Other causes of RHF include:
  - Acute pulmonary embolism
  - Acute RV myocardial infarction
  - Tricuspid and pulmonic valvular regurgitation
  - Congenital heart disease (atrial or ventricular septal defect, Ebstein's anomaly)
  - Total or partial anomalous pulmonary venous return

  - RV outflow tract (RVOT) obstruction
  - Infiltrative process/cardiomyopathy
  - Arrhythmogenic right ventricular cardiomyopathy (ARVC)
  - Chronic accumulating pericardial effusion (mimics acute RHF)
  - Constrictive pericarditis (caused by fibrosis and calcification of the pericardium)
- Volume overload states (tricuspid/pulmonic regurgitation, ASD) are more tolerated by the RV resulting primarily in dilation.
- Pressure overload states (left HF, pulmonary embolism, or pulmonary HTN) often progress from dilation to dysfunction and RHF [23].

Risk Factors for Left Heart Failure

- Coronary artery disease/myocardial infarction
- Hypertension
- Valvular heart disease
- Diabetes mellitus
- Smoking
- Obesity

History/Physical Exam

History

- Patients presenting with acute decompensated heart failure are likely to provide a history of prior heart failure diagnosis or may already be taking medications prescribed for HF.
- The following historical symptoms are frequently associated with HF:
  - Progressive dyspnea
  - Weight gain
  - Fatigue
  - Congestive symptoms
    Right heart congestion
      Peripheral edema
      Abdominal bloating
      Early satiety
    Left heart congestion
      Orthopnea
      Paroxysmal nocturnal dyspnea (PND)

- The presence of orthopnea or PND is 83% specific for HF [24].
- Dyspnea is the only HF symptom with high sensitivity but lacks specificity [25].

Physical Exam

- Exam findings consistent with HF include the following:
  - Resting tachycardia indicative of physiologic compensation for reduced ventricular stroke volume.
  - Narrow pulse pressure due to poor ventricular performance and reduced stroke volume.
  - Signs of intra- and extravascular volume overload.
    Peripheral edema with pitting when skin depressed by the examiner.
    Elevated jugular venous pressure (JVP) indicates increased intravascular volume and is estimated by measuring the height of the internal jugular venous pulsation above the sternal angle (typically assumed to be 5 cm). The measurement is indicative of the right atrial pressure and is generally considered to be elevated if greater than 8 cm [26].
    Pulmonary congestion with discontinuous rattling or cracking sounds on auscultation known as rales. Although, some HF patients may have an unremarkable lung exam due to well-developed lymphatics system.
  - An S3 heart sound is indicative of elevated left atrial pressure and left ventricular end-diastolic pressure (LVEDP) but is limited by interobserver variability [27].
  - Elevated JVP and S3 heart sound are each associated with poor outcomes and HF progression [28].
  - Precordial palpation revealing laterally displaced apical impulse beyond the midclavicular line is suggestive of ventricular enlargement.
  - Cool, pale, and/or cyanotic extremities may indicate peripheral vasoconstriction and cardiogenic shock.
  - Peripheral edema, elevated JVP, pulmonary congestion, S3 heart sound, and cardiomegaly are considered specific physical exam findings for HF but lack sensitivity [25].
  - Holosystolic murmur at the apex can be noted with mitral regurgitation in the setting of dilated left ventricle.
  - Increased JVP is a specific sign of right heart failure and reflects raised right atrial pressure.
  - Kussmaul sign (an increase of JVP on inspiration) can be seen in constrictive pericarditis and RV infarction.
  - An accentuated pulmonic component of the second heart sound indicates elevated right ventricular systolic pressures.
  - A parasternal holosystolic murmur (tricuspid regurgitation) increases with inspiration in RHF.

- Left parasternal lift can be present with RHF.
- Enlarged tender liver and ascites can be present with RHF [21].

Diagnostic Testing

Although diagnostic testing may suggest features of HF, there is no individual test which confirms the diagnosis. HF remains a clinical diagnosis based on history and physical exam supported by objective data.

Electrocardiogram (ECG)

- ECG evaluation may diagnose systolic dysfunction by demonstration of prior myocardial infarction (presence of Q waves in a vascular distribution suggesting myocardial infarction). A normal ECG has high negative predictive value for systolic dysfunction [29]. Conversely, an abnormal ECG increases likelihood of HF but has low specificity.
- ECG may also diagnose acute ischemia as cause of new-onset HF.
- Other information provided by ECG which may suggest HF etiology as follows:
  - Cardiac arrhythmias causing tachycardia-mediated HF.
  - Left ventricular hypertrophy (LVH) indicating hypertensive etiology.
  - Conduction delay or heart block indicating possible infiltrative cause of HF.
  - Low voltage criteria may be suggestive of infiltrative process, like cardiac amyloidosis.
  - Right atrial enlargement (P pulmonale), right axis deviation, or RV hypertrophy (dominant R in V1 and dominant S in V5/V6).

Laboratory Studies

- Cardiac enzymes—elevations in cardiac troponin may diagnose acute infarction as a cause of new-onset HF. Unchanging low-level troponin elevations may indicate suboptimal cardiac hemodynamic suggesting acute decompensated HF or myocarditis.
- Brain natriuretic peptide (BNP) and N-terminal BNP (NT-proBNP)
  - A hormone released from the ventricles with the purpose of natriuresis.
  - Increased natriuretic peptide level is indicative of ventricular dysfunction.
  - Measurement of BNP or NT-proBNP is suggested in patients whom HF is suspected but uncertain [4].
  - There are several caveats to natriuretic peptide testing:
    BNP and NT-proBNP do not exclude other coexisting medical conditions leading to the patient's symptoms [30].

Some patients, particularly those with HFpEF, may have acute decompensated HF without elevation of BNP and NT-proBNP.
Natriuretic peptide levels can be elevated in disease such as sepsis, renal failure and pulmonary HTN, and falsely low in patients with obesity.
Neprilysin inhibitors such as sacubitril will cause elevated BNP levels regardless of HF compensation state, but NT-proBNP levels will be unaffected.

- Complete blood counts—untreated and worsening anemia can contribute to acute decompensation of existing HF.
- Chemistry panels
  - Hyponatremia may be suggestive of severe hypervolemia but may also be the result of aggressive diuresis; it portends a poor prognosis.
  - Renal dysfunction may be caused by renal hypoperfusion but may contribute itself to acute decompensated HF (e.g., cardiorenal syndrome).
  - Identification of hyperkalemia will guide the appropriateness and timing of HF therapies including angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), and mineralocorticoid antagonists.
- Liver function panels—elevated liver enzymes in the absence of suspected hepatic etiology of patient presentation may be suggestive of hepatic congestion secondary to acute decompensated HF.

Imaging

- Chest radiographs
  - Helpful in identifying cardiac vs. pulmonary etiology for patients presenting with HF symptoms
  - The following factors are helpful in identifying acute decompensated HF on chest radiography [31]:
    Cardiomegaly defined as ratio of cardiac width to chest width greater than 50%
    Kerley B lines
    Cephalization of pulmonary vessels
    Pleural effusions
- Echocardiography
  - Useful in determining the etiology of heart failure—systolic, diastolic, valvular dysfunction
  - Also useful in estimation of pulmonary capillary wedge pressure (PCWP), right ventricular systolic pressure (RVSP), pulmonary artery pressure (PAP), and cardiac output (CO) by noninvasive means (although limited by available acoustic windows)
  - Useful in determining the etiology of RHF (evaluation for right atrial enlargement, right ventricular (RV) enlargement, RV systolic dysfunction, tricuspid regurgitation, pulmonary hypertension, congenital heart defects, tricuspid or pulmonic pathology, and left heart pathology)

- Cardiac magnetic resonance imaging (MRI)
  - If renal function is adequate, cardiac MRI may be useful in defining myocardial scar by late gadolinium enhancement (LGE).
  - LGE patterns aid in identification of ischemic (vascular distribution LGE), non-ischemic, or infiltrative cause (patchy or global distribution LGE) of HF in addition to the amount of viable myocardium [32–34].
  - Cardiac MRI is an important test in evaluation of right heart structure and function such as ARVC.
- Single photon emission computed tomography (SPECT)—Allows identification of ischemia and infarction, measurement of ventricular volumes and EF as well as myocardial viability
- Positron emission tomography (PET)—Allows measurement of ventricular volumes and EF, but metabolic PET techniques allow identification of infiltrative cardiomyopathies

Procedures

- Cardiopulmonary testing
  - Exercise testing in combination with measurement of inspired and expired gases allows identification of cardiovascular contribution to patient symptoms and functional limitations.
  - Useful when comorbidities are present and contribution of HF is unclear.
  - Also useful to monitor patients over time and evaluate prognosis.
- Right and left heart catheterization
  - Right heart catheterization allows direct measurement of cardiac filling pressures and cardiovascular hemodynamic parameters. It is typically employed to determine eligibility for advanced HF therapies when patients are already on optimal medical therapy.
  - Right heart catheterization is also an important part of the evaluation of right heart disease and pulmonary HTN, including the assessment of pulmonary vascular resistance, pulmonary pressures, cardiac output shunt fraction, and pulmonary vasoreactivity [22].
  - Left heart catheterization allows direct measurement of left heart filling pressures and visualization of coronary artery anatomy.
  - Revascularization (coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI)) should be considered in selected patients with coronary artery disease (CAD) and heart failure [35].
- Endomyocardial biopsy (EMB)
  - Not part of routine HF diagnostic evaluation
  - Useful for determining the etiology of acute onset HF in patients whom other testing has not yielded a diagnosis and the treatment strategy would greatly change, as in giant cell myocarditis [36].

Treatment

Pharmacologic

- Diuretics
  - Loop diuretics are indicated for initial therapy of volume overload from acute decompensated HF regardless of the etiology in patients who are hemodynamically stable.
  - Thiazide diuretics are added to potentiate the effect of loop diuretics in patients who do not adequately respond.
  - Diuretics have failed to demonstrate mortality benefit in patients with chronic HF but are effective in reducing symptoms in acute decompensated HF.
  - Continuous vs. intermittent intravenous diuretics do not appear to alter outcomes, but high-dose intravenous diuretic demonstrated a trend toward more rapid improvement in symptoms [37].
  - High-dose diuretics are typically considered an intravenous dose up to 2.5 times the patient's maintenance oral dose.
  - Torsemide has extremely good oral bioavailability and a long duration of action and can be dosed once daily. The conversion from furosemide to torsemide is 2:1 (e.g., 40 mg PO furosemide:20 mg of PO torsemide).
- Vasodilator therapy
  - Not part of routine therapy for acute decompensated HF but may be of benefit in cases of severe hypertension and acute mitral or aortic regurgitation.
  - Agents in this class are nitroprusside, nesiritide, and nitroglycerine.
- Fluid and sodium restriction
  - In patients with refractory HF and hyponatremia, fluid restriction may be helpful [4].
  - Sodium restriction is not evidence-based but may be useful in symptomatic and refractory cases of acute decompensated HF or those with extreme dietary indiscretions.
- Inotropic agents
  - Recommended for patients with acute decompensated heart failure of systolic etiology who are in cardiogenic shock until definitive therapy can be achieved [4].
  - Also useful as bridge to transplantation or long-term mechanical support for severe, refractory HF.
  - Patients on inotropic agents must be closely monitored for blood pressure and cardiac arrhythmias.
  - Routinely used agents include dopamine, dobutamine, and milrinone.
  - Not associated with mortality benefit.
- Vasopressin antagonists
  - Not routinely used for HF but considered an option for those patients with acute decompensated HF and severe hyponatremia (Na < 120 mEq/L) at risk

for hyponatremia-related symptoms despite water restriction and attempts at correcting volume overload

- Long-term HF therapies
  - Extensive clinical trials have evaluated beneficial HF therapies as summarized below (Table 13.1).

Additional Management of RHF

- A detailed discussion of the management of specific etiologies of RV failure is beyond the scope of this manual. However, simultaneous optimization of RV preload, afterload, and contractility is important in management of RHF [57].

Table 13.1 Clinical trials that have evaluated beneficial HF therapies

Therapy	HF etiology	Benefit/recommendation
ACE inhibitors	HFrEF	*Recommended* for all patients with HFrEF due to mortality benefit [38–40]
Aldosterone antagonists	HFpEF and HFrEF	*Recommended* for NYHA II-IV HFrEF due to mortality benefit if renal function and potassium allow [41–43]. Reduces hospitalizations in patients with HFpEF [44]
ARB	HFrEF and HFpEF	*Recommended* for all patients with HFrEF who are intolerant of ACE inhibitors due to mortality benefit [45, 46]. May be considered in patients with HFpEF in order to decrease hospitalizations [47]
ARB + neprilysin inhibitor (ARNI)	HFrEF	*Recommended* for NYHA II-IV HF due to improved survival and reduced hospitalizations [48]. It may be used as initial therapy in place of or as a replacement for ACE inhibitor or ARB therapy. Note that ACE inhibitors must be ceased 36 h prior to initiation of ARNI
Beta blockers	HFrEF	*Recommended* for all patients with HFrEF due to mortality benefit [49–52]. Studied agents include bisoprolol, carvedilol, and metoprolol succinate
Digoxin	HFrEF	Reduction in HF hospitalizations but not mortality [53]
Diuretics	HFpEF and HFrEF	*Recommended* for improvement in symptoms but no mortality benefit [37]
Hydralazine + nitrates	HFrEF	*Recommended* for African-Americans with NYHA III-IV HF already on or intolerant of ACE inhibitors and beta blockers due to improved survival and reduced hospitalizations [54]. *Recommended* for all patients with HFrEF intolerant of ACE inhibitors/ARBs [55]
Ivabradine	HFrEF	Reduction in HF mortality or hospitalizations in patients with resting HR $\geq$ 70 bpm despite beta blocker therapy [56]

Atrial Fibrillation and HF

- Atrial fibrillation can have a deleterious effect in patients with heart failure. Elevated resting heart rate and exaggerated heart rate response to exercise can shorten diastolic filling time, which together with loss of effective atrial contractile function (atrial "kick") can lead to a reduction in cardiac output.
- Rapid atrial fibrillation can also have significant hemodynamic effects in patients with acute RHF or severe RV dysfunction.
- Maintenance of sinus rhythm and heart rate control is important in treatment and prevention of HF exacerbation.
- As the combination of HFrEF with AF significantly increases the risk of stroke compared with AF alone, anticoagulation of patients with HF is important [20, 58].

Devices

- Implantable cardioverter defibrillator (ICD)
  - Sudden cardiac death (SCD) is responsible for a significant proportion of deaths in those with reduced EF and is frequently caused by ventricular tachyarrhythmias.
  - ICD therapy can terminate ventricular tachyarrhythmias and decrease incidence of SCD.
  - ICD is recommended for the following clinical scenarios [59, 60]:
    NYHA class II or III status non-ischemic cardiomyopathy (NICM) with EF ≤ 35% despite optimal medical therapy for 90 days and anticipated survival is >1 year
    NYHA class II or III status ischemic cardiomyopathy (ICM) at 40 days post-infarction or 90 days post-revascularization with EF ≤ 35% despite optimal medical therapy and anticipated survival is >1 year
    NYHA class I status ICM at 40 days post-infarction or 90 days post-revascularization if EF ≤ 30% despite optimal medical therapy and anticipated survival is >1 year
  - Recent data suggests that ICD therapy may not be beneficial in NICM with EF ≤ 35%, but guidelines remain supportive of ICD therapy in these patients [61].
- Cardiac resynchronization therapy (CRT)
  - Patients with reduced EF often have ventricular electrical dyssynchrony further contributing to their poor cardiac function.
  - CRT can reduce ventricular dyssynchrony and improve symptoms in appropriate patients.
  - CRT is recommended for HFrEF with EF ≤35% and NYHA class II, III or IV status, and QRS duration ≥150 ms. If QRS duration is between 120–150 ms LBBB QRS morphology should be present [62].

Advanced Therapies

Mechanical

- For patients with severe HFrEF with hemodynamic compromise and/or cardiogenic shock, mechanical support may be indicated.
- Temporary mechanical support options are intended to act as a "bridge" to either decision of candidacy for transplant/LVAD or recovery.
- Mechanical devices available for short-term support include extracorporeal membrane oxygenation (ECMO), percutaneous ventricular assist devices (pVAD), and intra-aortic balloon pump (IABP).

Surgical

- Cardiac transplantation
  - For patients with severe HFrEF with hemodynamic compromise and/or cardiogenic shock, cardiac transplantation may be an option.
  - Referral to a HF specialist at a regional transplantation center is indicated for further evaluation.
- Left ventricular assist device (LVAD)
  - LVAD implantation is increasingly more utilized as a long-term cardiac support option for patients with severe HFrEF refractory to medical therapy particularly in those who are not cardiac transplantation candidates and given the limited donor pool [63].
  - LVAD implantation requires adequate right heart function to accept the improved cardiac output from the LVAD postoperatively.
  - Referral to a surgical center specializing in LVAD implantation is indicated for patients requiring further evaluation.
- Total artificial heart (TAH)
  - Patients with inadequate right heart function for LVAD implantation may be candidates for a TAH [64].
  - Adequate body habitus is required for surgical implantation of a TAH.
  - Referral to a surgical center with experience in TAH implantation is indicated for patients with biventricular failure requiring further evaluation.
- Right ventricular assist device (RVAD)
  - RVAD implantation can provide mechanical circulatory support in patients with RHF refractory to medical therapy and may be considered as a bridge to recovery or as definitive management [57].

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Chapter 14
Hypertrophic Cardiomyopathy

Tyler J. Slyngstad and Christopher J. Cove

Epidemiology

- HCM occurs in 1 in 500 people and is the most common genetic cardiovascular disease in North America [1].
- Number one cause of nonviolent death in young adults.
- Occurs equally by autosomal dominant inheritance or sporadic mutation [2].

Etiology and Risk Factors

- Caused by mutations of cardiac sarcomere myofilaments or Z-discs.
- Classic histological triad includes myocardial disarray, intramural arteriole thickening, and intracellular/interstitial fibrosis.
- There is a broad phenotypic expression that presents at any age, but most go undiagnosed throughout their lifetime [1].
- Most with diagnosis have no significant disability or diminished life expectancy [1].
- Clinical presentations typically occur from three causes:
  - Sudden cardiac death—more common in patients <35 years old.
  - Heart failure—HFpEF is more common than HFrEF.
  - Atrial fibrillation—~25% of patients with HCM.

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H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7_14

Left Ventricular Hypertrophy (LVH)

- LVH pattern is variable though asymmetric hypertrophy is most common.
- Basal anterior septal hypertrophy can lead to left ventricular outflow tract (LVOT) obstruction and systolic anterior motion (SAM) of the mitral valve [3, 4].
- HCM is less commonly diagnosed with a concentric or isolated hypertrophy pattern.
- Yamaguchi syndrome is an apical variant that occurs in 10% of HCM patients [5].

Pathophysiology: Typically Occurs Through Four Distinct Mechanisms

1. LVOT obstruction. Seen with asymmetric hypertrophy involving the basal septum. Seventy percent of these patients develop significant LVOT obstruction with gradients ≥30 mmHg [1, 6]. Obstruction leads to increased velocities and venturi forces at the anterior basal segment causing the anterior mitral valve leaflet to be pulled into contact with the septum, referred to as SAM. This results in dynamic LVOT obstruction and often mild to moderate posteriorly directed MR.

   The degree of LVOT obstruction varies with loading conditions if SAM is present.
   - Decreased preload = Increased LVOT obstruction. Increase in murmur.
     Examples: Valsalva, nitroglycerin, and dehydration.
     Mechanism: Basal septum overriding outflow tract is in closer proximity to MV, which increases SAM-septal contact.
   - Increased preload = Decreased LVOT obstruction. Decrease in murmur.
     Examples: Squatting and beta-blockers.
   - Increased afterload/decreased contractility = Decreased LVOT obstruction.
     Examples: Phenylephrine, handgrip, and beta-blockers.
     Mechanism: LVOT gradient and velocities decrease, which lessen SAM.
   - Decreased afterload/increased contractility = Increased LVOT obstruction.
     Examples: Vasodilators and inotropes.
     Mechanism: LVOT gradient and velocities increase, which worsen SAM.
2. Diastolic dysfunction.
   - Increased myocardial thickness, interstitial fibrosis, and replacement scarring in HCM all lead to impaired relaxation and filling.
   - Increased oxygen consumption in the setting of elevated left ventricular end-diastolic pressures (LVEDP) and resultant decreased coronary perfusion can cause cardiac ischemia [7, 8].
   - Longer standing elevations in LVEDP lead to left atrial dilation and increased risk of atrial fibrillation [9].

3. Myocardial disarray and arteriole hypertrophy.
   - Chaotic myocyte distribution with surrounding fibrosis results in electrically unstable substrate that may increase the risk of sudden cardiac death (SCD).
   - Coronary arteriole hypertrophy diminishes luminal area and the ability to augment appropriate vasodilatory responses and leads to microvascular ischemia, which further increases the risk of SCD and heart failure [8] (Fig. 14.1).
4. Mitral valve abnormalities.
   - Commonly associated with HCM and acts to increase dynamic LVOT obstruction.

Physical Exam

Murmur Characteristics

- Medium-pitched to harsh systolic ejection murmur
- Most prominent at left lower sternal border and apex

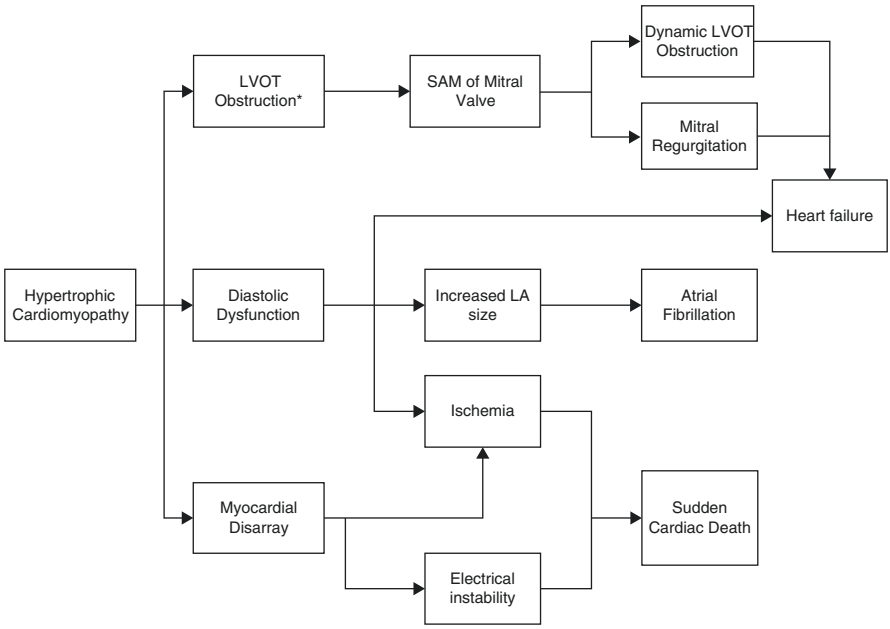

Fig. 14.1 Pathophysiology and clinical manifestations of HCM. *LVOT obstruction present in 2/3 of HCM patients with provocation. *HCM* indicates hypertrophic cardiomyopathy, *LVOT* left ventricular outflow tract, *SAM* systolic anterior motion, *LA* left atrium, *AF* atrial fibrillation, and *SCD* sudden cardiac death

- Increases with maneuvers that decrease preload (Valsalva, changing position from squatting to standing)
  - Aortic stenosis murmur diminishes with these maneuvers.
- Diminishes with maneuvers that increase afterload (handgrip) or preload (squatting)
- Grade ≥ 3/6 likely have significant LVOT gradients (≥30 mmHg)

Other Exam Findings

- Holosystolic murmur of MR may be heard at apex.
- Pulsus bisferiens (rapidly rising, double-peaked arterial pulse).
- Sustained PMI, S4, and/or split S2 if outflow obstruction is severe.

Diagnostic Testing

Electrocardiogram

- Baseline ECG should be performed on all patients with suspected HCM. Serial 48-h Holter monitoring should be performed if diagnosis of HCM is made.
- One or more nonspecific EKG abnormalities are seen in 90% of patients with HCM and include:
  - Left ventricular hypertrophy
  - Left atrial enlargement
  - Anterolateral and inferior deep, narrow Q waves ("pseudo-Q waves")
  - Nonspecific ST-segment changes
  - T-wave inversions (apical variant classically with deep TWI in the lateral precordium) [10]

Transthoracic Echocardiogram

- An echocardiogram should be performed at the initial evaluation in all patients with suspected HCM. Provocative testing with amyl nitrate, Valsalva, or exercise may be needed if there is suspected HCM but no obstruction on resting TTE [11].
- Common TTE findings:
  - Asymmetric hypertrophy
  - Septum/posterior wall thickness ≥ 1.3
  - Septal thickness > 15 mm
  - SAM
  - Posteriorly directed MR jet

Cardiac Magnetic Resonance (CMR) Imaging

- CMR imaging is primarily indicated in those with suspected HCM and inconclusive TTE (i.e., unclear of magnitude and distribution of LV wall thickening or anatomy of mitral valve apparatus) or to help further stratify the patient's risk of SCD.
- Late gadolinium enhancement (LGE) identifies fibrosis. Greater than 15% LGE is associated with increased risk of SCD [12].

Cardiac Catheterization

- Brockenbrough sign: During the beat following a PVC, a decrease in pulse pressure, increase in LV systolic pressure, and increase in LV-Ao gradient. The pause following a PVC augments preload and contractility that leads to net worsening of dynamic LVOT obstruction (Fig. 14.2).

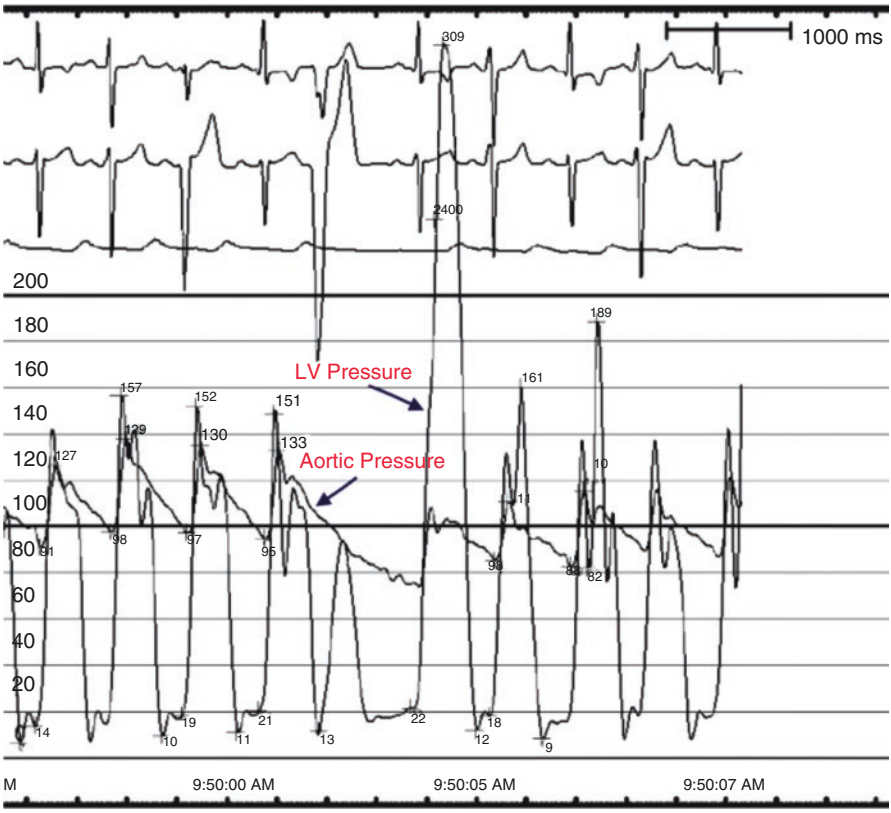

Fig. 14.2 Brockenbrough response. PVC results in compensatory pause that increases contractility. Normally, this increases aortic pulse pressure. The increased contractility in HCM causes increased LVOT obstruction and a decrease in pulse pressure in the post-PVC beat

– Post-PVC beat in normal subjects and patients with aortic stenosis results in increased LV AND pulse pressures.

Diagnosis

- Proposed clinical diagnostic criteria of HCM: All three items should be present.
  - Left ventricular wall thickness ≥ 15 mm (13–14 mm is considered borderline)
  - Non-dilated LV chamber
  - No alternative explanation of LV hypertrophy which includes:
    Long-standing hypertension
    Aortic stenosis
    Athlete's heart
    Renal failure
    Cardiac amyloid
    Glycogen storage diseases
    Anderson-Fabry's disease
    Friedreich's ataxia

Athlete's Heart

- Long-term intense athletic training can lead to a benign physiologic response of increased LV mass and wall thickness that is difficult to discern from HCM (Fig. 14.3). If there is sufficient concern for HCM, refraining from athletic activity for 4–6 weeks and repeating echocardiogram to assess for LVH regression are advised.

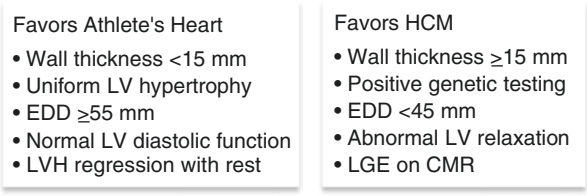

Fig. 14.3 Clinical findings differentiating athlete's heart and hypertrophic cardiomyopathy. *LV* indicates left ventricle, *EDD* end-diastolic diameter, *LVH* left ventricular hypertrophy, *LGE* late gadolinium enhancement, and *CMR* cardiac magnetic resonance imaging

Other Diagnostic Considerations

- Subclinical HCM. Pathologic HCM gene mutation (+) without above criteria. Patients require serial monitoring.
- Comorbidities associated with LVH AND suspected HCM.
- HCM is often presumed if LV septal thickness >25 mm and/or LVOT obstruction with systolic anterior motion of the mitral valve (SAM) [11].

Common Findings NOT Required for the Diagnosis of HCM

1. Flow obstruction. Absent in 2/3 of HCM patients at rest [13].
2. Asymmetric septal hypertrophy.
3. Systolic anterior motion of the mitral valve (SAM).

Screening

- Pre-participation screening. ECG screening for competitive athletes in high school and college sports is not currently mandated in the USA.
  - Personal and family history dictates whether further testing is indicated.
- Initial family screening is determined by whether or not a pathogenic mutation is identified in the proband.
  - If a genetic mutation is present, then family members should undergo genetic testing for the specific identified pathogenic mutation.
  - If no HCM mutation is identified in the proband, family members should be screened with serial imaging.
- The frequency of clinical follow-up in family members where no genetic mutation was identified or in patients with subclinical HCM (positive genetic testing, negative phenotype) is dependent on multiple factors (Fig. 14.4).

Activity Restrictions

- Patients with diagnosis of HCM should refrain from competitive athletics or strenuous activity due to SCD risk.
- Low-level activities such as bowling and golf are generally acceptable.

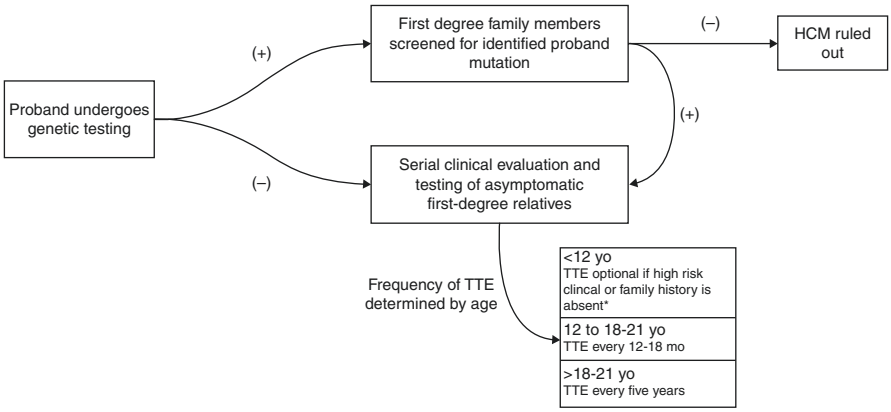

Fig. 14.4 Proposed genetic screening strategy in families with HCM. *Family history of sudden cardiac death or other complications from HCM, competitive athletes in intense training programs, suspicion of LVH or early onset of symptoms. Adapted from Maron, BJ, 2012 [2]

Treatment

Treatment of HCM is aimed at three distinct cardiac pathologies.

1. Sudden cardiac death.
   - Because the lifetime risk of SCD is <2% in HCM patients, AICD should be considered only in patients with ≥1 of the following risk markers [11]:
     History of cardiac arrest or hemodynamically unstable VT
     Family history of death due to HCM
     Unexplained syncope within 6 months
     - Patients with reduced LVEF, scarring, LVOT gradient ≥50 mmHg, multiple mutations, participation in intense sports, CAD, or prior alcohol septal ablation have lower thresholds for AICD placement including:
       Repetitive NSVT
       Abnormal BP response during exercise
   - ICD implantation to permit participation in competitive athletics or in subclinical HCM is contraindicated.
   - The use of the European Society of Cardiology SCD Risk Calculator is recommended in deciding who may benefit from an AICD (http://www.doc2do.com/hcm/webHCM.html).
2. Heart failure. Treatment is designated specifically for patients with symptoms.
   - Beta-blockers are first-line therapy regardless of underlying obstruction and/or systolic dysfunction.
   - Verapamil is a favored second-line agent due to its negative inotropic effect and improved effects on relaxation.

- Disopyramide is often added for improved relaxation with the added benefit of antiarrhythmic effects. It should be used with concomitant beta-blocker therapy as disopyramide can increase A-V nodal conduction.
- Invasive management options are considered if symptoms persist despite medical therapy when outflow tract obstruction is >30 mmHg either at rest or >50 mmHg with provocation [11] (Fig. 14.4).
  - Surgical myectomy: >95% success rate, LVOT decreased to <10 mmHg, and 3–10% risk of post-procedure permanent pacemaker (PPM) [1, 11, 14]
  - Alcohol ablation: >85% success rate, LVOT decreased to <25 mmHg, and 12–27% risk of post-procedure PPM [1, 11, 15, 16]

3. Atrial fibrillation.
   - Most prevalent sustained arrhythmia in HCM (~25%).
   - Patients with HCM tolerate atrial fibrillation poorly, owed to decreased diastolic filling time with faster heart rates and loss of atrial contraction in the setting of underlying diastolic dysfunction [17].
   - Rhythm control is often preferred with amiodarone or sotalol. Digoxin should be avoided due to potential worsening of obstruction from increased contractility.

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Chapter 15
Diagnosis, Prevention, and Treatment of Hypertensive Emergency/Hypertensive Crisis/Refractory Hypertension

Jesse Alan Doran and John Bisognano

Definitions

- **Hypertensive emergency**: Severe elevation in BP (commonly SBP ≥ 180 mmHg and/or DBP ≥ 120 mmHg) *and* acute end-organ damage. Most commonly affects cardiovascular, renal, and/or CNS: hypertensive encephalopathy, intracerebral hemorrhage, acute myocardial infarction, acute left ventricular failure with pulmonary edema, unstable angina, dissecting aortic aneurysm, eclampsia, etc. (Table 15.1).
- **Hypertensive urgency**: Severe elevation in BP (commonly SBP ≥ 180 mmHg and/or DBP ≥ 120 mmHg) *without* evidence of progressive end-organ damage. May have mild or moderate HA, SOB, epistaxis, pedal edema, and/or severe anxiety [1]. More frequently in patients who are nonadherent to Rx's or low-Na diet [2].
- Multiple terms with changing definitions: Malignant HTN, accelerated HTN, and hypertensive crisis/emergency/urgency. Currently nomenclature includes hypertensive crisis, which can be emergency or urgency [1].

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H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7_15

Table 15.1 Hypertensive emergencies

Cerebrovascular
• Hypertensive encephalopathy
• Ischemic stroke
• Intracerebral/subarachnoid hemorrhage
Cardiac
• Acute aortic dissection
• Acute left ventricular failure
• Acute or impending MI
• After CABG
Renal
• Acute renal failure
• Acute glomerulonephritis
• Tubulointerstitial nephritis
• Renal crises from collagen vascular disease
• Post-kidney transplant
• Microangiopathic hemolytic anemia
Excessive circulating catecholamines
• Pheochromocytoma crisis
• Food/drug interactions with MAOIs
• Sympathomimetic drug use (e.g., cocaine, amphetamines)
• Rebound HTN after sudden cessation of antihypertensive Rx (clonidine)
Obstetric
• Severe preeclampsia/eclampsia
• HELLP syndrome
Surgical
• Severe HTN in patients requiring immediate surgery
• Postoperative HTN
• Postoperative bleeding from vascular suture lines
Severe body burns
Severe epistaxis

[3–6]

Epidemiology and Clinical Significance

- Risk factors for hypertensive emergency: female sex, obesity, CAD, somatoform disorder, high # BP Rx's, noncompliance, sedentary lifestyle, increased age, and Caucasian [1].
- One study showed that hypertensive emergencies presented most commonly with chest pain (27%), dyspnea (22%), and neurological deficits (21%). Types of end-organ damage: cerebral infarction (24%), acute pulmonary edema (23%), hypertensive encephalopathy (16%), CHF (14%), and acute MI (12%) [3].
- Another study showed cerebral infarction (39%) and acute pulmonary edema (25%) were the most common types of end-organ damage [3].

Pathophysiology

Causes of Blood Pressure Spikes

- Most common is essential HTN—undertreatment, noncompliance, and antihypertensive withdrawal (especially clonidine). Most common in older patients.
- Less common cause is secondary to underlying pathological condition—renovascular HTN, renal parenchymal disease, collagen vascular disease, drug use/withdrawal, tyramine crisis, preeclampsia/eclampsia, pheochromocytoma, acute glomerulonephritis, head injury, renin- or aldosterone-secreting tumor, and vasculitis [7]. Most common in young Caucasian patients.

Pathological Changes of Chronic Hypertension Versus Acute Blood Pressure Elevation

- Blood flow to end organs (heart, brain, kidneys, etc.) is maintained by an intricate system of vascular autoregulation.
  - In the setting of elevated BP, arterial and arteriolar vasoconstriction occurs and protects against dangerously high perfusion pressures.
  - Likewise, a BP drop results in compensatory vasodilation to prevent hypoperfusion and ischemia.
- In response to chronic HTN, the muscular vessel walls hypertrophy.
  - Arterial thickening alters autoregulation to protect vital organs from persistently elevated pressure → "right shift" of normal regulatory curve—body's way of adapting to chronic HTN.
- Hypertensive crises occur at lower levels of BP in previously normotensive patients when compared to patient with chronic essential HTN.
  - Previously normotensive patients have unaltered regulatory range and are relatively less protected against end-organ damage.
  - Acute BP elevation in previously hypertensive-naïve patient (eclampsia or acute glomerulonephritis) may result in hypertensive emergency at a BP tolerated by a person with chronic essential HTN.
- Due to the "right shift," the low end of the autoregulatory control is relatively higher in chronic hypertensives.
  - More prone to ischemic events from hypoperfusion.
  - Great care must be taken not to lower BP too much or too rapidly when instituting antihypertensive therapy in chronic hypertensives [8, 9].
- Acute HTN results from known or unknown stimulus followed by compensatory mechanisms arising from vascular endothelium.

- Endothelium initially releases NO to compensate for high pressures.
- Arterioles sense high BP and smooth muscle (SM) contracts to protect downstream organs → prolonged contraction → endothelial dysfunction → inability to release more NO → further increase in BP.
- Shear wall stress → endothelial damage/dysfunction → expresses inflammatory cytokines → promotes (among other things) vasoconstriction [4].
- Elevated BP is then transmitted downstream causing damage to unprotected endothelium.
  - Permits enhanced vascular permeability with resultant leakage and deposition of plasma proteins and fibrinogen in the vessel walls as well as activation of mediators of coagulation and cellular proliferation
  - Ultimately results in a picture of microangiopathic hemolytic anemia and fibrinoid necrosis
- Endothelial damage ultimately results in arteriolar occlusion and consequent renal ischemia → hyperactivation of the renin-angiotensin system → hyper-renin state and increase levels of angiotensin II → further vasoconstriction and renal ischemia (cycle).
- Pressure natriuresis secondary to elevated BP → volume depletion → stimulating further renin release exacerbating this cycle of HTN

Approach to the Patient with Hypertensive Emergency/Urgency

- Good history, thorough physical exam, and basic diagnostic tests should yield sufficient information to determine whether a patient is experiencing hypertensive emergency and in immediate need of intensive care [9].
- Must confirm BP on evaluation.

History

- Prior diagnosis and treatment of HTN; use of prescribed or OTC Rx's (e.g., sympathomimetics); use of recreational drugs; current BP Rx's with doses, adherence, and last dose; and MAOi use.
- Chest discomfort (MI or dissection); acute, severe back pain (dissection); dyspnea (pulmonary edema); generalized neurologic symptoms such as agitation, delirium, stupor, seizures, or visual disturbances; focal neurologic symptoms (ischemic or hemorrhagic stroke); nausea/vomiting (increased intracranial pressure); symptoms of oliguria or azotemia (AKI); and pregnancy (preeclampsia/eclampsia).
- Table 15.2 demonstrates important aspects of the history.

Table 15.2
Important history in the hypertensive patient

Duration of HTN
• Last known normal BP
• Course of BP
Prior treatment of HTN
• Drugs: types, doses, side effects
Intake of agents that may cause HTN
• NSAIDs
• Cocaine/amphetamines
• Sympathomimetics
• MAOIs
• Estrogens/adrenal steroids
FHx
• HTN
• Premature CVD or death
• Familial diseases: pheochromocytoma (MEN 2A/2B), renal disease, DM, gout
Sx of secondary causes
• Spells of tachycardia, sweating, tremor
• Thinning of skin
• Flank pain
• Muscle weakness
Sx of target organ damage
• HA
• Transient weakness or blindness
• Loss of visual acuity
• Seizure
• Chest pain
• Dyspnea
• Claudication
Presence of other risk factors
• Smoking
• DM
• HLD
• Physical inactivity
Dietary Hx
• Sodium
• Processed foods
• EtOH
• Saturated fats
Psychosocial
• Stress
• Family structure
• Work status
• Education level
Sexual function
Features of sleep apnea
• Early morning HA
• Daytime somnolence
• Loud snoring
• Erratic sleep

[5, 6, 9, 10]

Physical

- Main goals of the physical examination are to evaluate for signs of end-organ damage and for evidence of a cause of identifiable HTN.
- Always check manual BP.
- The patient should sit quietly for 5 min before the BP is measured [11].
- Check BP in both arms: if there is a large disparity due to a unilateral arterial lesion (usually subclavian stenosis), the arm with higher pressure should be used [12].
- BP should be taken at least twice, with the measurements separated by 1–2 min to allow the release of trapped blood. If the second value is more than 5 mmHg different from the first, continued measurements should be made until a stable value is attained. The recorded value on the patient's chart should be the average of the last two measurements.
- Cuff should be inflated to a pressure approximately 30 mmHg greater than systolic, as estimated from the disappearance of the pulse in the brachial artery by palpation [13].
- Initial estimation of the systolic pressure by palpation avoids potential problems with an *auscultatory gap*, wherein the Korotkoff sounds transiently disappear as the cuff is deflated. (As an example, the Korotkoff sounds in a patient with a systolic pressure of 180 mmHg may be first heard at 180 mmHg, disappear at 165 mmHg, and then be reheard at 140 mmHg. If the cuff is only inflated to a pressure of 160 mmHg, no sounds will be heard until 140 mmHg; as a result, the latter value will be mistakenly considered to be the systolic pressure.)
- Alternative sites:
  - *Leg*—systolic pressure in the leg in normal subjects is usually 10–20% higher than that in the brachial artery.
  - *Wrist*—hydrostatic pressure related to the lower position of the wrist relative to the heart can result in a further false elevation of BP. This can be minimized by taking the BP with the wrist kept at the level of the heart.
- General exam (alertness); fundoscopic exam (flame hemorrhages, exudates [cotton wool spots], papilledema); cardiac exam (S3 or S4 [no S4 with Afib], PMI, JVP, auscultate for carotid/abdominal bruits[1], edema); pulmonary exam (rales); peripheral pulses; neurological exam (changes from baselines, orientation, visual changes, focal deficits) (Table 15.3).

Laboratory Evaluation and Other Studies

- Helps differentiate between emergency and urgency.
- Focused laboratory and diagnostic studies are valuable in evaluating the patient with hypertensive crisis. The following should be considered initially:

[1] The presence of an upper-abdominal bruit with a diastolic component that lateralizes toward one side is highly suggestive of renal artery stenosis.

Table 15.3 Important aspects of the physical exam in the hypertensive patient

Accurate measurement of BP
General appearance
• Distribution of body fat
• Skin lesions
• Muscle strength
• Alertness
Fundoscopy
• Hemorrhage
• Papilledema
• Cotton wool spots
• Arteriolar narrowing and arteriovenous nicking
Neck
• JVP
• Palpation/auscultation of carotids
• Thyroid
Heart
• PMI
• Rhythm
• Sounds
Lungs
• Rhonchi
• Rales
Abdomen
• Renal masses
• Bruits over aorta/renal arteries
• Femoral pulses
Extremities
• Peripheral pulses
• Edema
Neurologic assessment
• Visual disturbance
• Focal weakness
• Confusion

[5, 6, 9, 10]

  - BMP—may demonstrate features of renal insufficiency (i.e., elevated creatinine and potassium); hypokalemic metabolic alkalosis with or without concurrent hyponatremia may represent secondary aldosteronism, while hypernatremia may be a sign of primary aldosteronism.
  - CBC w/ diff—may demonstrate microangiopathic hemolytic anemia and intravascular coagulation.
  - UA—may demonstrate protein, RBCs, and oliguria.
  - ECG—may demonstrate evidence of LVH and strain or ACS [9].

- If ACS is suspected → cardiac enzymes.
- If heart failure is suspected → CXR.
- If aortic dissection is suspected → CTA chest.

- If stroke or encephalopathy is suspected → CT head or MR head.
- If intoxication/ingestion is suspected → urine toxicology.
- If pheochromocytoma is suspected → spot urine metanephrine level.
- If primary aldosteronism is suspected → plasma renin activity (PRA) and aldosterone level.
- If renovascular HTN is suspected → PRA before and 1 h after administration of an ACEi.

Differential Diagnosis

- Other pathologies may mimic the presentation of hypertensive crises.
- Included but are not limited to acute LV failure, uremia, CVA, SAH, brain tumor, head injury, epilepsy (postictal), collagen vascular disease (SLE), encephalitis, drug overdose/withdrawal, and acute anxiety disorder

Treatment

Hypertensive Emergency, Approach

- Severe elevation in BP (commonly SBP ≥ 180 mmHg and/or DBP ≥ 120 mmHg) *and* acute end-organ damage.
- Hypertensive emergencies are by definition medical emergencies.
- These patients require immediate admission to an intensive care setting.
- Best managed with continuous infusion of a short-acting, titratable Rx.
- Due to unpredictable pharmacodynamics, SL and IM formulations should not be used.
- In patients with more severe clinical manifestations or more labile BP, intra-arterial BP monitoring may be prudent.
- It is important to consider volume status. Due to pressure natriuresis, patients with hypertensive emergency may be volume depleted. IVF can help restore organ perfusion and prevent precipitous fall in BP with Rx's [5].
- JNC8 does not address acute HTN.
- JNC7: goal is to reduce MAP by no more than 25% within minutes to 1 h [14]. This is similar to European guidelines [15].
- Then, if stable, to 160/100–110 within next 2–6 h.
  - Antihypertensive therapy should be halted above this level if signs of tissue ischemia become evident.
- If this BP is well tolerated and patient is stable, one can further reduce toward normal BP over the next 24–48 h.

- It is imperative to avoid excessive and overly precipitous falls in BP as this may precipitate cerebral, myocardial, and/or renal ischemia. Elderly patients with known history of cerebrovascular disease have the highest risk of ischemia secondary to overaggressive treatment.
- As BP stabilizes and clinical improvement is apparent, oral antihypertensive Rx's should be initiated, and parental agents can then be slowly weaned [9, 14].
- There are two exceptions to the above when treating hypertensive emergencies:
  - In the treatment of acute ischemic stroke, the acute lowering of BP is contraindicated as increased cerebral perfusion pressures are necessary to provide adequate oxygenation to the penumbra. If SBP $\geq$ 220 mmHg or DBP > 120 mmHg, cautious lowering of the BP by approximately 15% during the first 24 h is suggested. In patients who are eligible for thrombolytic therapy, BP should be lowered to SBP $\leq$ 185 and DBP $\leq$ 110 [16].
  - In the treatment of aortic dissection, BP must be lowered rapidly and vigorously. Goal of rapid BP reduction to an SBP < 100 mmHg is reasonable if tolerated. BP lowering should be initiated once aortic dissection is seriously considered on the DDx and not delayed until the results of the imaging studies have been obtained [6, 8, 14].

Hypertensive Emergency, Therapy

- Due to their rapid onset of action, parenteral agents are preferred in the treatment of hypertensive emergencies (Table 15.4).
- Numerous effective parenteral agents exist today, and no one drug has been shown to have a mortality benefit over the others [17].
- In general, these Rx's can be divided into three broad categories based on their mode of action: *vasodilators, adrenergic antagonists*, and *diuretics*.
- Factors that must be considered during drug selection include rapidity of onset, ease of administration, and side effect profile [8, 14, 18].
- In the past nitroprusside has been the agent of choice for most hypertensive emergencies due to its immediate onset of action and ease of titration:
  - However, the administration of nitroprusside is a cumbersome task, commonly necessitating increased nursing care, continuous intra-arterial BP monitoring, and administration in an ICU setting.
  - Meeting these requirements can cost valuable treatment time.
- Administration of IV labetalol is less labor intensive and can be employed in a wide variety of settings.
  - While its time to onset may be longer than some other agents, the relative ease of IV labetalol administration may be more efficient and represent a preferable alternative profile [8].

Table 15.4 Parenteral Rx's for hypertensive emergency treatment

Drug	Mechanism of action	Dose range	Onset of action	Duration of action	Adverse effects	Role/special indications
Vasodilators						
Nitroprusside	Arterial and venous vasodilator	0.25–10 mcg/kg/min IV infusion Should not exceed 2 mcg/kg/min to avoid CN toxicity Patients who receive higher doses (>500 mcg/kg or rate > 2 mcg/kg/min) should receive thiosulfate to avoid CN toxicity	30 s–1 min	1–10 min	↑ICP, ↓cerebral blood flow, ↓coronary blood flow in CAD, CN toxicity, nausea, vomiting, muscle spasm, flushing, sweating	Generally avoided d/t toxicity Most hypertensive emergencies Should be avoided in patients with acute MI, CAD, CVA, ↑ICP, renal impairment, or hepatic impairment
Nitroglycerin	Arterial vasodilator	5–100 mcg/min IV infusion	2–5 min	5–10 min	Hypoxemia, reflex tachycardia, HA, vomiting, flushing, methemoglobinemia, tolerance w/prolonged use	ACS or acute pulmonary edema
Clevidipine	Dihydropyridine calcium channel blocker	Initially 1–2 mg/h IV infusion w/rapid titration Most patients respond to 4–6 mg/h with max dose 16 mg/h Delivered in lipid emulsion. 1000 mL max/24 h d/t lipid load	2–4 min	5–15 min	Afib, nausea, lipid formulation contains potential allergens (e.g., soy, egg)	Hypertensive emergencies, including postoperative HTN
Nicardipine	Dihydropyridine calcium channel blocker	5–15 mg/h IV infusion Some patients may require up to 30 mg/h	5–15 min	~1.5 min to ≥4 h	Reflex tachycardia, HA, dizziness, nausea, flushing, local phlebitis, edema	Most hypertensive emergencies including aortic dissection and pregnancy induced Avoid use in acute CHF Caution with coronary ischemia

Fenoldopam	Selective D1 and α2 agonists	Initially 0.1 mcg/kg/min IV infusion titrated to max 1.6 mcg/kg/min	5–10 min	30–60 min	Tachycardia, HA, nausea, flushing	Most hypertensive emergencies including aortic dissection Use caution with glaucoma or ↑ICP
Hydralazine	Arterial vasodilator	10–20 mg IV 10–40 mg IM	10–20 min IV 20–30 min IM	1 to ≥4 h IV 4–6 h IM	Sudden precipitous drop in BP, reflex tachycardia, flushing, HA, vomiting, aggravation of angina, SLE-like syndrome	In general, avoid d/t prolonged and unpredictable hypotensive effect Eclampsia Caution in aortic dissection and AMI
Enalaprilat	ACE inhibitor	1.25–5 mg q6h IV	15–30 min	~6 to ≥12 h	Precipitous fall in BP in high-renin states, hyperkalemia, variable response, HA, dizziness	Acute LV failure Avoid use in AMI, renal impairment, hyperkalemia, dehydration, or pregnancy Rarely use d/t slow onset and long duration
Adrenergic antagonists						
Labetalol	α and β antagonists	Initial bolus 20 mg IV → 20–80 mg IV bolus q10 min (max 300 mg) *or* 0.5–2 mg/min IV loading infusion following initial 20 mg IV bolus (max 300 mg)	5–10 min	2–4 h	Nausea/vomiting, paresthesias, bronchospasm, dizziness, nausea, heart block	Most hypertensive emergencies including MI, aortic dissection, hypertensive encephalopathy, pregnancy, and postoperative HTN Avoid use in acute CHF Use cautiously in COPD/asthma
Esmolol	Selective β1 antagonist	250–500 mcg/kg loading dose over 1 min; then 25–50 mcg/kg/min IV infusion; titrate to max 300 mcg/kg/min	1–2 min	10–30 min	Nausea, flushing, bronchospasm, heart block, infusion site pain, half-life prolonged in setting of anemia	Aortic dissection, perioperative HTN Avoid use in acute CHF, COPD/asthma, heart block
Phentolamine	α antagonist	5–15 mg IV bolus q5–15 min	1–2 min	10–30 min	Tachycardia, flushing, HA, nausea/vomiting	Alternative option for catecholamine excess (e.g., adrenergic crisis secondary to pheochromocytoma or cocaine)

[4–6, 17, 18, 20, 21]

- The use of diuretics as an initial therapeutic agent must be undertaken with caution.
- In a patient who is volume depleted, due to pressure-induced natriuresis and/or copious vomiting, the use of diuretics could hazardously result in renin-angiotensin axis hyperactivity:
  - These patients may instead have improvement in BP with IV saline repletion [10, 18].
- The effects of non-diuretic drugs may be blunted by reactive sodium retention caused by the initial therapeutic decrease in BP:
  - Further lowering of BP in this setting may be achieved with diuretics [8, 18].

Vasodilators

Nitrates—Vasodilators provide nitric oxide that induces vasodilatation (of both arterioles and veins) via generation of cyclic GMP, which then activates calcium-sensitive potassium channels in the cell membrane [6].

- **Nitroprusside**—Begins to act within 1 min or less, and once discontinued, its effects disappear within 10 min or less. Cyanide toxicity. High doses should never be given for more than 10 min. Sodium thiosulfate can be used in affected patients to provide a sulfur donor to detoxify cyanide into thiocyanate [19].
  - Acute pulmonary edema, severe LV dysfunction, and/or aortic dissection [5].
  - Arterial and venous vasodilator decreases both afterload and preload. Decreases cerebral blood flow while increasing intracranial pressure, which is problematic in patients with hypertensive encephalopathy or following CVA. In patients with CAD, coronary steal can occur. Onset seconds, duration 1–2 min, half-life 3–4 min. Tachyphylaxis. Forty-four percent of CN by weight. CN metabolized by liver to thiocyanate, which is 100× less toxic than CN. Thiocyanate excreted largely by kidneys. CN removal therefore requires liver/kidney function. Infusion rates >4 μg/kg/min for 2–3 h can lead to toxic levels. Infusion rate should not be >2 μg/kg/min. Infusion of thiosulfate should be used in patients receiving higher doses [5].
- **Nitroglycerin**—Similar in action and pharmacokinetics to nitroprusside except that it produces relatively greater venodilation than arteriolar dilation. It has less antihypertensive efficacy compared with other drugs used to treat hypertensive emergencies, and its effects on BP are variable from person to person and, potentially, from minute to minute. HA and rebound tachycardia.
  - NTG causes reflex tachycardia and reduces preload and CO (undesirable effects in patients with compromised cerebral and renal perfusion), can be used in low dose if emergency is a/w coronary ischemia or pulmonary edema [5], and is useful as a short-term bridge to the initiation of other Rx's.

Calcium Channel Blockers

- **Clevidipine**—Ultrashort-acting dihydropyridine CCB. Half-life 5–15 min. Reflex tachycardia. Contraindicated with severe AS (risk severe hypotension), disordered lipid metabolism (it is administered in a lipid-laden emulsion), or known allergies to soy or eggs (these are used to produce the emulsion).
  - Third-generation dihydropyridine CCB. Ultrashort selective arteriolar vasodilator. Reduces afterload without affecting cardiac filling pressures or causing reflex tachycardia. Stroke volume and CO usually increase [5].
- **Nicardipine**—Dihydropyridine CCB. Long onset of action. Half-life 3–6 h.
  - Second-generation dihydropyridine CCB. High vascular selectivity and strong cerebral and coronary vasodilatory activity. Onset 5–15 min, duration 4–6 h. Shown to reduce cardiac and cerebral ischemia. Dosing is independent of weight; start infusion at 5 mg/h, and increase by 2.5 mg/h every 5 min to maximum 15 mg/h. It has been demonstrated to increase both stroke volume and coronary blood flow with a favorable effect on myocardial oxygen balance, is useful in patients with CAD and HFrEF [5], and often has high volume of administration.

Dopamine-1 Agonist

- **Fenoldopam**—Peripheral DA-1 receptor agonist. Unlike other parenteral antihypertensive agents, it maintains or increases renal perfusion while it lowers BP and may be particularly beneficial in patients with renal impairment [18].
  - Peripheral vasodilation by acting on peripheral DA-1 receptors. Rapidly and extensively metabolized by liver without P-450. Onset within 5 min, max response by 15 min, duration 30–60 min. No adverse effects have been reported. Start 0.1 μg/kg/min. It improves CrCl, urine flow rate, and Na excretion in severely hypertensive patients with both normal and impaired renal function [5].

Others

- **Hydralazine**—Direct arteriolar vasodilator with little or no effect on the venous circulation. Precautions are needed in patients with underlying CAD or aortic dissection (reflex tachycardia), and a beta-blocker should be given concurrently to minimize reflex sympathetic stimulation.
  - Hydralazine is a direct vasodilator; following IM or IV administration, there is latent period of 5–15 min followed by progressive and often precipitous fall in BP that can last up to 12 h. Circulating half-life is 3 h, but effect on BP lasts around 10 h. Prolonged and unpredictable effects and inability to titrate [5].

- **Enalaprilat**—Parental des-ethyl ester of the ACEi enalapril. Hypotensive response to enalaprilat is unpredictable and depends upon the plasma volume and plasma renin activity. Hypovolemic patients with high plasma renin activity more likely excessive hypotension. ACEi contraindicated in pregnancy, severe renal artery stenosis with global ischemia, and severe hyperkalemia. Onset of action begins in 15 min, but the peak effect may not be seen for 4 h. The duration of action ranges from 12 to 24 h.

Adrenergic Antagonists

- **Labetalol**—Combined beta-adrenergic and alpha-adrenergic blocker. Rapid onset of action (≤5 min). However, one trial found that labetalol has less antihypertensive efficacy as compared with nicardipine [20] and should not be used without prior adequate alpha blockade in patients with hyperadrenergic states.
  - Alpha-beta ratio = 1:7. Metabolized in liver. Hypotensive effect begins within 2–5 min, reaching peak at 5–15 min, lasting 2–4 h. HR maintained or reduced d/t BB effect. Maintains CO unlike pure BB. Can be given as load 20 mg, followed by repeat dose 20–80 mg at 10-min intervals. Can also start infusion at 1–2 mg/min. Bolus of 1–2 mg/kg is shown to produce precipitous drop in BP and should be avoided [5].
- **Esmolol**—Effects begin almost immediately, and it has both a short half-life (about 9 min) and a short total duration of action (about 30 min), permitting rapid titration.
  - Ultrashort, cardioselective BB. Onset within 60 s, duration 10–20 min. Metabolized by RBC esterases, not dependent on renal or hepatic function. Especially useful with severe postoperative HTN. Typically, 0.5–1 mg/kg load over 1 min, followed by infusion at 50 μg/kg/min and increasing up to 300 μg/kg/min [5]
- **Phentolamine**—Nonselective alpha-adrenergic blocker. Only for increase catecholamine activity. PO—phenoxybenzamine.

Diuretics

Volume depletion is common in hypertensive emergencies. Diuretics should only be used in setting of volume overload.

Disease-Specific Recommendations [4]

- **Myocardial ischemia**—Elevated SVR increases LV myocardial wall tension and O2 demand, myocardial perfusion insufficient. Patients with longstanding HTN may have LVH, which itself increases myocardial O2 demand; this

increased mass can also cause some degree of coronary artery compression (decreased luminal flow). Prefer nitrates (lower LV preload and improve coronary blood flow) and BB (reduce HR, decrease afterload, and improve diastolic coronary perfusion). Hydralazine should be avoided as it can induce reflex tachycardia and increase cardiac work.

- **Acute heart failure**—Pulmonary edema (incidence 36%), which is the second most common sign of end-organ damage. It was thought to be due to diastolic dysfunction due to ischemia, not depressed EF. Sodium nitroprusside—thought to be best—decreases both preload/afterload and has rapid onset of action and short half-life. CN toxicity is rare. Thiocyanate toxicity is uncommon and occurs in those with high doses and renal insufficiency. Clevidipine = new third-generation dihydropyridine CCB shown in small study to be effective at reducing BP without adverse events. Selectively inhibits extracellular Ca influx through L-type channels → smooth muscle relaxation → decrease PVR. Metabolized by plasma esterases so independent of renal or hepatic function. Loop diuretics.
- **Aortic dissection**—Can be misdiagnosed as coronary ischemia, pleurisy, CHF, stroke, MSK, or acute abdomen. Dissection can extend into coronary arteries and present with history/EKG findings identical to those of acute MI. Presentation—3 Rs (rapid onset, ripping, and radiating in the chest, back, or both). Dx with CT w/ contrast, MR, or TEE (CT best since rapid). Type A—dissection is surgical emergency. Type B—dissection can be managed medically. Goal SBP < 100 and HR < 65. IV BB (esmolol or labetalol) reduces shear stress on aorta. Nitroprusside.
- **Acute renal insufficiency**—Endothelial dysfunction and impaired vasodilation, altering autoregulation in chronic HTN → increased intraglomerular pressure with increased systemic arterial pressure. Emergency can occur in acute GN, HUS, RAS, on HD receiving EPO with an accelerated rate of Hct, renal transplant patients especially those on cyclosporine and corticosteroids. Proteinuria, elevated Cr, hypokalemic metabolic alkalosis, and MAHA. Minoxidil—direct arteriolar vasodilator, useful when a/w renal failure, can cause reflex tachycardia and fluid retention. ACEi (captopril, enalapril) in scleroderma renal crisis. Fenoldopam—it is a selective DA-1 receptor agonist that activates DA at the level of the kidney and is recommended because it increases renal perfusion. CCB and BB can also be used but have no effect on glomerular filtration.
- **Hyperadrenergic states**—Pheo, cocaine/amphetamine, phencyclidine overdose, clonidine withdrawal, and MAOi tyramine reaction—there is surge in catecholamine levels. Pheo and MAOi—phentolamine, phenoxybenzamine, or nitroprusside. No BB alone due to unopposed alpha. Can get paradoxical HTN with labetalol even though alpha and beta. Cocaine or amphetamine—anxiolytics 1st, phentolamine can be added.

Hypertensive Urgency, Approach

- Severe elevation in BP (commonly SBP ≥ 180 mmHg and/or DBP ≥ 120 mmHg) *without* evidence of progressive end-organ damage. Often present with mild HA.

- Can be alarming for both patients and physicians; however, in the absence of impending or ongoing tissue damage, it is important to realize that the patient is not at imminent risk.
- Should not require hospital admission and in almost all cases can be safely treated in the outpatient office setting.
- The JNC7 recommends treatment with oral antihypertensives and observation to safely lower BP gradually. Special emphasis is placed on the importance of prompt outpatient follow-up to ensure BP control is achieved [14].
- More frequently in patients nonadherent to Rx's or low-Na diet [2].
- Severe HTN can develop in medication-adherent patients following ingestion of large quantities of salt and can be controlled by resuming a low-salt diet [22, 23].
- Rapidity of lowering BP is controversial and not based on high quality evidence:
  - Gradual over hours to days. Those with high risk of cardiovascular events (e.g., known aortic aneurysm) should have BP lowered over hours. Those not at high risk of cardiovascular event should have BP lowered over hours to days.
  - No proven benefit of rapid BP reduction with severe asymptomatic HTN [14, 15, 24].

Hypertensive Urgency, Therapy

- There is lack of compelling evidence to recommend one antihypertensive agent or class of agents over another in treating hypertensive urgencies, but a list of commonly used and well-tolerated medications is shown in Table 15.5.
- Certain agents, however, should be avoided:
  - Data suggests that sublingual nifedipine and sublingual captopril have the potential to lower BP in a rapid and uncontrolled fashion and may result in morbidity from cardiac and cerebral ischemia [18, 25].
- Goal is to reduce BP to $\leq$160/$\leq$100 mmHg, but the mean arterial pressure should not be lowered by more than 25–30% over the first several hours [14, 24].
- Many hypertensive urgencies occur in known hypertensives who are inadequately treated:
  - For these individuals, it may make sense to restart or increase the dose of a current Rx.
  - On the other hand, if a Rx's side effects are causing noncompliance, it would be prudent to offer a Rx with more tolerable profile.
  - Addition of diuretic and dietary sodium restriction if etiology is high Na intake.
- In other situations, it may be useful to add an additional agent to a patient's regimen for additional BP lowering.

Table 15.5 Oral antihypertensives for hypertensive urgency treatment

Drug	Mechanism of action	Dose range	Onset of action	Duration of action	Adverse effects
Nifedipine	Dihydropyridine calcium channel blocker	10–20 mg	5–15 min	3–5 h	Avoid sublingual administration
Captopril	ACE inhibitor	6.25–50 mg	15 min	4–6 h	Hyperkalemia, angioedema
Clonidine	Selective α2 agonist	0.2 mg then 0.1 mg/h–0.7 mg/h	0.5–2 h	6–8 h	Sedation, dry mouth, rebound HTN on d/c
Labetalol	α and β antagonists	200–400 mg	0.5–2 h	4 h	Caution in pts with beta-blocker contraindications

[8, 26]

- Be sure to remember that medication noncompliance can be a result of a drug's cost (financial side effects) as well as its true physical side effects.
- Certain Rx's, though effective, may be less desirable to use in hypertensive urgencies:
  - Clonidine is an effective antihypertensive; however, risks of rebound HTN may outweigh its benefits when used in an urgent care situation where follow-up and patient compliance cannot be guaranteed.
  - Other antihypertensives such as amlodipine and HCTZ can take days to affect BP.

Approach to the Patient with Refractory HTN

Introduction, Definitions, Epidemiology, and Risk Factors

- Patients with persistent HTN despite multiple Rx's are at high risk for adverse cardiovascular events and are more likely than those with controlled HTN to have a secondary (i.e., identifiable) cause, which is usually at least in part reversible.
- **Resistant HTN** = uncontrolled BP on ≥3 Rx's of different classes *or* controlled BP on ≥4 Rx's of different classes [15, 27].
- **Refractory HTN** = uncontrolled BP on maximal medical therapy (≥5 Rx's including chlorthalidone and mineralocorticoid receptor antagonist) under the care of a HTN specialist [28].
- Pseudoresistant HTN = attributable to other factors. Most common: inaccurate measurement (small cuff), noncompliance, suboptimal therapy, noncompliant lifestyle/diet, white coat HTN, untreated OSA, and use of NSAIDs.
- If tolerable, one agent should be diuretic and all agents should be prescribed at optimal dose [27].

- 1.9% of patients diagnosed with HTN meet criteria for resistant HTN at 1.5 years (excluded nonadherence and pseudoresistance) [29].
- In an unselected, population-based sample of 15,968 adults in the United States, the prevalence of resistant HTN was 8.9% among all individuals with HTN and 12.8% among those treated with antihypertensive Rx's [31].
- In selected populations of hypertensive patients who seek medical care, the prevalence may be higher, ranging from 12.3% in Spain to 16% in the southeastern United States [32–34].
- An analysis of antihypertensive medication prescriptions written in the United States suggested that the prevalence of more difficult-to-control HTN is increasing. The proportion of hypertensive patients receiving three or more BP Rx's increased from 14 to 24% between 1994 and 2004. Possible reasons for the increase in difficult-to-control HTN include increases in the average age and the average weight of the population. Data were not given on resistant HTN [29, 30].
- Predict difficult-to-control HTN: older age, higher baseline BP (particularly systolic), presence of left ventricular hypertrophy, obesity, African-American race, chronic kidney disease, and diabetes [35].
- Potentially reversible factors (Table 15.6):
  - Suboptimal therapy: most often due to the lack of administration of more effective drugs and failure to prevent volume expansion with adequate diuretic therapy [15].
  - Lifestyle/diet: obesity, high-Na diet, and physical inactivity.
  - Medications: NSAIDs, sympathomimetics (decongestant, diet pills, cocaine), stimulants (amphetamines), EtOH, OCP, cyclosporine, EPO, licorice, and herbal compounds (ephedra, ma huang).
  - Extracellular volume expansion: CKD, Na retention (vasodilators or diet).
  - Secondary causes (Table 15.7):

Table 15.6 Agents that can interfere with blood pressure control

Non-narcotic analgesics (NSAIDs, selective COX-2 inhibitors, ASA)
Sympathomimetic agents (decongestants, diet pills)
Stimulants (methylphenidate, dexmethylphenidate, dextroamphetamine, amphetamine, modafinil)
Illicit drugs (cocaine, methamphetamine)
EtOH
Oral contraceptives
Glucocorticoids, mineralocorticoids
Cyclosporine, tacrolimus
Atypical antipsychotics (clozapine, olanzapine)
EPO
VEGF inhibitors
Natural licorice
Herbal compounds (ephedra or ma huang)

[27, 37, 38]

Table 15.7 Secondary causes of resistant HTN

Common
• OSA
• Renal parenchymal disease
• Primary aldosteronism
• Renal artery stenosis
• Medications
Uncommon
• Pheochromocytoma
• Cushing's disease
• Hyperparathyroidism
• Aortic coarctation
• Intracranial tumor

[27, 37]

Common: primary aldosteronism (10–20%) with unexplained hypokalemia, but >50% of patients have normal K; RAS (atherosclerosis or fibromuscular dysplasia in younger patients); CKD; OSA (severity of HTN correlates with severity of disease; screen if resistant HTN and having obesity, loud snoring, or daytime sleepiness [36]).
Uncommon: pheochromocytoma, Cushing's syndrome, and coarctation of aorta.
Clinical features of these causes of secondary HTN are shown in Table 15.8.

Evaluation

- History, physical exam, and basic labs.
- Workup for potentially reversible causes or secondary causes.
- 24-h urine collection should be obtained on the patient's usual diet for determination of sodium excretion, creatinine clearance, and aldosterone excretion.
- If primary aldosteronism is suspected (HTN with hypokalemia and metabolic alkalosis)—paired morning measurement of the plasma aldosterone concentration (PAC) and plasma renin activity (PRA) to determine whether the patient has an elevated or high-normal PAC, suppressed PRA, and elevated PAC/PRA ratio.
- Most patients should undergo noninvasive evaluation for renal artery stenosis (RAS). Clinical clues to renovascular disease:
  - HTN before 30 y.o. (especially w/o FHx) or recent onset of significant HTN after 55 y.o.
  - Abdominal bruit, particularly if it continues into diastole and is lateralized.
  - Recurrent (flash) pulmonary edema.
  - Renal failure of uncertain etiology, especially with normal urinary sediment.

Table 15.8 Clinical features of different causes of secondary HTN

Disorder/etiology	Suggestive clinical features
General	Severe or resistant HTN Acute rise in BP over a previously stable value Age of onset before puberty Age < 30 years with no FHx of HTN and no obesity
Renovascular disease	Acute elevation in Cr of at least 30% after administration of ACEi or ARB Moderate-to-severe HTN in a patient with diffuse atherosclerosis, unilateral small kidney, or asymmetry in renal size >1.5 cm that cannot be explained by another reason Moderate-to-severe HTN in patients with recurrent episodes of flash pulmonary edema Onset of stage II HTN after age 55 years Systolic or diastolic abdominal bruit (not very sensitive)
Primary renal disease	Elevated serum Cr Abnormal UA
Pheochromocytoma	Paroxysmal elevation in BP Triad of HA (usually pounding), palpitations, and sweating
Primary aldosteronism	Unexplained hypokalemia with urinary K wasting (>50% patient normokalemic)
Cushing's syndrome	Cushingoid facies, central obesity, proximal muscle weakness, ecchymoses May have Hx of glucocorticoid use
Sleep apnea	Common in patients with resistant HTN, particularly overweight or obese Loud snoring or witnessed apneic episodes Daytime somnolence, fatigue, morning confusion, or headache
Coarctation of the aorta	HTN in the arms with diminished or delayed femoral pulses and low or unobtainable BP in legs
Hypothyroidism	Symptoms of hypothyroidism Elevated TSH
Primary hyperparathyroidism	Elevated Ca
Medications	New HTN temporally related to use

[27, 38]

  - Coexisting diffuse atherosclerotic vascular disease, especially in heavy smokers.
  - Acute renal failure precipitated by anti-HTN therapy, especially ACEi/ARB.
  - Noninvasive screening tests: captopril-enhanced radionuclide renal scan, duplex Doppler flow studies, or MRA.
  - Definitive Dx is with renal angiogram [14].

- If pheochromocytoma is suspected (episodic HTN, HA, sweating, tachycardia)—24-h urine fractionated metanephrines and catecholamines.
- If Cushing's syndrome is suspected (weight gain, plethora, round face, hirsutism, dorsal fat pad)—late-night salivary cortisol (two measurements), 24-h urinary

free cortisol excretion (two measurements), or the overnight dexamethasone suppression test.

Treatment Refractory HTN

- General principles of treatment:
  - Identify and treat secondary causes of HTN.
  - Stop medications that raise BP.
  - Refer to HTN specialist if uncontrolled despite 6 months of therapy.
  - Out-of-office BP monitoring.
  - Non-pharmacologic therapies: low-Na diet, weight loss, and moderation of EtOH.

    A 24-h urine collection can be used to estimate sodium intake.

Pharmacologic Therapy

Diuretics

- Persistent volume expansion (typically not sufficient to produce edema) contributes to resistant HTN, even among patients who have been on conventional doses of thiazide diuretics [2].
- Little renal impairment: chlorthalidone and indapamide preferred over HCTZ [39, 40].
  - Chlorthalidone and indapamide have a more potent antihypertensive effect than hydrochlorothiazide due, in part, to their much longer half-life.
  - Change HCTZ to chlorthalidone/indapamide.
- GFR < 30: thiazides less effective and loop diuretics (furosemide, torsemide, bumetanide) may be needed for volume control. Torsemide longer lasting, preferred.

Mineralocorticoid Receptor Antagonists

- Spironolactone and eplerenone = mineralocorticoid receptor antagonists and potassium-sparing.
- Potassium-sparing diuretics (amiloride and triamterene) = block collecting tubule sodium channels that are normally opened by aldosterone.

- Spironolactone, eplerenone, and amiloride provide significant antihypertensive benefit when added to existing multiple-drug regimens in patients with resistant HTN [41–43]:
  - May reflect, at least in part, significantly higher plasma aldosterone levels in patients with resistant HTN compared with individuals who have normal BP or controlled HTN on one or two Rx's [2]

Choice of Regimen

- Following approach for those without reversible secondary causes with no specific indication for class of Rx (e.g., BB for rate control in Afib).
- ACEi/ARB + long-acting dihydropyridine CCB (e.g., amlodipine) + long-acting thiazide (chlorthalidone or indapamide) [44].
- If already on above regimen, add spironolactone.
- Most uncontrolled patients on three-drug regimen differ from ACEi/ARB + CCB + chlorthalidone, and most patients on four-drug regimens are not on mineralocorticoid receptor antagonist [45]:
  - Change HCTZ to chlorthalidone or indapamide.
  - If missing a class as above, add it.
  - Do not stop other Rx's if tolerated prior to achieving BP control.
  - If on three Rx's as above, add mineralocorticoid receptor antagonist.
- If on four Rx regimens, additional medications added sequentially:
  - Vasodilating beta-blockers (carvedilol, labetalol, bisoprolol, nebivolol)
  - Centrally acting agents (clonidine or guanfacine)

    Adverse effects are common.
  - Direct vasodilators (hydralazine or minoxidil)

    Fluid retention and tachycardia are common side effects. Hirsutism with minoxidil.

Blood Pressure Goals

- 2017 ACC/AHA Hypertension Guidelines redefine HTN and BP goals [38].
- Normal BP is <120/80 mmHg; elevated BP 120–129/<80 mmHg; HTN stage 1 SBP 130–139 mmHg or DBP 80–89 mmHg; HTN stage 2 SBP ≥ 140 mmHg or DBP ≥ 90 mmHg.
- Treatment to goal BP < 130/80 recommended for those with DM, CKD, or 10-year ASCVD risk ≥10%.
- Treatment to goal BP < 140/90 recommended for others.
- Significant emphasis placed on proper measurement.

Future Directions

Hypertensive Emergency/Urgency/Crisis

- HTN remains among the most important public health issues, leading to markedly increased risk of cardiovascular, renal, and neurological disease.
- Though we have an ever-expanding list of pharmaceuticals at our disposal for the treatment of high BP, HTN remains underdiagnosed and undertreated.
- Hypertensive crises—most commonly result of exacerbation of essential HTN [26].
- To decrease the incidence, morbidity, and cost of these events, the importance of adequately identifying and managing essential HTN by PCPs cannot be overemphasized.
- True hypertensive emergencies are just that: emergencies. General agreement exists in their management.
- In contrast, hypertensive urgencies do not represent such an imminent risk, and their management remains quite varied.
  - It is possible that hypertensive urgencies tend to be treated with too much enthusiasm and an unnecessary sense of impending crisis.

    This results in long ED visits and costly hospital admissions for a problem that could likely be managed in an outpatient setting (or even prevented in the first place).
  - It would be valuable to examine the course, treatment, and outcomes of hypertensive urgencies to reach treatment consensus on the "big numbers" of hypertensive urgencies which should be treated in this era of evidence-based medicine.

Refractory HTN

- Ongoing research on non-pharmacologic therapies for refractory HTN:
  - Catheter-based radiofrequency ablation of the renal sympathetic nerves

    Not been established. Initial study showed benefit but with many problems. Subsequent studies have not shown benefit.
  - Electrical stimulation of the carotid sinus baroreceptors or baroreflex activation therapy (BAT)

    Rheos Pivotal Trial and follow-up data have shown reductions in BP. But trial did not meet two of five end points (acute responders and procedural safety), so it is not FDA approved [46].

– Central arteriovenous anastomosis

  Shunts a substantial amount of blood into the high-capacity, low-resistance venous system, which can decrease total SVR
  Initial studies with lowered BP but still early (no data on hemodynamics or long-term safety)

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Chapter 16
Syncope

Ramy Abdelfattah and Hanna Z. Mieszczanska

Definition

- Syncope is defined as an abrupt, transient, complete loss of consciousness. It is associated with the inability to maintain postural tone, with rapid and spontaneous recovery. It is more commonly referred to as fainting or "passing out."
- The presumed mechanism is cerebral hypoperfusion.
- This excludes other non-syncope causes of loss of consciousness, such as seizure, or antecedent head trauma.
- Syncope most often is associated with a benign underlying mechanism. However, episodes can still be life-threatening.
- Presyncope (near-syncope):
  - Symptoms prior to syncope include extreme lightheadedness, nausea, diaphoresis, visual sensations (i.e., "tunnel vision" or "graying out"), and varying degrees of altered consciousness.
  - Presyncope could be self-limiting or progress to syncope.

Incidence

- Syncope is common, with a lifetime incidence of 30% (Fig. 16.1).
- It accounts for 1–3% of emergency department visits [1].

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© Springer International Publishing AG, part of Springer Nature 2018

H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7_16

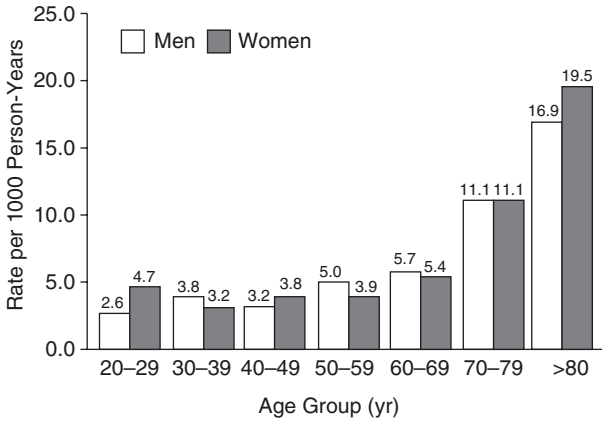

Fig. 16.1 Incidence rates of syncope according to age and gender reproduced with permission from Soteriades et al. [3]

- Syncope incidence increases with age, paralleled by a sharp increase at age 70.
- Females have been shown to report higher rates of syncope (22% versus 15%) [2].

Diagnosis [4, 5]

- In most patients, the cause of syncope can be determined from meticulous history and physical examination which includes orthostatic BP measurement [6].
- New 2017 ACC guidelines recommend avoiding unnecessary broad testing and only performing additional tests in selected patients based on previous records and physical examination [7].

History Taking

- Patient history should aim to identify the prognosis, diagnosis, reversible or ameliorable factors, comorbidities, medication use, and patient and family needs.
- When available, video recordings are helpful.
- Duration of the prodrome, time relationship to meals and physical activities are useful in differentiating neurally mediated from cardiac syncope.
- Comorbidities and medication use are important factors in older patients.
- A medical history involving the investigation for the presence of preexisting cardiovascular disease should be obtained.
- Family history should include determining whether there is a history of syncope or sudden unexplained death in family members.
- Medication lists should be carefully reviewed, especially in elderly patients and those with multiple medications. Several drug classes have been implicated in

syncope, including diuretics, vasodilators, negative chronotropes, proarrhythmic, QT-prolonging drugs, and sedatives [7].
- Syncope with lack of prodrome often favors an underlying cardiac cause (Table 16.1).

The Physical Examination

- Measurement of orthostatic blood pressure and heart rate changes in lying and sitting positions, on immediate standing, and after 3 min of upright posture. Orthostatic hypotension is a drop in systolic BP of ≥20 mmHg or diastolic BP of ≥10 mmHg with the assumption of an upright posture [8].
- Heart rate and rhythm should be recorded, as well as the presence of murmurs (aortic stenosis murmur, or hypertrophic obstructive cardiomyopathy (HOCM) murmur), gallops, elevation of JVD, edema, or pericardial rubs that would indicate the presence of structural heart disease.
- Neurological examination should be performed to identify any focal neurological defects or other abnormalities that would suggest the need for further neurological evaluation or referral.

Risk Stratification

- Evaluation of the cause and assessment of the short-term and long-term morbidity and mortality risk of syncope (class I) [7].

Table 16.1 History and physical characteristics with increased probability of cardiac and noncardiac causes of syncope

Favors cardiac syncope	Favors noncardiac syncope
• Older age (>60 years) • Male sex • PMH of IHD, CHD, structural heart disease, previous arrhythmias, or reduced ventricular function • Brief prodrome, such as palpitations, or sudden loss of consciousness without prodrome • Syncope during exertion • Syncope in the supine position • Low number of syncope episodes (1 or 2) • Abnormal cardiac examination • Family history of inheritable conditions or premature SCD (<50 years of age)	• Younger age • No known cardiac disease • Presence of prodrome: nausea, vomiting, feeling warmth • Presence of specific triggers: dehydration, pain, distressful stimulus, medical environment • Situational triggers: cough, laugh, micturition, defecation, deglutition • Syncope only in the standing position or positional change from supine or sitting to standing • Frequent recurrence and prolonged history of syncope with similar characteristics

Reproduced with permission from Shen et al. [7]
IHD ischemic heart disease, *CHD* congenital heart disease, *SCD* sudden cardiac death

- The short-term prognosis in syncope patients is mainly related to the cause of syncope in addition to the acute reversibility of the underlying condition.
- The long-term prognosis is primarily related to the progression and severity of the underlying disease and the effectiveness of therapy.
- Cardiac syncope carries a significantly worse prognosis (Table 16.2).

Classification of Syncope

Reflex (Vasovagal/Neurocardiogenic) Syncope

- Most common form of syncope
- Pathophysiology [11]:
  - A reduced central blood volume secondary to venous pooling (i.e., with standing) or blood loss leads to a decrease in the venous return and consequently reduced left ventricular (LV) filling and cardiac output (CO). Normally this decreased LV is filling, and CO leads to reduced stimulation of the mechanoreceptors (vagal C fibers) in the wall of the left ventricle and reduced stimulation of baroreceptors in the carotid sinus and aortic arch, respectively. The result is increased sympathetic tone and maintenance of the blood pressure.
  - Two different neural pathways are involved in reflex syncope, one originating in the hypothalamus (central type) and the other in the heart (peripheral type).

Table 16.2 Short- and long-term risk factors reproduced with permission from Shen et al. [7]

	Short-term risk factors (≤30 days)	Long-term risk factors (>30 days)
History: outpatient clinic or ED evaluation	Male sex Older age (>60 years) No prodrome Palpitations preceding loss of consciousness Exertional syncope Structural heart disease Heart failure Cerebrovascular disease Family history of SCD Trauma	The absence of nausea/vomiting preceding syncopal event [9] Ventricular arrhythmias Cancer Structural heart disease Heart failure Cerebrovascular disease High CHADS-2 score [10] Diabetes mellitus
Physical examination or laboratory investigation	Evidence of bleeding Abnormal ECG Persistent, abnormal vital signs Positive troponin	Abnormal ECG Lower GFR

CHADS-2 indicates congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and stroke or transient ischemic attack, *ECG* electrocardiogram, *ED* emergency department, *GFR* glomerular filtration rate, *SCD* sudden cardiac death, and *VA* ventricular arrhythmias

The central form of reflex syncope is the emotionally induced vasovagal faint (triggered by emotional stress or pain) which involves direct hypothalamic activation of the medullary cardiovascular centers causing a vasovagal response.
In patients with the peripheral form of reflex syncope, vigorous LV contraction occurs in response to reduced venous return. Hence the afferent signals (parasympathetic C fibers) from the left ventricle override the baroreceptor responses. This leads to an inappropriate decrease in sympathetic tone and an increase in parasympathetic (vagal) tone.

- Vasovagal responses include bradycardia (results from sudden augmentation of efferent vagal activity) and hypotension (results from sudden reduction or cessation of sympathetic activity and relaxation of arterial resistance vessels).

- Includes
  - Vasovagal syncope (VVS)

    Most common form of reflex syncope.
    Mediated by the vasovagal reflex (the development of inappropriate cardiac slowing and arteriolar dilatation).
    Triggers: upright posture (standing or seated) or with exposure to emotional stress, pain, or medical settings.
    Typically, it has a characteristic prodrome: diaphoresis, warmth, nausea, and pallor.
    Associated with vasodepressor hypotension and/or inappropriate bradycardia
    Often followed by fatigue.
    Typical features may be absent in elderly patients.
    Diagnosis is made primarily by a thorough history, physical examination, and eyewitness observation, if available.

  - Carotid sinus syndrome

    Defined as syncope plus carotid sinus hypersensitivity.
    Carotid sinus hypersensitivity is present when a pause $\geq$3 s and/or a drop in systolic pressure $\geq$ 50 mmHg occurs upon stimulation of the carotid sinus.
    It occurs more frequently in elderly patients.

  - Situational syncope

    Associated with coughing, laughing, swallowing, micturition, or defecation

Cardiac Syncope

- Syncope caused by bradycardia, tachycardia, or hypotension
- Explained by low cardiac index, blood flow obstruction, vasodilatation, or acute vascular dissection

Orthostatic Hypotension (OH)

- A decrease in systolic BP of ≥20 mmHg or diastolic BP of ≥10 mmHg with the assumption of an upright posture
- Includes:
  - Initial (immediate) OH: transient OH within 15 s after standing, with presyncope or syncope
  - Classic OH: sustained OH within 3 min of assuming an upright posture
  - Delayed OH: sustained but gradual OH (or drop of systolic BP 30 mmHg in patients with supine hypertension) which takes >3 min of upright posture to develop
  - Neurogenic OH:

    A subtype of OH that is due to dysfunction of the autonomic nervous system (autonomic insufficiency).
    This can be present in long-standing diabetics due to lesions involving the central or peripheral autonomic nerves.

Unexplained Syncope

- Syncope with undetermined cause after an initial evaluation that includes but is not limited to a thorough history, physical examination, and ECG
- Common: 34–37% of cases

  Noncardiac syncope: volume depletion, dehydration, and blood loss

Other Causes

- Postural (orthostatic) tachycardia syndrome (POTS):
  - A diagnosis of POTS must fulfill the following criteria:

    Frequent symptoms that occur with standing (e.g., palpitations, fatigue, lightheadedness, tremulousness, generalized weakness, blurred vision, and exercise intolerance)
    An increase in heart rate of ≥30 bpm during a positional change from supine to standing (or ≥40 bpm in those 12–19 years of age)
    The absence of orthostatic hypotension (OH) which is a drop of >20 mmHg in systolic BP
  - Symptoms:

    Lightheadedness and palpitations with standing.
    Bloating, nausea, diarrhea, and abdominal pain regardless of the posture.

Systemic: fatigue, sleep disturbance, and migraine headaches.
The standing heart rate is often >120 bpm.

- Psychogenic pseudo-syncope:
  - A syndrome of apparent but not actual loss of consciousness in the absence of identifiable cardiac, reflex, neurological, or metabolic causes.
  - Patients with PPM and ICD require an evaluation of the device to check for any possible malfunction.

Diagnostic Testing [12, 13] (Fig. 16.2)

The Electrocardiogram

- The diagnostic value of an electrocardiogram (ECG) is low yield. However, it does carry a significant prognostic value and is recommended by 2017 ACC guidelines [14] (Table 16.3).
- A history, a physical, and an ECG are sufficient for patients with obvious vasovagal syncope.
- Further cardiac evaluation is recommended in patients with structural heart disease or an abnormal ECG [6].

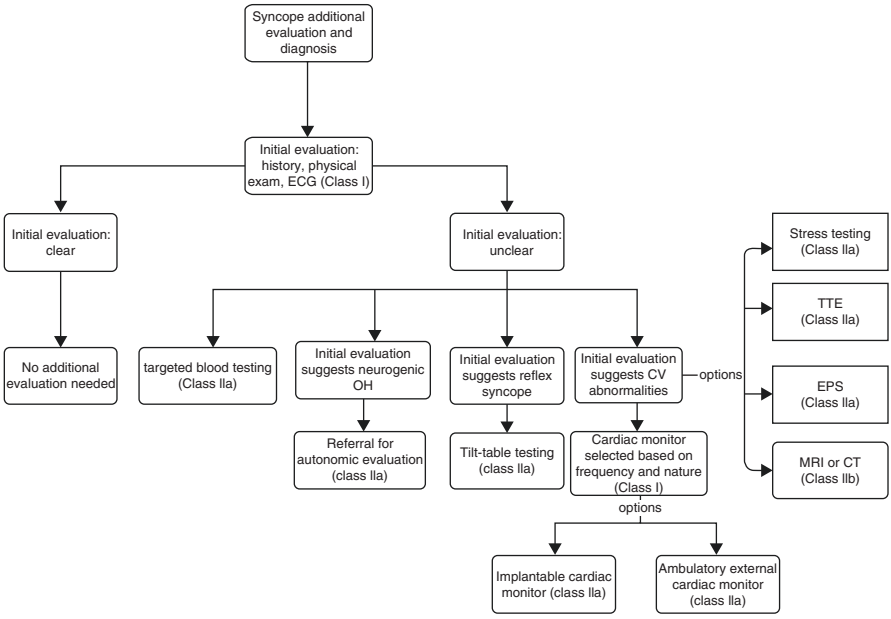

Fig. 16.2 Syncope additional evaluation and diagnosis reproduced with permission from Shen et al. [7]

Table 16.3 ECG abnormalities in syncope

• Conduction abnormalities (AV block, BBB)
• Sinus node dysfunction
• Prior MI (Q waves)
• QRS duration > 120 ms
• QT prolongation
• Brugada syndrome
• Tachyarrhythmias (SVT, VT, AF)
• LV hypertrophy pattern suggestive of HOCM
• Evidence of WPW or preexcitation (delta waves)
• Evidence of ARVD: Repolarization abnormalities (TWI in the right precordial or inferior leads). A depolarization abnormality (QRS duration >110 ms, presence of epsilon wave, or presence of TAD)

AV block atria-ventricular block, *BBB* bundle branch block, *SVT* supraventricular tachycardia, *VT* ventricular tachycardia, *AF* atrial fibrillation, *HOCM* hypertrophic obstructive cardiomyopathy, *WPW* Wolff-Parkinson-White syndrome, *ARVD* arrhythmogenic right ventricular dysplasia, *TAD* terminal activation duration

- The presence of atrial fibrillation, intraventricular conduction disturbances, voltage criteria for left ventricular (LV) hypertrophy, and ventricular pacing was associated with increased risk of death from all causes at 1 year in a prospective observational study.

Echocardiography

- Echocardiography is extremely helpful to identify obstructive causes of syncope such as aortic stenosis or LV outflow tract obstruction. It also provides prognostic value as it is well established that LV systolic dysfunction carries a poor prognosis in the setting of syncope.

Ambulatory ECG Monitoring

- Ambulatory ECG monitoring either by hospital telemetry, Holter monitor, event monitor, or implantable loop recorder can help to identify the potential arrhythmic cause of syncope.

Stress Tests

- Stress testing will help identify patients with advanced coronary artery disease but should only be used if clinical history is suggestive of this etiology.

Invasive Electrophysiologic Testing

- This is typically reserved for a patient with uncertainty regarding sinus node dysfunction. Similarly, it can be beneficial in patients with LV systolic dysfunction as it identifies patients at risk of ventricular arrhythmias. Most of the AV nodal conduction disease can be identified from ECG, but identification of prolonged HV interval (>100 ms) will help identify patients in need of a pacemaker. If any evidence was seen for supraventricular arrhythmias, an EP study will determine the mechanism of the tachycardia and allow for ablative therapy.

Tilt Table Testing

- For a selected patient with high suspicion of neurocardiogenic syncope, it can help to reproduce symptoms and can identify patients with a profound cardioinhibitory response. Similarly, it can identify POTS. When combined with video EEG monitoring, it can be beneficial to identify patients with fictitious syncope.

Cardiac Rhythm Monitors (Table 16.4)

Cardiac CT or MRI

- The new 2017 ACC/AHA guidelines do not recommend extensive cardiac imaging, computed tomography (CT), or MRI for patients with a normal ECG with-

Table 16.4 Different cardiac rhythm monitors and patient selection adapted with permission from Shen et al. [7]

Types of monitor	Patient selection
Holter monitor	Patients with frequent symptoms within a short period (24–72 h) of monitoring
Event monitor	Patients with spontaneous symptoms likely to recur within 2–6 weeks. Limited use in patients with frank syncope associated with sudden incapacitation
External loop recorder	Patients with spontaneous symptoms likely to recur within 2–6 weeks
Mobile cardiac outpatient telemetry	Patients with spontaneous symptoms related to syncope and rhythm correlation in high-risk patients whose rhythm requires real-time monitoring
Implantable cardiac monitor	Patients with infrequent, unexplained syncope (or suspected atypical reflex syncope) of the suspected arrhythmic cause. This modality provides the most significant diagnostic yield in patients in which routine workup is unable to identify the cause of syncope

out a prior history of heart disease. Also, extensive neurological imaging like carotid ultrasounds, CT scans, and MRI scans of the head and neck is not recommended.

Treatment

- Vasovagal syncope (VVS) [6, 13]
  - Reassurance about the benign nature of the condition should be provided.
  - Proper PO hydration so patients should be encouraged to drink more water.
  - Patients should be educated about the prevention of these episodes. This includes avoiding triggers such as dehydration, fasting, heat, prolonged standing, lack of sleep, large meals, and alcohol. Change in posture (i.e., lying or sitting down) when experiencing initial symptoms may avert or attenuate syncope or traumatic falls. Maneuvers such as handgrip and leg crossing combined with tensing of the muscles at the onset of symptoms may prevent vasovagal syncope by increasing the venous return.
  - Discontinuation of medications such as vasodilators and diuretics should be considered.
  - Beta-blockers, mineralocorticoids, and vasoconstrictors have not been proven to be helpful. For resistant cases, orthostatic training and isometric exercises that help to abort symptoms may be useful.
  - Implantation of a dual-chamber pacemaker in patients >40 years old with recurrent VVS should only be considered if there are documented spontaneous pauses >3 s correlating with symptoms or an asymptomatic pause ≥6 s (class IIb).
- Postural (orthostatic) tachycardia syndrome (POTS) [15]
  - Treatment is challenging.
  - Three measures are often beneficial: physical counter-maneuvers, wearing an abdominal binder, and water bolus therapy.
  - In physical counter-maneuvers: patients could try to contract muscles below the waist (typically for 30 s and could be repeated). This measure increases total peripheral resistance and reduces venous capacity.
  - Compression stockings are commonly prescribed, but their efficacy is unclear, mostly due to poor compliance.
  - Wearing an abdominal binder reduces splanchnic-mesenteric venous capacity and is especially helpful in patients with poor venomotor tone or who are hypovolemic.
  - Water bolus therapy results in a sympathetically mediated pressor response that is sustained for a short period.
- Autonomic insufficiency is usually difficult to treat. Certain measures can be helpful such as wearing stockings, strict diabetes control, and avoiding certain

medications, e.g., diuretics and vasodilators. Even though ACEi or ARB is beneficial in diabetic patients, they may need to be stopped and replaced with other antihypertensive medications that do not drop BP quickly, e.g., amlodipine.
- Other causes of syncope should be treated according to underlying etiology.
- Driving: suggested symptom-free waiting times after an episode of syncope are further specified in the 2017 ACC guidelines depending on underlying condition [13].

Prognosis [3, 6]

- Vasovagal syncope is primarily a benign condition.
- Cardiac syncope is associated with increased risks of cardiovascular events and premature death.
- Twenty-two percent of patients with syncope reported one or more recurrences.

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Chapter 17
Supraventricular Tachycardia

Adam S. Budzikowski

Approach to the Patient

- Patients typically present with palpitations and sensation of fluttering in the chest or neck pounding.
- At times only presenting symptoms may be presyncope, syncope, or dizziness.
- It is important to ask the patient what factors, maneuvers, or circumstances terminate the tachycardia. Breath holding, coughing, bearing down, or application of cold compresses may suggest AV nodal dependence of the tachycardia since these typically increase the vagal tone.
- SVT onset can be seen at any age but typically for AVNRT 32 ± 18 years of age and for AVRT 23 ± 14 years [1–6].
- Twenty-two percent of patients with preexisting SVT experience exacerbation of symptoms during pregnancy.

Physical Exam

Typically reveals rapid rates and on occasion hemodynamic instability.

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H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7_17

Laboratory Evaluation and Other Studies

Typically all laboratory studies are normal.

Differential Diagnosis

Sinus tachycardia

Fascicular VT (typically QRS is relatively narrow and RBBB configuration) (Fig. 17.1).

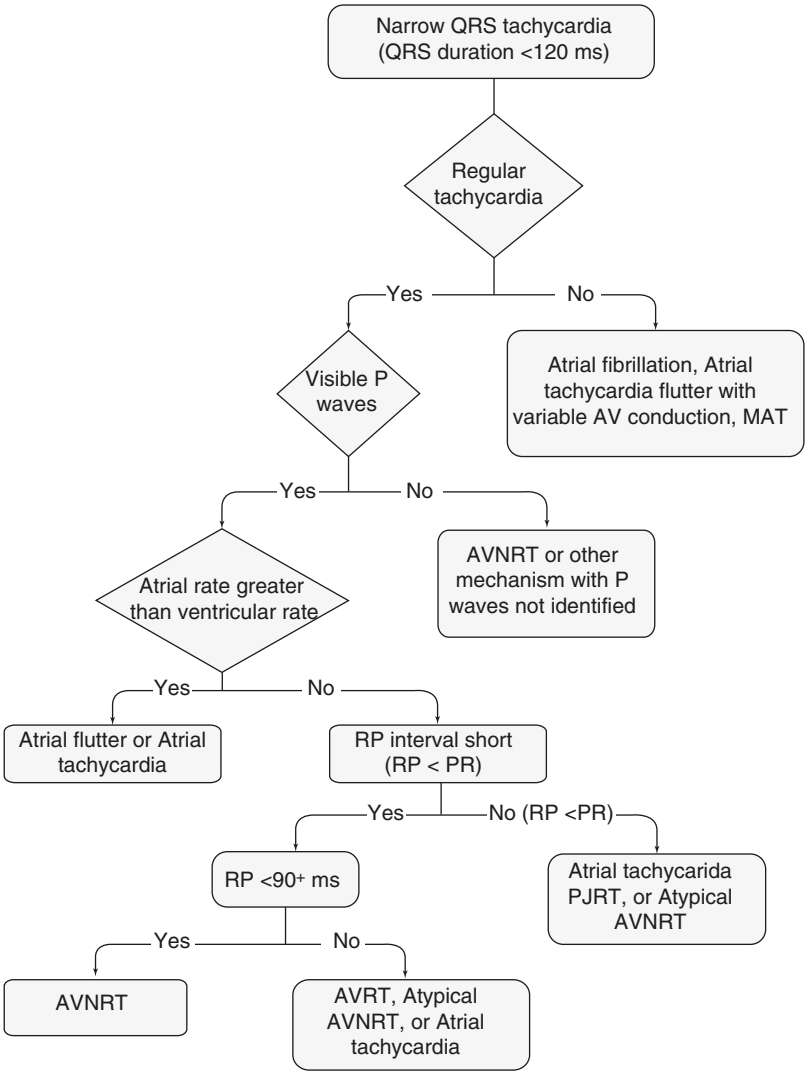

Fig. 17.1 Algorithm for determination of the mechanism of supraventricular tachycardias

AVNRT

- AVNRT is the most common SVT accounting for >60 % of all SVT [1].
- The incidence of AVNRT typically peaks in the 40s, and prevalence is slightly higher in female than in males.
- The tachycardia circuit involves the AV node and perinodal tissue. Because of the proximity of the circuit to both atrium and ventricle, this SVT has very short VA time typically shorter than 70 ms.
- Typically on the EKG, the retrograde P waves deform terminal portion of the QRS, best visible in the interior leads and in lead V1. The P wave is inverted in inferior leads (as the atrial activation moves from inferior to superior) and very narrow since both atria are activated at the same time [6].
- At times the VA conduction is so rapid that no P wave can be seen in 12 lead EKG—hallmark of AVNRT.
- Rarely AVNRT can be seen with 2:1 AV block. In this circumstance the P wave is found exactly half way in-between QRS complexes.
- Ablative therapy is first-line therapy for eligible patients.
- Alternative AV blocking agents can be tried: beta-blockers, verapamil, and diltiazem. If these fail class Ic (patients without structural heart disease) or class III medications can be tried as well as digoxin.

AV Reentry

- The circuit of AV reentry requires the atria, the AV node, the ventricle, and the accessory pathway.
- Most commonly the direction of the tachycardia circuit is orthodromic—namely, conduction overt the AV node is happening in an antegrade fashion [5]. This tachycardia will inscribe narrow complex QRS.
- Should the circuit proceed in an antidromic fashion with atrioventricular conduction over the accessory pathway, the inscribed QRS complex will be wide.
- With orthodromic AVRT VA time will be long although with retrograde conduction over septal accessory pathway, it can be short but almost never as short as in AVNRT.
- Most patients with asymptomatic preexcitation will develop symptoms later in life; hence, consideration for ablative therapy can be given in asymptomatic patients.
- Since presence of preexcitation is associated with risk of sudden death, patients should be risk stratified by either noninvasive methods or diagnostic electrophysiology study.
- Patients with manifest preexcitation have to be excluded from high-risk occupations until the pathway is ablated successfully.
- Some forms of preexcitation do not require any therapy (fasciculoventricular pathway) since they are not associated with AV reentry.

Atrial Tachycardia

- Atrial tachycardia is a narrow complex tachycardia originating in the atrium. It is typically a long RP tachycardia with 1:1 AV relationship.
- It is not unusual though to see AV block associated with it particularly when atrial rate is very rapid.
- Some of atrial tachycardias can be incessant and a cause of tachycardia-induced cardiomyopathy.
- Ablative therapy is first-line therapy for eligible patients.
- Beta-blockers, verapamil, and diltiazem can be tried as well. Class Ic antiarrhythmic drugs work well in patients without structural heart disease. Once structural heat disease is present class III antiarrhythmic should be used.

Multifocal Atrial Tachycardia

- This tachycardia is characterized by varying P wave morphologies (at least three) and varying PR interval.
- Typical setting for MAT is pulmonary embolism, severe lung disease, severe valvular disease, and hypomagnesemia or theophylline therapy.
- IV magnesium and verapamil can be helpful, but therapy should be directed predominantly at correcting the underlying cause.

Inappropriate Sinus Tachycardia

- IST is characterized by increase sinus rates that are not in proportion to physiologic demand.
- Typically resting heart rates are >100 bpm, and average rates are >90 bpm in a 24-h recording.
- Mechanism is unknown and treatment options are limited.
- Ivabradine has been found to be helpful in these situations since it flocks the I_f channel.
- Ablative therapy for IST unfortunately has ~45% long-term effectiveness.

Junctional Tachycardia (JT)

- JT results from enhanced automaticity in the AV junction.
- It is rare in adults but not infrequently seen in children particularly post cardiac surgery.
- At times isorhythmic AV dissociation may be seen ruling out AVRT.
- Beta-blockers, diltiazem, flecainide, propafenone, and verapamil are useful in medical management.
- Junctional rhythm which (non-paroxysmal form of tachycardia) is far more common in adults and can be seen in the setting of myocardial infarction and digoxin toxicity. Treatment of underlying cause is indicated [1].

- Beta-blockers, diltiazem, or verapamil are first-line therapies; for patients without structural heart disease, propafenone or flecainide can be tried as well.
- If ineffective consideration for ablative therapy should be given.

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Chapter 18
Atrial Fibrillation

Adam S. Budzikowski

Definitions

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by rapid and uncoordinated atrial activation consequently leading to deterioration of atrial mechanical function [1, 2].

Classification is presented in Table 18.1.

Acute Atrial Fibrillation

Typically associated with:

- Alcohol intoxication
- Hyperthyroidism
- Pulmonary embolism or other pulmonary process leading to hypoxia
- Myocarditis
- Surgery including cardiothoracic and electrocution
- Cannabis abuse

Resolution of the underlying pathology invariably results in termination of AF.

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H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7_18

Atrial Fibrillation with No Structural Heart Disease

- In younger population almost half of paroxysmal AF and up to 25% of persistent AF occur in patients without structural heart disease (Table 18.2).
- Genetic predisposition to AF has been reported.

Neurogenic Atrial Fibrillation

- An uncommon form of AF in which autonomic nervous system plays an important role in the initiation of arrhythmia.
- Exercise induced with increasing sympathetic tone.
- Vagal AF is typically present in females and develops during night with increasing parasympathetic tone.

Table 18.1 Classification of atrial fibrillation proposed by AHA/ACC/ESC task force

Terminology	Clinical features	Pattern
Initial event (first detected episode)	Symptomatic Asymptomatic Onset unknown	May or may not reoccur
Paroxysmal	Spontaneous termination <7 days and most often <48 h	Recurrent
Persistent	Not self-terminating Lasting >7 days or prior cardioversion	Recurrent
Permanent	Not terminated Terminated but relapsed No cardioversion attempt	Established

These definitions refer to episodes that are not due to reversible cause and last at least 30 s. Paroxysmal atrial fibrillation is defined as lasting less than 7 days. Any subsequent episode makes atrial fibrillation recurrent. Ultimately these episodes will lead to persistent atrial fibrillation that after a year becomes permanent

Table 18.2 Risk factors for stroke in atrial fibrillation

Risk factor	Assigned score
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior MI, PAD, or aortic plaque)	1
Age 65–74	1
Female gender	1

Epidemiology and Clinical Significance

- Most common sustained arrhythmia.
- Estimated 2.2 million Americans are affected by AF and this population is growing.
- Estimated lifetime risk ~25%.
- 15–20% of stroke is attributable to AF.

Pathophysiology

- Focal trigger points within the left and right atrium have also been identified as initiating impulses for AF (Fig. 18.1).
  - Specifically the ostia of the pulmonary veins, coronary sinus, inferior and superior vena cava, the ligament of Marshall, and muscular fiber making up the roof of the coronary sinus [3]
  - Increased sympathetic tone associated with increased atrial stretch
- The atria of patients with AF often reveal fibrosis, patchy infiltration by fat, and areas of inflammation.

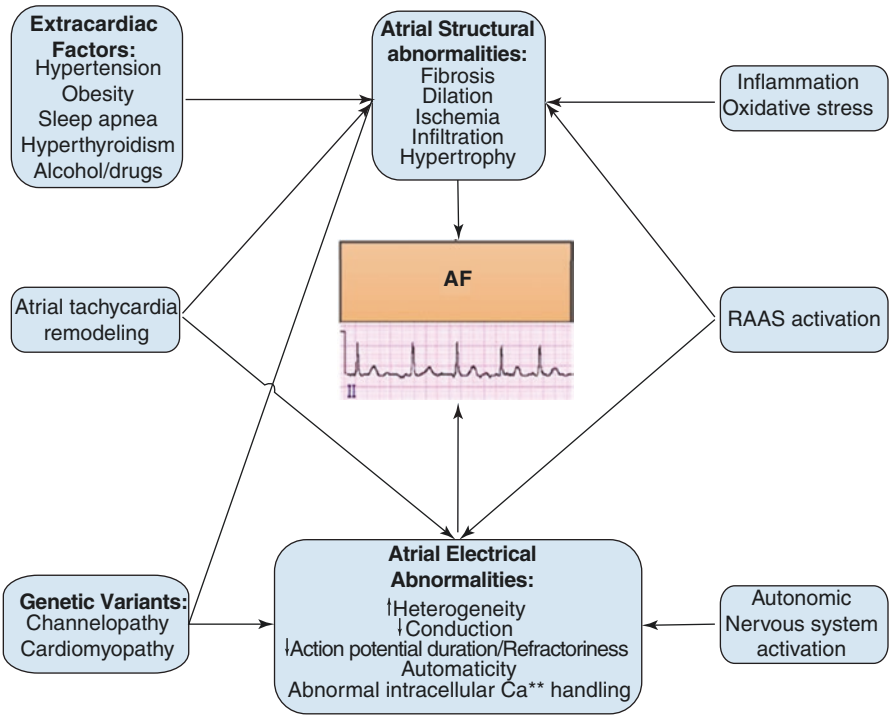

Fig. 18.1 Mechanisms of atrial fibrillation (reproduced with permission from [2])

Approach to the Patient

- Although palpitations are common symptoms, patient may present with a variety of complaints including dyspnea, fatigue, chest pain, and syncope.
- Other clues may include alcohol consumption or symptoms of other underlying pathologies like coronary artery disease, pulmonary disease, hyperthyroidism, or pheochromocytoma.
- Determining time of the day symptoms occur and duration of symptoms will be helpful as to identifying underlying etiology and provide guide to type and duration of therapy.
- Furthermore it is very helpful to establish whether the patient is at all symptomatic with the episodes of AF.

Diagnosis is usually easy and is based on history and EKG ambulatory EKG monitoring or via implantable devices.

Physical

- Absence of a wave in the venous pulse, variable pulse volume, irregular rate, and variation in the intensity of S1.
- Murmurs of mitral valve disease or S3 may indicate presence of structural heart disease.
- Pulse deficit may be apparent.

Laboratory Evaluation and Other Studies

EKG

- Absence of organized atrial activity, more or less organized fibrillatory waves, and irregular ventricular response.
- One has to pay close attention when examining either very fast or very slow ventricular response since the irregularity may not be readily apparent. Careful examination of RR intervals with calipers usually helps in those situations.
- One has to be aware that sudden regularization of ventricular response particularly in patients taking digoxin may herald presence of AV block and junctional escape rhythm.

Echocardiography

Once should pay attention to:

- Valvular disease
- Chamber geometry including left atrial size

- LV systolic and diastolic function
- Presence of thrombus—TEE far superior
- Pulmonary artery pressure
- Pericardial disease

Blood Test

- CBC
- Chemistries
- BNP or pro-NTBNP
- Thyroid panel—particularly with first episode, worsening ventricular rate control, or recurrence after cardioversion
- Drug levels if applicable

Exercise Stress Test

- Assess for the presence of ischemia as a precipitating factor and before initiation of therapy with class IC agents.
- Reproduce exercise-induced AF.
- Verify adequacy of rate control with exercise.

Event Monitoring or Home Telemetry or Implantable Loop Recorder

- Establishing diagnosis
- Verification of rate control
- Verification of frequency and duration of paroxysms
- Other concurrent arrhythmias

Differential Diagnosis

Typically diagnosis is straightforward when atrial activity is not apparent; one can utilize Lewis lead to visualize P waves.

Treatment

Rhythm Control

- It is reasonable to attempt restoration of sinus rhythm with a first episode of atrial fibrillation.

- It is reasonable to maintain sinus rhythm in patients experiencing symptoms of AF.
- In asymptomatic patients maintenance of sinus rhythm may not be needed as it does not offer mortality benefit provided the patients are adequately anticoagulated.

Electrical Cardioversion

- Urgent electrical cardioversion is indicated for patients who are hemodynamically unstable or those with preexcited AF who are at risk of developing ventricular fibrillation.
- Elective cardioversion can be safely performed in patients with AF duration of less than 48 h and those with AF duration of more than 48 and without left atrial thrombus on TEE and those who were adequately anticoagulated (all INRs >2) for at least 4 weeks or appropriate DOAC therapy.

Pharmacologic Therapy for Sinus Rhythm Maintenance

There are several medications that can be used for sinus rhythm restoration. One has to keep in mind though that similar precautions regarding presence of left atrial thrombus and anticoagulation should be followed as for electrical cardioversion. The characteristics and dosing information are listed in Table 18.3.

Ablative Therapy for AF

- Ablative therapy is indicated in symptomatic patients with paroxysmal AF who have failed single antiarrhythmic agent or those who do not want to take antiarrhythmic medications.
- It may be reasonable to undertake ablative therapy in symptomatic patients with persistent AF who fail antiarrhythmic therapy.
- There is a mortality benefit of ablative therapy in patients with systolic heart failure.

Rate Control

- Long-term choice of medical regiment for rate control is mostly dictated by presence or LV systolic dysfunction. For these patients β-blockers are mandatory. The use of calcium channel blockers is contraindicated since they have been associated with worse outcomes.
- If no LV dysfunction is present, calcium channel blockers are most effective particularly in combination with other agents.

Table 18.3 Antiarrhythmic medications for treatment of atrial fibrillation

Normal LV function	
Flecainide	300 mg PO as a single dose for cardioversion; can be used also for maintenance of sinus rhythm. It is a negative inotrope which increases pacing and defibrillation thresholds and has a decreased dose in renal failure
Propafenone	600 mg PO as a single dose results in restoration of NSR in 76% of patients after 8 h. Can be used for maintenance of NSR. Check levels, drug-drug interactions
Disopyramide	100–400 mg TID-QID has anticholinergic properties hence effective with vagal AF. May be well suited for patient with hypertrophic cardiomyopathy
Sotalol	Start with 80 mg BID and titrate to 640 mg a day. Purely renally excreted; may cause QT prolongation and torsades; initiate therapy in hospital
Dronedarone	400 mg BID for maintenance of sinus rhythm
LV systolic dysfunction	
Amiodarone	Oral load 800–1600 mg in divided doses × 1–2 weeks then 200 mg QD. Marginally effective in restoration of NSR but useful for maintenance. Multiple drug-drug interactions including warfarin. Check baseline TFT, LFT, and CXR. Warn patients of possible side effects particularly phototoxic skin reactions
Dofetilide	Start in hospital 500 μg PO BID; monitor QT and if >550 or 20% prolongation, stop the medication. Renal dosing 250 mg bid for CC 60 to 40 mL/min and 250 mg daily for CC 40 to 20 mL/min. Most common adverse reaction torsades. You will need to complete a course to be able to rx medication
Ibutilide	1 mg iv over 10 min if >60 kg or 0.01 mg/k if <60 kg. Repeat dose if no response in 10 min. Only IV preparation for cardioversion or to improve result of DC cardioversion. Cannot be used if QT >440 ms. You will need ACLS monitoring to administer the medication

- Digoxin that has been very popular for rate control in the past is currently not frequently used particularly since newer data suggests that the use of digoxin may be associated with increased mortality.
- The rate control will be considered satisfactory when resting heart rate is maintained less than 110 bpm.
- It is not uncommon for patients with rate control that medication regimen controls well ventricular rate during exertion and results in bradycardia at rest. For those with permanent AF, VVI pacemaker will provide bradycardia protection. Patients with paroxysmal AF should be considered for a dual chamber device since there is evidence that ventricular pacing alone may predispose to the development of AF.
- For patients in whom rate control is difficult, implantation of biventricular pacemaker and ablation of the AV node are helpful.

Acute Rate Control Management

- Before any treatment is instituted, one has to look for possible cause precipitating AF or poor rate control. Post-op volume contraction and unsatisfactory pain control are common causes of poor rate control.

- Diltiazem is a better choice than verapamil because of lesser negative inotropic properties. The key to the use of this medication is to give appropriate iv bolus—0.25 mg/kg over 2 min—and **immediately** start drip at 5–15 mg/h. Patients can be rebolused with additional 25 mg if needed. If this is ineffective, it can be combined with iv β-blockers. If there is concern over the side effects of β-blockers, one should use ultrashort-acting compounds like esmolol (bolus 500 μg/kg/min for 1 min then 50 μg/kg/min for 4 min; if response remains unsatisfactory, repeat the bolus and increase maintenance rate by 50 μg/kg/min until satisfactory response). Most of the time combination of calcium channel blocker and β-blocker will be effective.
- If ventricular rate remains high, iv amiodarone is a good choice. It is an effective AVN blocking agent, and hypotension that is inherent to other agents is avoided (dosing 150 mg iv bolus (over 10 min) and continue with infusion at 1 mg/min for 6 h and 0.5 mg/min for 18 h).
- Digoxin iv can be also used in this situation, but one has to keep in mind that it will take anywhere between 14 and 24 h for the effect.

Prevention of Thromboembolic Complications

- Loss of mechanical contraction of the atrium results in slowing of flow and formation of dense smoke and subsequently thrombus. Within the left atrium, the left atrial appendage is the most common location for a thrombus. The presence of low velocities on left atrial appendage (<30 cm/s), spontaneous echo contrast, and thrombus have been associated with high risk for embolic events.
- Nevertheless approximately 25% of patients with AF have a stroke related to other causes, namely, disease of carotid arteries.
- In patients with rheumatic mitral stenosis anticoagulation is mandatory as the risk of stroke is increased 20-fold in these patients (provided there are no absolute contraindications) [4].
- All other patients should be risk stratified and appropriate decision made whether long-term anticoagulation is beneficial. The most accepted risk stratification score is $CHADS_2$-Vasc score.
- Patients considered high risk with $CHADS_2$-Vasc score of ≥2 should be anticoagulated with either warfarin or DOAC.
- With warfarin therapy the optimal INR should be in the range of 2–3. Any INR less than 1.8 appears to offer no benefit.
- The available DOACs are a reasonable alternative for patients who do not have severe valvular disease or mechanical valve prosthesis.
- Those patients that have no risk factors score 0; no anticoagulation is a reasonable consideration.
- For patients with intermediate score of 1, a consideration may be given to full anticoagulation.

- In rare patients that are at high risk and at the same time have absolute contraindications to anticoagulation, amputation or oversewing of left atrial appendage has been an effective strategy. Recent evidence suggests that percutaneous LAA closure with Watchman device may reduce thromboembolic risk in the population of patients [5].

Special Considerations

AF in a setting of preexcitation requires prompt attention.

- Conduction over accessory pathway can happen at high rate and results in high ventricular rates and hemodynamic compromise and leads to ventricular fibrillation.
- AV nodal blocking agents are contraindicated in this situation, and their use will result in ventricular fibrillation.
- These patients should be either cardioverted promptly or procainamide administered to control AF.

Periprocedural management of anticoagulation

- Many procedures can be performed with warfarin anticoagulation being uninterrupted and INR within therapeutic range 2–3, and these include cardiac device implants and generator changes, cataract surgery, and tooth extractions [6, 7].
- In most patients receiving DOAC interruption of therapy for 24–48 h is sufficient. Longer period maybe needed in patients with severe renal insufficiency.
- High-risk patients
  - Mechanical mitral valve
  - Two or more mechanical valves
  - Mechanical aortic valve other than bileaflet
  - Prior CVA or known cardiac thrombus
  - High $\geq$4 $CHADS_2$-Vasc score

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Chapter 19
Atrial Flutter

Adam S. Budzikowski

Epidemiology and Clinical Significance

- Incidence of atrial flutter is 88/100,000 person-years.
- Atrial flutter is 2.5 times more common in men.
- The risk of developing atrial flutter increased 3.5 times higher in patients with heart failure and 1.9 times in patients with chronic obstructive pulmonary disease.

Pathophysiology and Definitions

- Typical AFL is caused by a macroreentry mechanism located in the right atrium and involving cavo-tricuspid isthmus. The rotation of reentry wave is counter-clockwise (as seen from the left anterior projection) and proceeds from the cavo-tricuspid isthmus medially to the interatrial septum then right atrial roof and in a cranial to caudal direction along the crista terminalis to complete the circuit [1, 2].
- There are also other forms of AFL (atypical) in which the reentrant circuit does not use the cavo-tricuspid isthmus. Usually in these cases, the area of slow conduction is commonly a scar of previous right atrial surgery or is located in the left atrium, for example, circulating around the mitral annulus or around a large posterior inexcitable scar. See Fig. 19.1.

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H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7_19

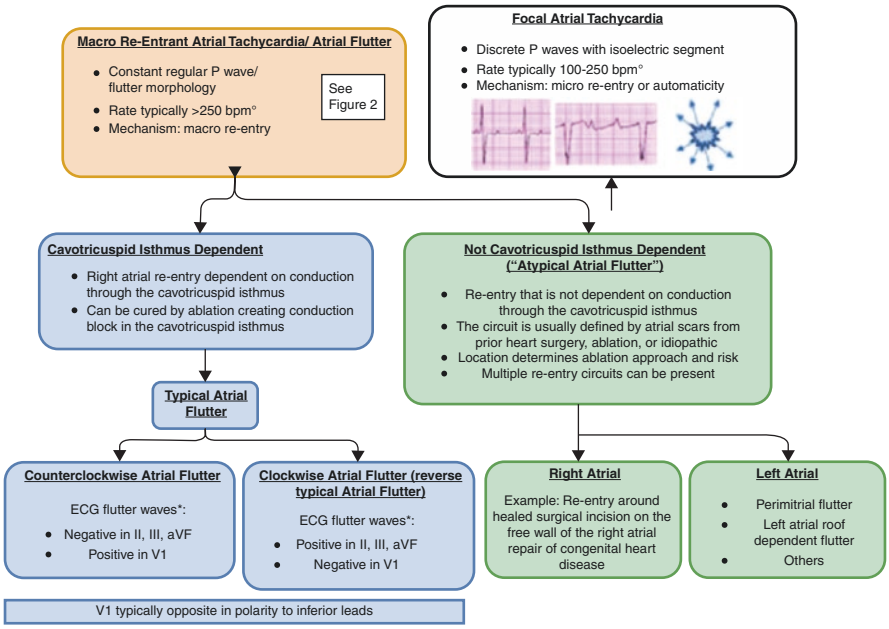

Fig. 19.1 Classification of atrial flutter (adapted with permission from [1])

Approach to the Patient

- The most common pattern of AV conduction in AFL is 2:1, especially in the patient presenting de novo as opposed to the patient being treated with rate control agents, but other degrees of AV block are not uncommon including 4:1 or higher-grade block patterns. A 3:1 pattern is less common but can occur (Figs. 19.2 and 19.3).
- Not infrequently, the degree of block is variable resulting in an irregular ventricular rate. A rapid (1:1) AV conduction pattern can occur and is usually associated with significant hemodynamic compromise possibly resulting in syncope and if sustained requires urgent DC cardioversion.

Physical Exam

Irregularity of heart tones and variability of S1 are common.

Exceedingly rarely flutter waves may be identified in jugular venous waveform.

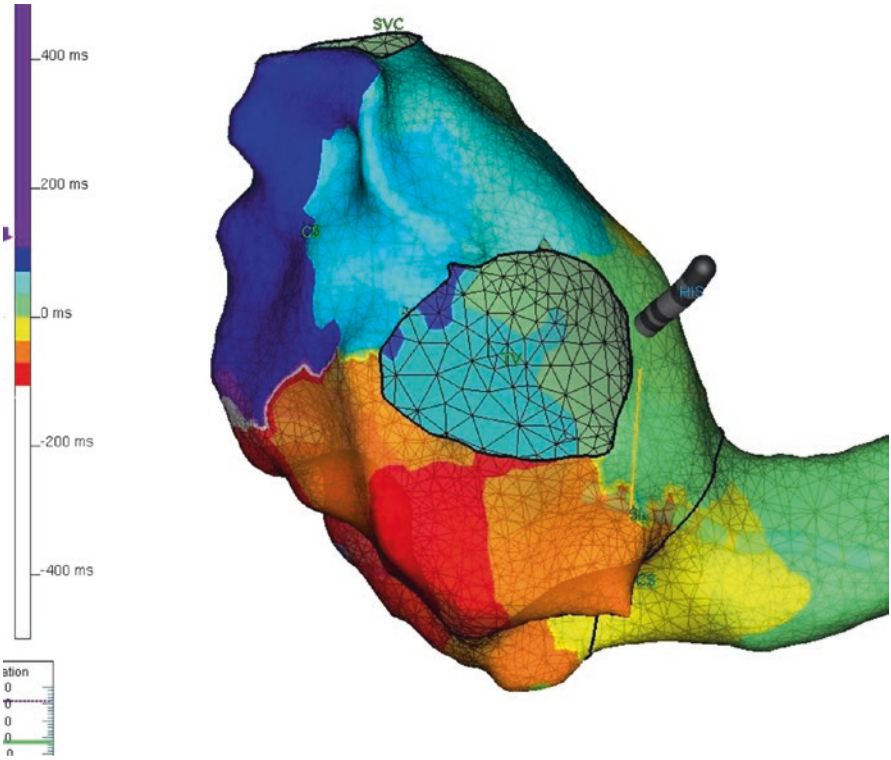

Fig. 19.2 Activation map of the right atrium showing counterclockwise moving macroreentrant waveform in the atrium. On the surface EKG downward directed F waves are present. The earliest activation is coded in white and latest in purple (see also scale). *SVC* the superior vena cava, *TV* the tricuspid valve, His annotates location of the His bundle potential, *CS* the coronary sinus

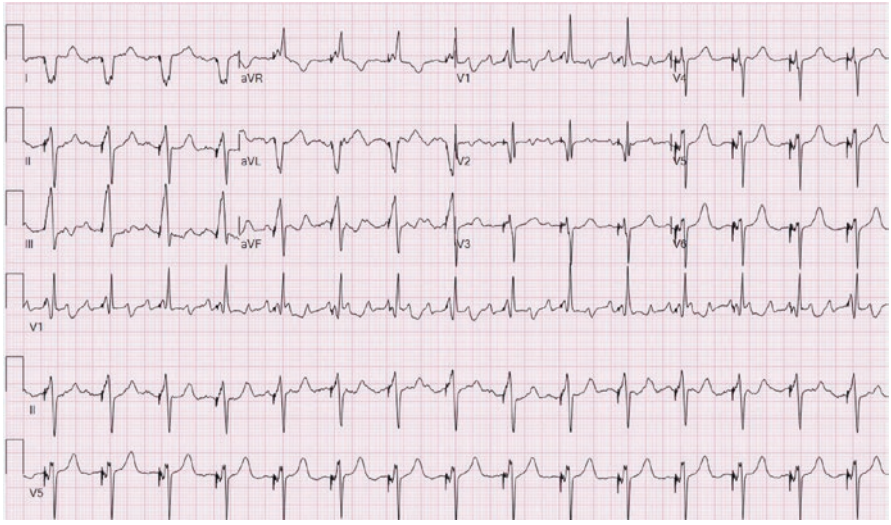

Fig. 19.3 Example of left atrial atypical atrial flutter. Ventricular complexes are result of biventricular pacing as this patient underwent the AV node ablation

Laboratory Evaluation and Other Studies

EKG is a key to diagnosis.

Counterclockwise direction of reentry describes in inferior leads typical negative P waves in a sawtooth pattern which is largely due to the caudal-cranial activation of the left atrium. Lead V_1 has upright "P" waves. Occasionally the direction of reentry is opposite to described above and that results in positive P waves in the inferior leads (reverse typical AFL) and negative P waves in V_1 (Fig. 19.2).

Echocardiography

Once should pay attention to:

- Valvular disease
- Chamber geometry including left atrial size
- LV systolic and diastolic function
- Presence of thrombus—TEE far superior
- Pulmonary artery pressure
- Pericardial disease

Blood Test

- CBC
- Chemistries
- BNP or pro-NTBNP
- Thyroid panel—particularly with first episode, worsening ventricular rate control or recurrence after cardioversion
- Drug levels if applicable

Differential Diagnosis

- Great deal of variation in the EKG appearance of atrial flutter exists, yet most of the flutters are typical flutters.
- At times atrial tachycardia may resemble atrial flutter.

Treatment

Restoration of Sinus Rhythm

- If necessary due to hemodynamic intolerance especially in the setting of 1:1 conduction, sinus rhythm can be rapidly established with electrical cardiover-

sion. Typically lower energies will be needed for cardioversion than those used for atrial fibrillation.
- As with atrial fibrillation, precautions should be taken to prevent thromboembolic complications (see also atrial fibrillation chapter). Although the propensity for atrial thrombus formation is lower in AFL than in atrial fibrillation, patients with AFL should be anticoagulated especially when it lasts more than 24 h.

Ventricular Rate Control

- Acute ventricular rate management is not different from that employed in patients with atrial fibrillation but typically more difficult.
- Calcium channel blockers and β-blockers are very effective in that respect. One has to remember that patients receiving class IC drug for management of atrial fibrillation frequently can convert the arrhythmia to AFL, and due to slowing of the atrial flutter rate, a 1:1 conduction pattern can occur. Therefore these agents should be combined routinely with AV blocking medications.

Antiarrhythmic Medications

- Medications in the class I or class III groups can be used to prevent the recurrence of atrial flutter usually after cardioversion. The use of these agents requires evaluation of cardiac and noncardiac comorbidities as discussed in the atrial fibrillation chapter. Amiodarone probably carries a slightly higher success rate for preventing atrial flutter but requires even more intensive monitoring. This is an off-label usage for this complex agent.

Ablation

- Ablation of AFL is extremely effective long term (approximately 90%) and is the primary treatment modality.
- Atypical AFL not involving cavo-tricuspid isthmus can also be successfully ablated, but the success rate is not as high as for typical AFL.
- In approximately 30% of cases, AFL will either coexist with paroxysmal atrial fibrillation or atrial fibrillation will become evident in short-term follow-up. Factors such as left atrial enlargement, LV dysfunction, and age and presence of lung disease make atrial fibrillation more likely.

Prevention of Thromboembolic Complications

- In acute setting either unfractionated heparin or LMW heparin are actable choices.
- Long-term anticoagulation follows the guidelines developed for atrial fibrillation.
- Following ablation of atrial flutter anticoagulation is maintained for ~4 weeks and can be stopped provided patients remain low risk for the development of atrial fibrillation.

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Chapter 20
Pacemakers and Implantable Cardioverter Defibrillators

Zachary M. Lill and Abrar H. Shah

Bradycardia

Brady arrhythmia could be due to sinus node dysfunction or atrioventricular (AV) block. Treatment is needed when there is no reversible cause and the patient is symptomatic. Asymptomatic patients with bradycardia might not need PPM, and also any bradycardia during night could be due to vagal tone and might not need treatment with PPM placement.

PPM Background

- Modern pacing systems have one to three leads.
- Leads are positioned in the RA, RV, and sometimes the LV epicardium via a branch of the coronary sinus, with a pulse generator placed subcutaneously in below the clavicle.
- The system delivers a current to myocardial tissue that initiates depolarization.
- Pacemakers also sense spontaneous cardiac depolarization.
- A dual-chamber pacing system implanted in a patient with complete heart block will sense intrinsic P waves and deliver an appropriately timed ventricular stimulus.

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© Springer International Publishing AG, part of Springer Nature 2018

H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7_20

Pacemaker Codes and Indication

- First letter is the chamber(s) being paced (**A**trium, **V**entricle, or **D**ual).
- Second letter is the chamber being sensed (**A, V, or D**).
- Third letter is the response to a sensed event (**I**nhibited pacing output, **T**riggered pacing after a sensed event, or **D**ual response including inhibition and triggering).
- Fourth letter indicates presence of rate responsiveness (**R**).

Sinus Node Dysfunction

- Group of arrhythmias related to degenerative changes in the sinus node manifesting as sinus bradycardia, sinus pause, and sinoatrial exit block
- Clinical Indications for pacing
  - Sinus pauses
  - Sick sinus syndrome
  - Tachycardia-bradycardia syndrome
- Device options
  - Single-chamber atrial pacemaker (rare)

    Maintains AV synchrony
  - Dual-chamber pacemaker (common)

AV Blocks

- First-degree AV block: prolonged PR interval (greater than 0.20 s).
- Second-degree AV block
  - Type I Mobitz I (Wenckebach) AV block: gradually progressive prolongation of the PR interval before blocked sinus impulse. There is a shorter PR interval after the blocked beat. Type II Mobitz II AV block: fixed PR intervals before and after blocked beats. When AV conduction occurs in a 2:1 pattern, block cannot be classified unequivocally as type I or type II, although the width of the QRS can be suggestive. Wider QRS will indicate block below the HIS bundle. A pause encompassing the blocked P wave is equal to exactly twice the sinus cycle length.
  - In the setting of AF, a prolonged pause (e.g., greater than 5 s) should be considered to be due to advanced second-degree AV block.
- Third-degree AV block (complete heart block) is defined as absence of conduction through the atrioventricular node (AVN). AV dissociation of the atrial and ventricular activity is present.

AV Conduction Abnormalities

- Clinical indications for PPM (Table 20.1)
  - Symptomatic patients with AV block.
  - Asymptomatic patients with complete heart block or type II 2° AV block who has effective HR <40 BMP.
  - Not indicated for enhanced vagal tone causing asymptomatic block, often nocturnal found incidentally on telemetry or Holter monitoring.
- Device options
  - Dual-chamber pacemakers are preferred.
  - Single-chamber (rate-adaptive) ventricular pacemaker if chronic atrial fibrillation, severe incapacitation or limited life span due to comorbidities.

    Pacemaker syndrome less common than in sinus node dysfunction because retrograde VA conduction is absent in 70–75%.

Cardiomyopathy

- Pacing may help with advanced CHF by optimizing A-V timing and by improving the pattern of ventricular activation.
- Five percent to fifteen percent of patients with cardiomyopathy have a wide QRS (>0.12 s) due to delayed ventricular activation leading to a relative decrease in diastolic filling time and worsened mitral regurgitation.
- In biventricular pacing, a separate lead is placed over the left ventricle via the coronary sinus to deliver earlier and more coordinated activation of the LV. Cardiac resynchronization therapy (CRT) helps to restore AV and inter- and intraventricular synchrony, improving LV function and reducing mitral regurgitation, and has shown to decrease mortality and hospitalization in patients with cardiomyopathy, LBBB, and heart failure. Cardiac resynchronization therapy (CRT) is a proven effective therapy for patients with heart failure to correct impaired ventricular electromechanical coupling or dyssynchrony. CRT in the right patient can improve peak oxygen consumption, 6-min walk test, left ventricular size and function, mitral regurgitation, functional capacity, and overall quality of life.
- Class I indications for CRT are restricted to those patients with NYHA class II, III, and ambulatory class IV symptoms with LBBB and QRS duration of ≥150 ms. However, there is evidence to suggest that CRT therapy can be useful in the sickest class IV HF patients especially to improve overall morbidity but not necessarily mortality.
- CRT therapy can also be useful in class II patients with a QRS duration of ≥130 ms secondary to substantial reduction if heart failure events.

Table 20.1 Class I indications for pacemaker implantation [1]

Sinus node dysfunction	AV node	Hypersensitive carotid sinus syndrome and neurocardiogenic syncope	Chronic bifascicular block (wide QRS)	Post-MI (not in acute phase)
Documented sinus bradycardia including frequent sinus pauses when symptoms are clearly related (LOE C)	Complete 3rd-degree AV block and advanced 2nd-degree AV block (two or more non-conducted P waves) with symptomatic bradycardia (LOE C)	Recurrent syncope caused by spontaneously occurring carotid sinus stimulation and carotid sinus pressure that induces ventricular asystole of more than 3 s (LOE C)	Advanced 2nd-degree AV block or intermittent 3rd-degree AV block (LOE B)	Persistent 2nd-degree AV block in the His-Purkinje system with alternating bundle branch block or 3rd-degree AV block within or below the His-Purkinje system after ST-segment elevation MI (LOE B)
Symptomatic chronotropic incompetence (failure to reach 85% of age-predicted max HR) (LOE C)	3rd-degree and 2nd-degree AV block associated with arrhythmias and other medical conditions that require drug therapy that results in symptomatic bradycardia (LOE C)		Mobitz II AV block (LOE B)	Permanent ventricular pacing is indicated for transient advanced 2nd- or 3rd-degree infranodal AV block and associated bundle branch block. If the site of block is uncertain, an electrophysiological study may be necessary (LOE B)
Symptomatic sinus bradycardia that results from required drug therapy for medical conditions (LOE C)	Asymptomatic awake patients in sinus rhythm resulting in periods of asystole longer than 3.0 s or ventricular rates less than 40 beats per minute (LOE C)		Alternating bundle branch block (LOE C)	Persistent and symptomatic 2nd- or 3rd-degree AV block (LOE C)

	3rd-degree and advanced 2nd-degree AV block in awake, asymptomatic patients in sinus rhythm, with: (a) Documented periods of asystole greater than or equal to 3.0 s or any escape rate less than 40 bpm or with an escape rhythm that is below the AV node-wide QRS (LOE C) (b) A.Fibrillation and bradycardia with one or more pauses ≥5 s (LOE C)				
	Exercise induced 2nd- or 3rd-degree AVB in the absence of ischemia (LOE C)				
	2nd-degree AV block with associated symptomatic bradycardia regardless of type or site of block (LOE B)				

- Data from most CRT trials have consistently demonstrated increase benefit in regard to CRT in those patients with very wide QRS duration (>150 ms). There is currently no convincing data to suggest benefit of CRT in those patients with a QRS duration of <120 ms even with evidence of echocardiographic dyssynchrony.
- There is greater benefit from CRT in patients with LBBB and often lack of benefit or even harm in other patients with non-LBBB QRS prolongation [2].
- The benefit of CRT in patients with atrial fibrillation may be dependent of the frequency of BiV pacing achieved. Often patients with AF will require AV nodal ablation concomitantly with CRT to allow for near 100% BiV pacing.
- The benefit of CRT therapy appears to be more pronounced in those patients with NICM. However, guidelines make no differentiation between ischemic and non-ischemic patients with regard to recommendations for CRT therapy.

New Emerging Indication for CRT

- Chronic RV pacing can have detrimental effects on LV systolic function. CRT therapy should be considered in those patients with LVEF ≤35% with anticipated requirement of RV pacing of >40%.
- The Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block trial (BLOCK-HF) was a prospective RCT randomizing 691 patients with indication for pacemaker for high-grade AV block, classes I–III HF with LVEF <50% to BiV vs RV pacing [3].

  BiV pacing was associated with 10% absolute reduction in death, urgent heart failure care, and adverse LV remodeling compared with RV pacing.

- Indications for biventricular pacing are listed in Table 20.2.

Hemodynamic Effects of Biventricular Pacing

- Increased left ventricular ejection fraction and cardiac output
- Prolonged diastolic filling time with reduced end-diastolic and end-systolic volumes
- Increased peak oxygen uptake
- Decreased pulmonary capillary wedge pressure
- Decreased mitral regurgitation

Limitations of the Technique

- Selection of patients and prediction of patients' response
- Technical difficulties: difficult anatomy, phrenic nerve stimulation, and suboptimal lead placement

Table 20.2 Indications for biventricular pacing [1]

Class I: CRT is indicated for patients with:	Class IIa: CRT can be useful for patients with:
• Systolic heart failure (HF) with LVEF ≤35% • Sinus rhythm • Symptomatic heart failure (New York Heart Association (NYHA) class (II LOE B; III-IV LOE A) • Optimal guideline-directed medical therapy • Ventricular dyssynchrony: left bundle branch block with QRS ≥150 ms	(LOE A): • Systolic HF with LVEF ≤35% • Sinus rhythm • A non-LBBB pattern with a QRS ≥150 ms • NYHA class III/ambulatory class IV symptoms • Optimal guideline-directed medical therapy (LOE A)
	(LOE B): • Systolic HF with LV EF ≤35% • Sinus rhythm • LBBB with a QRS duration 120–149 ms • NYHA class II, III, or ambulatory IV symptoms • Optimal guideline-directed medical therapy
	(LOE B): • Systolic HF with LVEF ≤35% • Atrial fibrillation • Optimal guideline-directed medical therapy • if (a) the patient requires ventricular pacing or otherwise meets CRT criteria and (b) AV nodal ablation or pharmacologic rate control will allow near 100% ventricular pacing with CRT
	(LOE C): • Systolic HF with LVEF ≤35% • Optimal guideline-directed medical therapy • Patients who are undergoing new or replacement device placement with anticipated requirement for significant (>40%)

Autonomic Nervous System Disorders

- Vasovagal syncope is associated with transient vasodilation and bradycardia.
- Usually isolated events that do not require treatment.
- Rarely symptoms can be frequent and debilitating.
  - Management of the vasodepressor component with fluids, mineralocorticoids, and alpha-agonists
  - Pacemakers only useful for attenuating symptoms from marked bradycardia
- Early randomized pacemaker studies resulted in fewer episodes, but recent studies showed most benefit is due to placebo.
  - Pacemaker are not recommended for vasovagal syncope, except in selected patients with severe cardioinhibitory response, failure of medical therapy, or advanced age.

- Pacing may be useful for patients with symptomatic carotid sinus hypersensitivity (CSH), in which CS massage leads to profound bradycardia (>3-s pauses) or >50-mmHg decrease in blood pressure.
  - CSH is rare in patients under 50 but may be present in 25–40% of older patients with syncope or unexplained falls.

Implantable Cardioverter Defibrillator (ICD) Background

- Sudden cardiac death (SCD) accounts for approximately 50% of all deaths from cardiovascular causes which remain the leading cause of death in developed countries.
- Patients with significant coronary artery disease (CAD), LV dysfunction, and prior ventricular tachycardia (VT) are at higher risk for SCD.
- ICDs treat VT by delivering either antitachycardia pacing (ATP) to break VT or shocks to convert to sinus rhythm and prevent SCD.
- Many randomized trials of ICD therapy versus medical therapy for the prevention of SCD in survivors of cardiac arrest or in patients at high risk of have been reported.
- ICD therapy has reduced mortality in both primary and secondary prevention trials and in patients having both ischemic and nonischemic cardiomyopathy.
- Optimal usage of ICD therapy in populations and individual patients should be based on clinical trials, clinical guidelines, and evolving clinical trial data.

Secondary Prevention of SCD Trials

- Patients with sustained VT or out-of-hospital cardiac arrest have an anticipated recurrence rate of 20–30% per year.
- Three major studies have shown that ICD is superior to medical therapy for secondary prevention of SCD.

  A meta-analysis of AVID, CIDS, and CASH substantiated a 28% mortality reduction ($P = 0.0006$) with ICD therapy for the secondary prevention of hemodynamically significant VT or cardiac arrest. Subgroup analysis of these studies showed that improved survival with the ICD appeared principally in patients with an LVEF less than 35% [4–6].

Primary Prevention of SCD Trials

- Multiple studies have shown the benefit of ICD in primary prevention of SCD in patient with cardiomyopathy with LVEF ≤35% and heart failure.

Ischemic Cardiomyopathy Trials

A series of trials designed in the 1990s investigated the prophylactic role of the ICD in postinfarction patients at high risk for SCD without prior sustained ventricular arrhythmia.

- The Multicenter Automatic Defibrillator Implantation Trial (MADIT) showed that ICD implantation in patients with ischemic cardiomyopathy (CM), LVEF ≤35%, prior MI, NYHA I–III, asymptomatic NSVT, and positive EP study was associated with significantly improved survival when compared to conventional therapy [7].
- MADIT II trial showed that prophylactic ICD implantation in patients with ischemic CM, LVEF ≤30%, at least 30 days post-MI was associated with significantly improved survival [8].
- IRIS trial showed that prophylactic ICD implantation in patients early post-MI with HR of 90 beats per minute or more and an LVEF ≤40%. Criterion 2 was non-sustained ventricular tachycardia consisting of three or more consecutive ventricular premature beats with a heart rate of 150 beats per minute or more and did not reduce overall mortality among patients with acute myocardial infarction and clinical features that placed them at increased risk [9].
- DINAMIT trial: In high-risk patients, early (6–40 days) post-myocardial infarction (MI) patients with LVEF ≤35%, NYHA IV, and ICD therapy did not reduce mortality. There was a reduction in risk of arrhythmic death in the ICD arm, but it was offset by an increase in non-arrhythmic death compared with control. Therefore ICD is not indicated for 3 months post-revascularization and within 40 days after MI without revascularization [10].

Nonischemic Cardiomyopathy Trials

- Heart failure of any etiology increases both overall mortality and SCD. Prospective randomized trials evaluated the potential benefit of ICD therapy in patients with nonischemic cardiomyopathy.
- The Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation [11] and the Sudden Cardiac Death-Heart Failure Trial [12] showed that ICD implantation in patients with NICM and LVEF ≤35% and NYHA classes II–III improves survival.
- The Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure (DANISH) trial was a multicenter RCT of 1116 patients randomized to ICD (556) vs. standard care (560) with a primary outcome of overall mortality [13].
  - It was a negative study and did not show any improvement with ICD therapy.

  - The trial was powered to detect a 25% difference in mortality. A smaller benefit with ICD therapy cannot be ruled out.
  - A relatively high (31%) incidence of non-cardiovascular mortality may cause underestimation of the effect of ICD therapy on mortality by introducing a prevalent competing risk for which ICD therapy would be expected to have no benefit.

Combined Cardiomyopathy Trials

- The Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) prospectively investigated the effect of medical therapy versus cardiac resynchronization therapy (CRT) versus CRT-ICD on the composite endpoint of hospitalization or death [14].
  - Ischemic (55%) and nonischemic (45%) etiologies were included. Patients with New York Heart Association (NYHA) classes III–IV CHF, EF ≤35%, LV end-diastolic diameter ≥60 mm, and QRS duration greater than 120 ms were randomized in a 1:2:2 ratios to medical therapy, CRT pacemaker (without ICD), and CRT-ICD.
  - After 12 months of follow-up, there was a 43.4% relative risk reduction in total mortality in the CRT-ICD group compared with medical therapy. There was also a trend toward reduction in total mortality in the CRT group compared with medical therapy.
  - Ischemic and nonischemic patients benefited similarly from ICD therapy.
- COMPANION trial concluded that prophylactic use of ICD in patients with heart failure (classes III–IV) and QRS greater than 120 ms decreases mortality. COMPANION results agree with the subgroup analysis of DEFINITE, which showed 37% relative reduction in class III patients, and with MADIT II, which showed 63% mortality reduction in patient with QRS longer than 120 ms.
- MADIT CRT trial showed that implantation of CRT combined with ICD in relatively asymptomatic patients with ischemic or nonischemic CM with LVEF ≤30%, NYHA I–II, and QRS complex ≥130 ms was associated with significantly decreased the risk of heart failure events when compared with use of ICD alone. CRT-ICD therapy was associated with a greater benefit in women [15].
- The Sudden Cardiac Death-Heart Failure Trial (SCD-HeFT) enrolled patients with ischemic (48%) or nonischemic (52%) cardiomyopathy with LVEF less than or equal to 35% and NYHA classes II (70%)–III (30%) heart failure [12].
  - 2521 patients randomized to one of three treatment arms: ICD therapy, amiodarone, or placebo. After a median follow-up of 45.5 months, the risk of mortality in the patients assigned to an ICD was reduced by 23% compared with those assigned to placebo ($P = 0.007$). Subgroup analysis showed no difference in ICD benefit between ischemic and nonischemic cardiomyopathy.

Inherited Arrhythmia Syndromes

- A number of hereditary arrhythmia syndromes can cause ventricular arrhythmias and SCD.
- As relatively uncommon conditions, randomized trials of defibrillator therapy are less feasible.
- Case-control studies or observational studies reporting appropriate ICD therapy event rates support a role for ICD therapy in selected patients with hypertrophic cardiomyopathy, Brugada syndrome, long-QT syndrome, and arrhythmogenic right ventricular dysplasia.
- Only Brugada syndrome has been studied in randomized fashion in the Defibrillator Versus Beta-Blockers for Unexplained Death in Thailand (DEBUT) trial [16]. DEBUT included idiopathic VF survivors and inducible Brugada pattern patients and randomized subjects to beta-blocker therapy or ICD. Including the pilot data, seven deaths occurred, all in the beta-blocker group. Seven ICD arm subjects received appropriate ICD therapy.

Class I indications for ICD implantation are listed in Table 20.3.

Current guidelines recommend a 40-day waiting period prior to ICD placement after acute MI and 90 days after revascularization.

Implantable Loop Recorders

- Subcutaneous monitoring device used to record and wirelessly transmit rhythm data (Fig. 20.1)
- Consider in the evaluation of syncopal episodes or palpitations occurring less than monthly when external monitors have been unrevealing or in cryptogenic stroke for detection of atrial fibrillation

Table 20.3 Class I indications for ICD implantation [1]

Indications	Studies
Survivors of cardiac arrest due to VF or hemodynamically unstable sustained VT after evaluation to determine the cause and exclusion of reversible causes (LOE A)	AVID, CIDS,
LVEF ≤30% due to prior MI, at least 40 days post-MI, NYHA I (LOE A)	MADIT II
Nonischemic DCM, or prior MI; LVEF ≤35%, NYHA class II or III (LOE B)	SCD-HeFT
NSVT due to prior MI, LVEF ≤40%, and positive EP study for inducible VF or VT (LOE B)	MADIT I; MUSTT
Syncope of undetermined origin with inducible VT or VF during EP study (LOE B)	CIDS
Sustained VT with structural heart disease (LOE B)	CASH, AVID, CIDS

Fig. 20.1 Image of implantable loop recorder

Table 20.4 Device-related complications and management

Infection	Pre- and postoperative antibiotic prophylaxis
Bleeding	Hold heparin products pre- and post-op. Avoid bridging and supratherapeutic INR, and use novel oral anticoagulants cautiously in the perioperative period
Pneumothorax	CXR, CT scan, surgery consult for chest tube
Lead perforation and tamponade	Device interrogation, CXR, echocardiogram, CT scan, IVF, coagulation studies, reversal of anticoagulation, reposition lead
Inappropriate ICD shocks	Treat underlying SVT/AT/AF. Reprogramming if available or apply magnet in emergency if truly inappropriate and recurrent
Lead dislodgement	Activity restrictions, CXR, interrogation shows high threshold, poor sensing, and high impedance

- Dimensions of about three stacked paper clips

Device-related complications and management are described in Table 20.4.

MRI and Cardiac Implanted Electronic Devices

- Many PPM and ICDs are now MRI conditional, meaning it may be possible to safely obtain an MRI. Any device or lead placed before 2011 most likely are not MRI compatible.
- Determine if the patient is pacemaker dependent, and consult with electrophysiologist for advice on temporary programing changes and scanning safety.

Management of PPM and ICD During Surgery

- Local electrocautery use may lead to oversensing and underpacing.
- Patient dependence on pacing is determined.
- Settings are programmed to asynchronous modes without sensing for those dependent on pacing.
- ICD therapy may be turned off.
- Positioning of a doughnut magnet will temporarily change settings to asynchronous mode in pacemakers and temporarily hold tachytherapy in ICDs.

For further information, refer to the ACCF/AHA/HRS or ESC guidelines on cardiac device therapy

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Chapter 21
Ventricular Arrhythmias: Sudden Cardiac Death

Granit Veseli and Adam S. Budzikowski

Epidemiology [1, 2]

- Cardiovascular diseases are the most common cause of morbidity and mortality worldwide with approximately 17 million deaths every year.
- Risk of SCD is higher in men than in women, and it increases with age due to the higher prevalence of CAD in older age.
- SCD in younger individuals has an estimate of 1100–9000 deaths in Europe and 800–6200 deaths in the USA every year.
- Among younger populations, SCD is predominantly caused by channelopathies, cardiomyopathies, myocarditis, and substance abuse, whereas in older populations, it is caused more frequently by chronic degenerative diseases (CAD, valvular heart diseases, and heart failure (HF)).
- When an inherited disease is identified in a deceased individual, the victim's relatives may be at risk of similar conditions and sudden death, unless a timely diagnosis is made and preventive measures are taken.
- Overall, a properly conducted autopsy should provide answers to the following questions:
  - Is there a history of toxin exposure or illicit drug use; are there any other unnatural causes that led to death?
  - Is the death attributable to a cardiac disease, and does it fit the profile of cardiac disease?
  - Was the death caused by arrhythmia?

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H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7_21

  - Was there evidence of an inherited channelopathy? If so, screening and counseling of relatives are advised.

- The collection and storage of biological samples for DNA extraction to allow a "molecular" autopsy are encouraged; it allows the diagnosis postmortem of the presence of cardiac channelopathies that may explain 15–25% of sudden arrhythmic death syndrome (SADS) cases.
- Genetic study of the SCD patient allows for further genetic screening of the family members of SCD victims and potential therapy to prevent death of those family members with inherited disease.
- The most effective approach to prevent SCD in the general population is to quantify an individual's risk of developing ischemic heart disease, followed by controlling for cardiac risk factors such as lipids, blood glucose, blood pressure, smoking, and body mass index.
- The most useful indicator that has consistently shown an association with increased risk of sudden death in the setting of myocardial infarction and left ventricular (LV) dysfunction is LV ejection fraction (LVEF).
- Despite the fact that LVEF is not an accurate and highly reproducible clinical parameter, its use is widespread in selecting patients for ICD implantation in primary prevention of SCD.
- Obstructive sleep apnea resulting in a reduced mean nocturnal oxygen saturation of less than 93% and a lowest oxygen saturation less than 78% was found to be independent risk factor for SCD.

Screening family members of SCD victims and postmortem diagnostic workup for accurate diagnosis for SCD:

- Family screening of first-degree relatives of sudden death victims is important in identifying individuals at risk and advising on available treatments to prevent potential SCD in the future.
- Currently, only 40% of family members are screened, partially due to a lack of adequate screening infrastructure but also due to the anxiety and distress associated with the personal experience of a life-threatening arrhythmia or a recent family bereavement from an inheritable cardiac condition.
- The psychosocial needs of these patients and their families should be evaluated and a multidisciplinary approach within specialized centers.
- Accurate history taking is important after death of the victim and is a primary step in finding out etiology and exploring potential risk among family members**.**
- The evaluation of premonitory cardiac symptoms (including syncope or "epilepsy"), together with an exhaustive exploration of the circumstances of death and the collection of antemortem clinical cardiac investigations, is recommended. In addition, a complete three-generation pedigree should be created, recording all sudden deaths and cardiac diseases.
- In the absence of a diagnosis in the family, young children should be screened at least with a baseline ECG and an echocardiogram.

- When an inheritable arrhythmogenic disease is suspected, DNA samples from the victim are the best source of information in performing a molecular autopsy. In the event of a positive result, family members should be offered the opportunity to undergo predictive genetic screening. It is essential to proceed with genetic testing only after phenotypic diagnosis is established.
- Making family members aware of the "right not to know" and the possibility to decline molecular screening should be included in any pre-informative communication with the relatives.
- A positive family history of SCD is a strong, independent predictor of susceptibility to ventricular arrhythmia (VA) and SCD.

Differentiating benign ST elevation from other malignant forms of ST elevation:

- Abnormal ECG of athletes often is a normal variant and can present a challenge in deciding the prognostic value and risk of SCD for these individuals (Fig. 21.1).
- Early repolarization on ECG is a common finding in young healthy adults, but adverse cardiac events are rare. Early repolarization pattern (ERP) is described

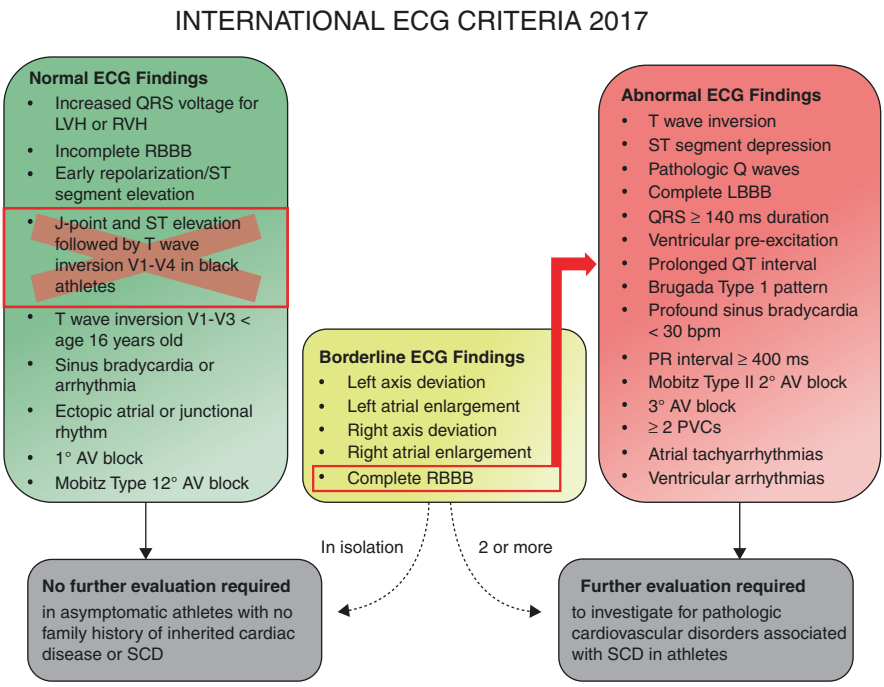

Fig. 21.1 Summary of normal and abnormal ECG findings in athletes. *AV* atrioventricular, *LBBB* left bundle branch block, *LVH* left ventricular hypertrophy, *PVC* premature ventricular contraction, *RBBB* right bundle branch block, *RVH* right ventricular hypertrophy, *SCD* sudden cardiac death. Reproduced with permission from [3]

as ST elevation in absence of chest pain or acute coronary syndrome (ACS). Terminal QRS slurring or notching can be noted. Another definition is elevation of QRS-ST junction, (e.g., J point elevation) often associated with late QRS slurring or notching (J wave) in inferior and/or lateral leads.

Diagnostic approach for family members of sudden unexplained death syndrome victims [1, 4]:

- Personal clinical history and family history focused on cardiac disease or sudden deaths.
- A standard resting 12-lead ECG may reveal signs of inherited disorders associated with VAs and SCD such as channelopathies (LQTS, SQTS, Brugada syndrome) and cardiomyopathies (arrhythmogenic right ventricular dysplasia (ARVD) and hypertrophic cardiomyopathy (HCM)). Other ECG parameters suggesting underlying structural disease include bundle branch block, atrioventricular(AV) block, ventricular hypertrophy, and Q waves consistent with ischemic heart disease or infiltrative cardiomyopathy. Electrolyte disturbances and the effects of various drugs may result in repolarization abnormalities and/or prolongation of the QRS duration.
- Exercise ECG is most commonly applied to detect silent ischemia in adult patients with ventricular arrhythmias. Exercise-induced non-sustained VT was reported in nearly 4% of asymptomatic middle-age adults and was not associated with an increased risk of total mortality. Exercise testing in adrenergic-dependent rhythm disturbances, including monomorphic VT and polymorphic VT (such as CPVT), is useful for diagnostic purposes and evaluating response to therapy. Exercise testing in patients with life-threatening VAs may be associated with arrhythmias requiring cardioversion, intravenous (i.v.) drugs, or resuscitation but may still be warranted because it is better to expose arrhythmias and evaluate risk under controlled circumstances. It should be performed where resuscitation equipment and trained personnel are immediately available.
- Continuous or intermittent signal-averaged ECG (SA-ECG) improves the signal to noise ratio of a surface ECG so that low-amplitude (microvolt level) signals, referred to as “late potentials,” can be identified at the end of the QRS complex, such as epsilon wave in ARVC. Late potentials indicate regions of abnormal myocardium with slow conduction (e.g., adjacent scar tissue), a substrate abnormality that may allow for reentrant ventricular tachyarrhythmias. SA-ECG is recommended for differential diagnosis of structural heart disease, such as ARVD, in patients with VAs.
- Ambulatory ECG monitoring is a very useful diagnostic tool to record arrhythmias. A variety of commercial ambulatory cardiac monitoring are available (Holter monitor, event monitor, implantable loop recorder).
- Echocardiography is the most commonly used imaging technique and recommended because, compared with cardiac magnetic resonance imaging (CMR) and cardiac computed tomography (CT), it is inexpensive, is readily available, and provides accurate diagnosis of myocardial, valvular, and congenital heart disorders associated with VA and SCD. In addition, LV systolic function and regional wall motion can be evaluated.

- CMR with gadolinium, or cardiac PET scan imaging, has a paramount role in identifying scar or inflammatory or infiltrative cardiomyopathy that may be responsible for VAs, and it will guide the appropriate next step in management.
- The combination of echocardiography with exercise or pharmacological stress (stress echo) is applicable to a selected group of patients who are suspected of having VA triggered by ischemia and who are unable to exercise or have resting ECG abnormalities that limit the accuracy of the ECG for ischemia detection.
- To evaluate ventricular arrhythmias (VA), electrophysiological study (EPS) is often the test of choice in documenting inducibility of clinical ventricular tachycardia (VT), guiding ablation and risk stratification of patients for recurrent VT, and assessing the indication for ICD therapy.
- EPS is not useful in HCM and channelopathies (LQTS, SQTS, CPVT). Its use in Brugada syndrome is controversial.

Ventricular Tachycardia (VT)

- Symptoms are variable and can include syncope, palpitations, dyspnea, chest pain, dizziness, and sudden death.
- Presentation is variable and may be hemodynamically stable to cardiac arrest.
- Spectrum of rhythm disturbance ranges from monomorphic PVCs to paroxysmal NSVT to sustained VT or VF.
- Reentry VT is due to the presence of slow and fast conducting tissue, and ablation therapy is usually successful. This this can be seen in:
  - Post-myocardial infarction or infiltrative cardiomyopathy scar-related border zones that allow slow conduction and a reentry mechanism for VT.
  - EP study with accurate 3D voltage mapping of ventricle is done to identify all the scar and peri-scar area then apply radiofrequency ablation therapy to cause scar modification. The idea is that by eliminating, the zones of slow conduction in heterogeneous scar will prevent reentry mechanism and suppress VAs. The reentry VA can also be induced and entrained during EPS to accurately localize the slow zone area and ablate there; however patients often do not tolerate hemodynamically VT.
  - Alternative methods such as voltage (substrate) mapping and targeting elimination of LAVA (local abnormal ventricular activation seen on EGMs) by ablation and causing scar modification are done in sinus rhythm therefore maintaining more favorable hemodynamic state during the procedure [5].
  - Bundle branch reentrant VT can be seen in dilated CMP, most commonly is LBBB like VT, so reentry mechanism involves antegrade right bundle limb and retrograde limb via left bundle; ablation of right bundle cures the VA; often these patients are known to have infra-Hisian disease and therefore may need pacemaker implant as well.

- Idiopathic VT in normal heart; it is terminated by calcium channel blockers or adenosine.
  - Fascicular VT presents as RBBB-like pattern VT; site of VT from left posterior fascicle will show negative QRS in inferior leads (superior axis); site of VT from left anterior fascicle will show positive QRS in inferior leads (inferior axis).
- Outflow tract VT:
  - Most commonly (80%) originating from the right ventricular outflow tract.
  - Typical pattern is of monomorphic, repetitive.
  - Have positive QRS in inferior leads (inferior axis).
  - LBBB like QRS configuration in precordial leads (Fig. 21.2).
  - Typically benign in nature but may be a cause of cardiomyopathy.
  - Width of the QRS (rather than PVC burden) is associated with development of cardiomyopathy (the wider the QRS that higher the chance for the development of cardiomyopathy).
  - Rarely idiopathic PVC with short coupling interval may be responsible for idiopathic VF.
  - Delayed afterdepolarization (DAD) triggered activity, cAMP, and intracellular calcium overload are underlying cellular mechanisms.
  - This is adenosine-sensitive VT; effective medical therapy is to lower intracellular ca/camp by calcium channel blocker, beta-blocker, class 1C AA flecainide, propafenone, and class III sotalol.
  - Ablation therapy is successful in >80% of cases.

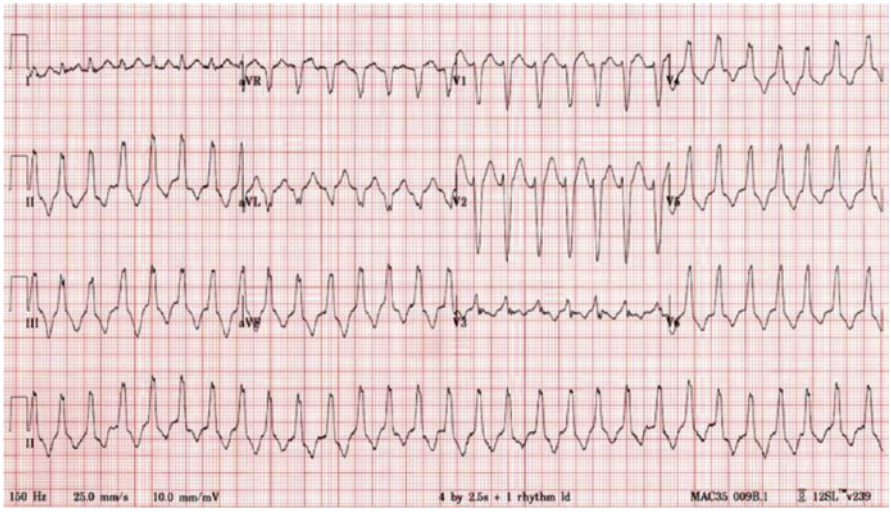

Fig. 21.2 RVOT ventricular tachycardia

- Mitral annular VT
  - Has typically positive precordial concordance with either superior or inferior axis.

Triggered Activity

- Early afterdepolarizations (EADs) are typically observed in cardiac tissues exposed to injury, altered electrolytes, hypoxia, acidosis, catecholamines, and pharmacologic agents, including antiarrhythmic drugs. The change in current-voltage relation results in net inward current during the phase 2 and 3 of action potential and reactivation of L-type calcium channel leads to a depolarization or EAD. EAD-related VTs are polymorphic VT-torsades de pointes and long QT syndrome, which are familial or acquired.
- Delayed afterdepolarization (DAD): induced triggered activity are observed under conditions that augment intracellular calcium, $[Ca^{2+}]_i$, such as after exposure to toxic levels of cardiac glycosides (digitalis) or catecholamines as in catecholaminergic polymorphic ventricular tachycardia (CPVT) and right ventricular outflow tract (RVOT) VT. This activity is also manifest in hypertrophied and failing hearts as well as in Purkinje fibers surviving myocardial infarction. In contrast to EADs, DADs are always induced at relatively rapid rates.

Differential diagnosis of wide QRS tachycardia (in order of frequency):

- VT
- SVT with aberrancy
- Preexcited tachycardia (with antegrade conduction via accessory pathway)

Wide QRS tachycardia more suggestive of VT may have some of the following features that are also part of Brugada and/or Vereckei algorithms [6] (Fig. 21.3):

- Most likely is VT rhythm if underlying CAD, history of MI, and LV systolic dysfunction (95% vs 70% without structural heart disease).
- Presence of A/V dissociation; fusion and capture beats; precordial QRS concordance (V1-V6); R-S >100 ms in any of the precordial leads.
- Extreme or (north-west) axis, precordial concordance, LB > 160 ms, RB > 140 ms.
- First part of R wave depolarization is slow >40 ms.
- aVR lead R > s.
- Hemodynamic stability does not rule out VT.

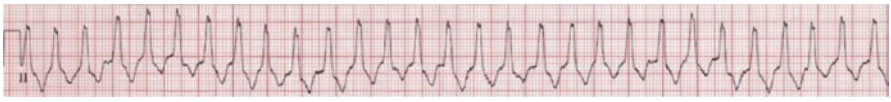

Fig. 21.3 Ventricular tachycardia

Monomorphic Ventricular Tachycardia (VT)

– Monomorphic VT is most commonly seen in patients with underlying structural heart disease.
– Scar related that may be a result of myocardial infarction(MI), cardiomyopathy, valve disease, and congenital HD. This leads to reentry tachycardia; and exit site of VT determines QRS morphology.
– Post-MI ventricular tachycardia can present with a different morphology QRS which reflects different exit sites from scar to normal tissue border.

- Purkinje-related VT is either reentry or automaticity mechanism; QRS resembles RBBB. Spontaneous Purkinje fibers activity may be seen early after myocardial infarction in the form of monomorphic PVC inducing ventricular fibrillation.
- Focal VT, monomorphic QRS morphology indicates focal location. Mechanism can be triggered, automaticity or microreentry. Known focal VAs are idiopathic VT such as RVOT, left ventricular outflow tachycardia (LVOT), papillary muscles, annular VT (mitral, tricuspid), and adrenergic monomorphic VT.

QRS morphology of monomorphic VT suggests location of VT exit site, and it is a substantial initial step to identify the site as the target for ablative therapy:

– LBBB like in V1 suggests exit site in RV or LV septum; common VAs are idiopathic RVOT, bundle branch reentry, RV scar (ARVC, sarcoid, tetralogy).
– RBBB in V1 suggests exit site in LV: scar related or idiopathic VT.
– Superior axis exit site inferior wall.
– Inferior axis exit site anterior wall.
– Dominant S waves V3-V4-exit near apical wall.
– Dominant R wave in V3-V4-exit near base (AV valve annulus).

Polymorphic VT causes:

- Active ischemic CAD/MI causes polymorphic VT or V fib
- Long QT syndrome and acquired Long QT due to electrolyte disturbance of drugs
- Brugada syndrome
- Short QT syndrome
- CPVT
- Idiopathic VT

Torsades de pointes (Fig. 21.4):

- Polymorphic VT in a setting of a prolonged QT interval.
- Triggered by reactivation of calcium channels, and delayed sodium current, or decreased outward potassium current resulting in early afterdepolarization (EAD).
- It is characterized by a waxing and waning QRS amplitude (twisting of the points pattern).

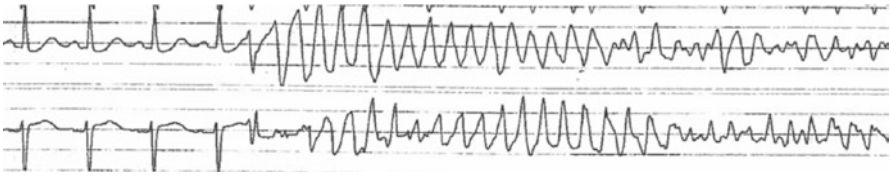

Fig. 21.4 Torsades de pointes

- If prolonged QT is acquired, then it should resolve with treatment of the underlying issue or removal of the causative agent.
- If the patient has an inherited long QT syndrome, long-term treatment with beta-blockers (nadolol) is helpful in preventing recurrence. Implantation of cardiac defibrillators may also be indicated in patients with recurrent event receiving beta-blocker therapy.
- The use of repolarization prolonging drugs (e.g., amiodarone) is contraindicated.
- Give magnesium (e.g., 2 g i.v.).
- Temporary pacing (preferably atrial) may be considered to shorten the QT interval as well as positive chronotropes (isoproterenol) as higher heart rate will result in QT shortening.
- IV lidocaine may be helpful particularly in a setting of ischemia.

Ventricular Fibrillation (VF)

- Rapid, grossly irregular, and erratic electrical activity, with marked variability in electrocardiographic waveform, ventricular rate usually >300–500 bpm. The ventricles are unable to contract in a synchronized manner with immediate loss of cardiac output.
- It is the most frequent cause of sudden cardiac death.
- VF is the most important shockable cardiac arrest rhythm. Emergency treatment includes immediate CPR and *unsynchronized cardioversion (defibrillation)* followed by advanced cardiac life support (ACLS) protocol.

Electrical storm:

- Defined as three or more sustained episodes of ventricular tachycardia, ventricular fibrillation, or appropriate ICD shocks within 24 h. Such patients should be managed in CCU.
- Mainstream therapy is beta-blockers, additional antiarrhythmic therapy, and sympathetic tone suppression including intubation and sedation.
- Reversible causes of VT such as drugs and electrolyte imbalance should be corrected or ruled out first.
- If no sufficient control of VT is achieved, consideration should be given to thoracic epidural anesthesia to suppress sympathetic input to the heart.

- Polymorphic VT/Vfib causing electrical storm should first be managed as follows: IV amiodarone, cardioversion and/or defibrillation, revascularization if indicated, hemodynamic support, reducing sympathetic tone, sedation and/or deep sedation with intubation, treat fever, and overdrive pacing.
- Cardiac sympathetic denervation is more permanent solution; few studies showing that bilateral sympathetic denervation is more effective then only left cardiac sympathetic denervation. Effective procedure includes removal of lower half of stellate ganglia and T2–T4 thoracic ganglia; specimen should be sent to pathology to confirm removal of sympathetic ganglia.
- Myocardial infarction is the most common cause of myocardial scar leading to VT hence in patient presenting with VT prompt coronary angiogram and revascularization should be pursued. Decompensated CHF, fluid overload can also trigger VTs. Treating CHF and optimizing hemodynamic state will subsequently control VT burden. Finally, if ventricular tachycardia is focal and/or triggered by PVC or scar causing reentry tachycardia, then electrophysiology study with ventricular mapping of the PVC exit site and scar may allow for succesful ablation of the VT.
- All cases of polymorphic VT or VF if clinically suspected to be triggered by PVC should also undergo catheter ablation if possible. Frequently PVCs that initiate polymorphic VT/VF are thought to originate from Purkinje fibers or outflow tract. This therapeutic approach applies to idiopathic VT, BS, LQTS, and cardiomyopathy.
- Catheter ablation of VT in LVAD patients is successful up to 77% of cases and an important therapeutic option since roughly 35% of LVAD patients have sustained VT or VF, and majority of them, although may remain clinically stable since they have mechanical circulatory support, remain very symptomatic from VT.
- Reducing ventricular tachycardia in patients with ICD is extremely important since we know that ICD shocks increase mortality. As suggested by MADIT II trial, there is 7.4-fold increase in mortality in first 3 months post-ICD shock.

Hemodynamic (HD) support in a timely fashion is a substantial treatment during electrical storm. There are a few different options:

- IABP requires a heart that has some function, is easiest to be deployed in descending aorta, and can be placed at bedside, 8Fr cannula and expected HD support is 0–1 L/min. Afterload is reduced, slightly reduced PCWP.
- Impella 2.5, 13Fr cannula, HD support 2.5 L/min.
- Impella5, 23Fr cannula, HD support 5 L/min, requires surgical cutdown for access.
- VAECMO 18–21f inflow cannula at femoral vein, 15–22Fr outflow cannula at femoral artery. Increased afterload and variable effect on PCWP. HD support 4.5 L/min and can do biventricular HD support.
- TandemHeart, 21F inflow cannula via femoral vein, and 15–17 Fr outflow cannula via femoral artery. Requires transseptal puncture. HD supports are 4 L/min. Increases afterload and reduces PCWP.

Antiarrhythmic medications (AA) for VTs:

- Besides beta-blockers use to suppress VT as a long-term management, it is best to avoid antiarrhythmic use if possible since they cause side effects and increase

mortality. Amiodarone arm higher mortality in NYHA class III as per SCD-HEFT trial. Sotalol, potassium channel blocker, also was shown to increase mortality in patients with reduced LVEF, SWORD trial; however this study included subjects without ICD implant [7].

For many of advanced cardiac disease patients, we have to use AA medications as the last and best available therapy, especially in the setting of electrical storm or frequent ICD shocks.

- Common antiarrhythmic medication is amiodarone. It is the only AA that has a safer profile and can be used in ischemic cardiomyopathy and CHF. It is class IIa indication and can be given as IV in critically ill patients, as loading dose over 24 h, starting with bolus 150 mg over 10 min, then 1 mg/min × 6 h, and then 0.5 mg/min. Intravenous amiodarone can cause hypotension. Amiodarone PO should also be loaded as 400 mg tid for 7–10 days then 400 mg daily. PO amiodarone has more propensities to cause bradycardia and long QT when compared to IV amiodarone.
- Amiodarone is effective in reducing ICD shocks. Amiodarone is the medication with properties of all antiarrhythmic classes I-IV. Also long-term adverse events are serious including pulmonary, liver, thyroid, and eye pathology. Hence annual screening for adverse effect on these organs is recommended.
- Procainamide IV is class IIa indication, less often used, and works well for stable monomorphic VT. Class Ia AA agent works by causing K+ channel blockade through its active metabolite N-acetylprocainamide. It is administered as IV 20–50 mg/min until VT stops; maximum dose is 17 mg/kg. It may prolong the QRS and QT, so one should follow closely and discontinue if QRS widening >50%. Should not be used in ischemic heart disease, caution use in liver and renal disease.
- Lidocaine class Ib AA, typically used as adjunct to amiodarone in ischemic VT. Should monitor for neurotoxicity. It is administered as 1 mg/kg bolus then 1–3 mg/min continuous drip. Mexiletine is the PO AA drug of the same class and also used as added therapy to amiodarone for controlling VT burden.
- Quinidine may be considered therapy in Brugada syndrome, short QTS, early repolarization syndrome (ERS), and idiopathic VF.

Other Causes of Ventricular Arrhythmias

Early Repolarization Syndrome

- Refers to patients with ERP who have survived idiopathic VF arrest. ERP may be caused by dispersion of refractoriness resulting in a net outward shift in repolarization current and susceptibility to phase 2 reentries.

- ERP is a common finding in the healthy population: up to 44% prevalence and more common in the young, athletes, males, and those of black ethnicity. It also appears in up to 45% of Caucasian athletes and 63–91% of black athletes.
- Further evaluation for the incidental finding of an ERP on an ECG in an asymptomatic patient, and without family history of SCD, is not recommended.
- Morphology of ST segment in ERP is thought to have prognostic value. ERP with J point elevation and rapidly ascending ST segment is a benign finding, whereas J point elevation followed by a horizontal or descending ST segment is associated with idiopathic VF. Also ST elevation ≥2 mm in inferior leads is associated with increase sudden cardiac death risk.

ARVD

- An inherited myocardial disease associated with ventricular arrhythmias and sudden cardiac death.
- Commonly presents with ventricular arrhythmia.
- EKG shows Epsilon wave in V1, T-wave inversion V1-V3.
- Degeneration of myocardium RV dysplasia/dysfunction due to fibro-fatty infiltration resulting in dilated RV. It is related to plakophilin gene mutation causing desmosome defect.

Fascicular VT

- Commonly presents as subtle widening QRS tachycardia. Right bundle branch block (RBBB) morphology suggests a focus from LV.
- Superiorly directed axis in inferior leads (negative QRS).
- More common in young males, it is associated with presence of LV false tendon seen on transthoracic echocardiogram (TTE).
- It is verapamil sensitive hence treatment of choice as initial therapy.
- Ablation is curative alternative therapy.

LV Non-compaction

- Endocardium does not form into dense smooth tissue, but it has a shaggy appearance of endocardium with fingerlike trabeculations.
- In asymptomatic patients would be considered stage B cardiomyopathy (CMP), at risk for CHF, and LV thrombus.
- Predisposes to ventricular tachycardia. Patients should avoid competitive sports.
- If systolic dysfunction with LVEF ≤35%, anticoagulation is advised.

- ICD is class I indicated in LV non-compaction if one of the following is present: reduced LVEF, or family history of SCD, or patient suffers VT.

  Myotonic dystrophy in rare cases can manifest with initial cardiac involvement causing myocardial scar of the infero-posterior segments and may present as a SCD.
  Hypertrophic cardiomyopathy (HCMP) (for detailed discussion, see separate chapter.)
  Dilated CMP (for detailed discussion, see separate chapter.)

Channelopahies

Brugada Syndrome (BrS) [8, 9]

- More common in men than women (9:1, especially among Asians) and up to 12% of all SCD (worldwide) and up to 20% of SCD in patients with structurally normal hearts. Prevalence is approximately 1 in 2000.
- BrS presents as sudden death, or syncope, often at night due to VF in absence of structural heart disease.
- Provoked by fever, Na channel blockers.
- ECG typical reflection is R′ and ST elevation in V1-V3 coved type seen in type 1 BrS as shown in Fig. 21.5; saddle back or any other shape ST elevation is type 2 BrS.
- There is new ECG criteria to identify Brugada type 2 pattern; triangle is drawn from R′ in the slope of ST and from R′ 5 mm down on S wave. If base of triangle is >4 mm, it is more suggestive of type 2 BrS (Fig. 21.6).
- Autosomal dominant inheritance in about 50% of cases. BrS type 1 associated with SCN5A mutation causing loss of sodium channel function leading to pro-

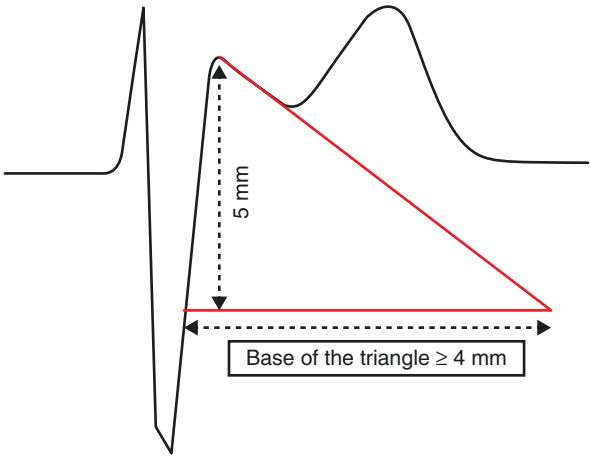

Fig. 21.5 Brugada syndrome type 1 (right), type 2 (middle). Reproduced with permission from [10]

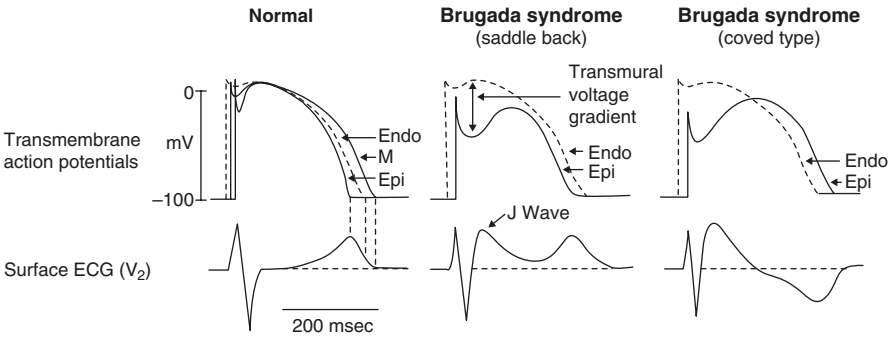

Fig. 21.6 New criteria for Brugada syndrome type 2 suggested by triangle if base ≥4 mm. Reproduced from [10]

longed PR; this mutation is identified in only 20% of affected patients. Over 70 mutations have been identified.

- BrS is associated with increased activity of Iko (K+ outflow) and loss of calcium channel function leading to short QT interval.
- If borderline ECG pattern concerning for BrS can use class 1 antiarrhythmic sodium channel blocker: procainamide, flecainide, or ajmaline (in Europe) to amplify ECG of type 1 BrS; or move V1V2 to 2nd ICS from 4th ICS to reveal Brugada pattern in suspected patients.
- If syncope and BrS are established, treatment of choice is ICD implant.
- Quinidine is used as first-line treatment. It is worth mentioning that isoproterenol (beta-adrenergic increases Na channel and Ca channel activity) alleviates or masks the ECG Brugada pattern.
- A Brugada pattern on an ECG of an asymptomatic patient with no history of syncope or a family history of SCD should be advised that fever, cocaine, and marijuana use can trigger BGS, especially in male patients, and thus should be avoided. ICD implant is not indicated in such cases.
- Genetic testing should be done on the patient; and if positive then screen first-degree family members only for the specific gene identified in the BrS patient.
- Differential diagnosis to be considered in patient that present with Brugada pattern ECG (r′ ECG pattern in leads V1, V2) is as follows:
  - Benign patterns due to incorrect, higher placement of electrodes V1-V2; partial RBBB with r′ from proximal origin or normal variant r′ more peripheral origin, athletes, and pectus excavatum.
  - Pathological cases: RV enlargement including RV hypertrophy, or RV dilatation, Ebstein anomaly, ARVD certain cases of ventricular preexcitation (WPW), and hyperkalemia.
- ECG recordings may change over time, as in this example, and serial ECGs may be important.

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

- A bidirectional VT (can mimic digoxin toxicity), normal resting ECG. VT exacerbated by surge of sympathetic tone, exercise. Clinical clue to diagnosing CPVT is progression of PVCs burden during exercise stress test.
- Genetic defect in ryanodine leaky Ca++ channels which results in diastolic calcium overload, DAD activity.
- Treatment of choice is nadolol, flecainide, and/or left cardiac sympathetic denervation.
- If SCD is present or medical therapy of VT fails ICD placement is warranted, syncope is not an indication for ICD placement as a first-line therapy.

Long QT Syndrome (LQTS)

- Most common of channelopathies is long QT syndrome 1:2000; most common inheritance is autosomal dominant, with exception to the long QTS associated with deafness, Jewell L. Nelson syndrome, and autosomal recessive inheritance. Andersen-Tawil syndrome: long QT with U wave and long isoelectric segment between T and U; loss of function of potassium channel in phase 4 of action potential.
- Ventricular tachycardia (VT) in LQTS is explained by early afterdepolarization triggered activity.
- Type 1 LQTS due to loss of voltage-gated potassium channels IKs leading to increase duration of repolarization. VT is commonly triggered by exercise or swimming.
- Type 2 LQTS is due to loss of IKr potassium channel function. VT commonly triggered by door bells, alarms, ringing phone, and postpartum.
- Type 3 LQTS is related to gain of function of Na channels (VT during non-activity sleeping resting).
- Family members of patient with LQTS may have normal EKG normal QTc and may still inherit the disease; the only way to rule out LQT syndrome is by genetic testing of specific gene mutation that is found on the victim patient with LQT syndrome.
- Confirm long QTc by looking at lead II or V5 or V6 for longest QT. In presence of a U wave to accurately measure QT and not overestimate it by including U wave, draw a tangential line on a downslope of T wave to baseline (Fig. 21.7). If T wave is biphasic, and the inverted T wave part is higher amplitude than first part, then consider it as part of T wave and measure at the end of biphasic T wave (Fig. 21.7).
- Several formulas have been developed for correction of the QT interval. The Hodges (QT_C = QT + 1.75 (heart rate – 60) and Fredericia (QT_C = QT/RR $^{1/3}$)) formulas have been shown to best predict risk of ventricular arrhythmias [11].

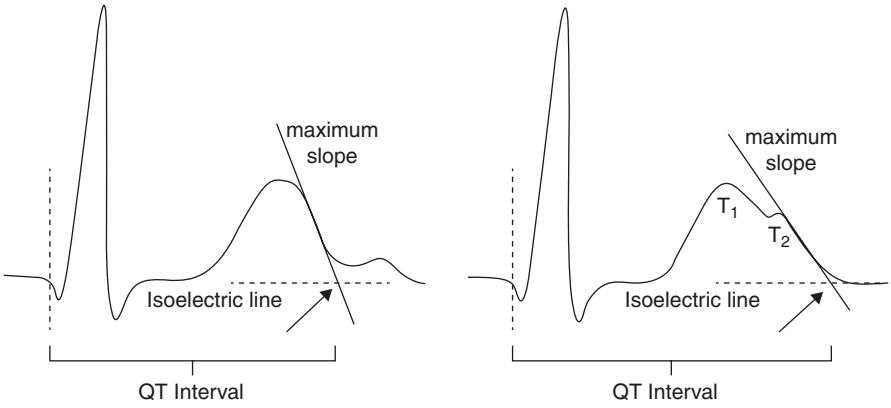

Fig. 21.7 Accurate measurement of QTc in presence of U wave (left) and in presence of notched T wave (right). Reproduced with permission from [12]

- Type 1 LQTS wide/broad ascending T wave. Type2 LQTS is double hump T wave; T3 LQTS is long isoelectric ST segment.
- Genetic testing should be offered to family members (because they may be positive for inheritance and the ECG may have normal QTc).
- Family members should be offered genetic testing because they may be positive for inheritance and the ECG may have normal QTc. As per current guidelines, long QT is defined as >450 ms in males and >460 ms in females. In clinical practice, an ECG with QTc >480 ms in females and >470 ms in males warrants further investigation. Patient that presents with long QT EKG, drugs that prolong QT including antiarrhythmic medications and electrolytes imbalance hypokalemia, hypocalcemia, and hypomagnesemia, should be ruled out first. One should refer to website **www.crediblemeds.org** for a detailed list of drugs that can cause long QT. Some of the common QT prolonging medications include:
  - Antimicrobials: fluoroquinolones, erythromycin, clarithromycin, ketoconazole, and itraconazole
  - Antidepressants: fluoxetine, sertraline, doxepin, and amitriptyline
  - Antipsychotics: haloperidol, quetiapine, and thioridazine
  - Others: ondansetron, sumatriptan, cisapride, and methadone
- If asymptomatic patient with incidental finding of QTc in >500 ms or >550 ms in IVCD and in absence of amiodarone therapy or other drugs that prolong QT warrants workup and genetic study for QT syndrome.
- Genetic tests likely to be positive in long QT syndrome (75%) so should do genetic testing in patient suspected to have more common types of long QT syndrome, types 1, 2, and 3 with genetic mutations KCNQ1, KCNH2, and SCN5A, respectively.
- Drugs of choice in LQTS are beta-blockers (e.g., nadolol).

- ICD placement recommended: SCD; male with QTC > 550 ms and not t1 LQTS, if female with QT > 500 ms, if syncope while on beta-blocker.
- Cardiac sympathetic denervation helps reduce the frequency of VT and should be done in cases of frequent appropriate ICD shock.
- For LQT-3 class I antiarrhythmics work well since disease mechanism is gain of Na function. Mexiletine, Flecainide, Ranolazine, Propanolol.

Implantable Cardioverter Defibrillator (ICD)

- ICD therapy is effective to reduce SCD and has shown to reduce mortality in two large clinical trials (SCD-HeFT and MADIT II) for all patients with CHF NYHA class II to III and reduced LVEF that remains less than 35% on repeat TTE despite optimal medical therapy for at least 3 months, and/or revascularization of ischemic cardiomyopathy for at least 3 months duration, or 40 days post-MI that is not amenable to coronary revascularization [13, 14]
- Secondary prevention of sudden cardiac death for patients who have sustained ventricular tachycardia or syncope that is thought to be due to ventricular arrhythmia, idiopathic VF, channelopathy syndromes (Brugada syndrome, etc.); structural heart diseases such as hypertrophic cardiomyopathy, ARVC, and LV non-compaction. ICD implant is appropriate only in clinical cases as mentioned or similar that are not due to irreversible causes of SCD (not due to medications, WPW, arrhythmia within 48 h of MI).
- ICD alone should not be placed in CHF with NYHA class IV. Although a subgroup of patients with NYHA class IV will benefit from CRT-P in presence of LBBB and wide QRS >120 ms.
- Common contraindications to ICD implants are terminal illness and predicted survival less than 1 year, active psychosis, active infection, incessant VT, and reversible causes of VAs.

Automated external defibrillators (AEDs) should be available in public areas where cardiac arrest is more likely to occur.

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Chapter 22
Vascular Medicine

Scott J. Cameron and Doran Mix

Peripheral Artery Disease (PAD)

Symptoms and Signs

The patient may describe pain and cramping in the thighs or calf muscles with walking which is relieved by rest. While it is important to distinguish from and consider coexistence of PAD with pseudoclaudication (referred hip pain, spinal stenosis, radiculopathy, peripheral neuropathy), it is critically important that these coexisting issues do not cause one to dismiss the possibility of PAD or screening to confirm the diagnosis.

Physical Exam

1. Diminished or absent dorsalis pedis pulses on palpation and the presence of femoral bruit are quite specific for detecting PAD [1].
2. *Dependent rubor*: bright red-appearing feet from superficial vessel vasodilation in ischemic limbs in the dependent position while sitting.
3. *Elevation pallor*: brisk loss of color on the plantar surface of the foot on leg raise in the supine position is suggestive of significant PAD.

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H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7_22

4. Rest pain or ulcers on acral areas (distal fingers or toes) suggest severe PAD manifesting as critical limb ischemia (CLI) and should immediately prompt consultation with a vascular specialist to consider revascularization.

Testing

1. Ankle-brachial index (ABI) (Table 22.1): This test is *diagnostic* for PAD. Caution: ABI *can be normal at rest in some claudicants*, and an exercise ABI is needed to show the disease. A decrease in ABI after exercise at 2.0 mph, 12% grade, and max 5 min by ≥0.2 suggests significant PAD. An ABI > 1.3 has a worse prognosis than a normal ABI, suggestive of advanced calcific disease. Non-compressible vessels are often seen in diabetics, in patients taking chronic steroid, and in patients with advanced kidney disease. Some labs will therefore result to using the toe-brachial index (TBI) in calcific arterial disease and with values <0.7 being diagnostic for PAD.
2. Segmental limb pressures: Any difference of ≥20 mmHg in blood pressure *from proximal to distal cuffs on the same limb* or between cuffs *on adjacent limb segments at the same level* suggests significant PAD.
3. Pulse volume recordings (PVRs, right): a qualitative way to imply arterial disease noninvasively by blood pressure cuffs on upper and lower extremities. Distortion on a normal triphasic arterial waveform by decrease in amplitude, decrease in upstroke, broadening of arterial signal, and biphasic or monophasic signals suggests arterial disease (Fig. 22.1).
4. Imaging studies: If ABI is moderately decreased with severe claudication refractory to medical treatment or if ABI is severely decreased, consider CT angiography of the extremity or referral to a vascular specialist for angiography. Arterial duplex imaging can be useful in certain situations.

Nonsurgical Treatment Is a Priority if Clinically Feasible

1. **Lifestyle modifications**: Smoking cessation using pharmacologic agents if necessary is the most important intervention for PAD. Supervised exercise training (SET) by treadmill was passed by CMS in 2017 as a reimbursable intervention in patients with PAD.

Table 22.1 Cut points in the Ankle Brachial Index (ABI) for grading severity

	ABI
Non-compressible	>1.3
Normal range	1.0–1.3
Borderline	0.91–1.0
Mild	0.71–0.9
Moderate	0.41–0.70
Severe	<0.40

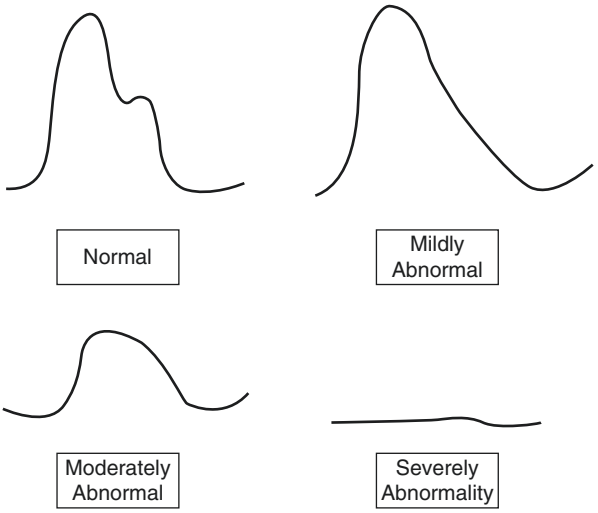

Fig. 22.1 Examples of normal and abnormal arterial waveforms with progression of obstructive arterial disease

2. **Antiplatelet therapy**: Either aspirin 81 mg or clopidogrel 75 mg for every patient with PAD (ABI < 0.9) for myocardial infarction and stroke prophylaxis [2]. No significant benefit of aspirin + clopidogrel unless another clinical indication exists.
3. **Phosphodiesterase (PDE) inhibition**: In patient with claudication refractory to SET, cilostazol 100 mg twice daily is reasonable to improve vascular blood flow. Contraindicated in patients with systolic heart failure.
4. **Statin medications**: Intense-dose atorvastatin (40–80 mg) or rosuvastatin (20–40 mg), for every patient with significant PAD for myocardial infarction.
5. **ACE inhibitors**: If the patient is hypertensive and can tolerate ACE inhibitors, ramipril has been demonstrated to have efficacy in PAD [3].
6. **Surgery**: a patient with severe PAD, with arterial ulcers (which constitutes critical limb ischemia), and favorable targets for bypass, should immediately be seen by a vascular surgeon in consideration of an arterial bypass procedure.

Carotid Artery Disease

Signs and Symptoms

Transient monocular visual field disturbance (amaurosis fugax), vertigo, and drop attacks suggest potential atheroembolic events from the aorta or the aortic branch vessels. Often carotid disease is asymptomatic, and so a high clinical index of suspicion should be present.

Physical Exam

1. A diminished or delayed carotid pulse is nonspecific though may suggest severe carotid artery stenosis (CAS).
2. The presence of carotid bruit has only around 50% sensitivity in ultimately detecting hemodynamically significant carotid artery stenosis, though it can be helpful in assessing patients with symptoms suggestive of CAS. A carotid bruit portends a fourfold risk for transient ischemia attack (TIA) or a 2.7-fold risk of stroke [4].
3. Indirect ophthalmoscopy in skilled hands can be used to visualize central or branch retinal artery Hollenhorst plaques suggesting atheroembolic events.

Testing

1. Arterial duplex imaging of the internal carotid artery is not appropriate for screening according to established guidelines, though it should be conducted in patients with findings suggesting CAS. Great care should be taken to interrogate the vertebral artery as arterial waveform spectral broadening, decreasing signal amplitude, or retrograde flow may suggest severe disease of the vertebrobasilar system ("steal") from proximal subclavian or brachiocephalic artery stenosis.
2. Contrast CT angiography of the chest and neck is useful for clarifying anatomic findings in pre-intervention in patients with suspected or known symptomatic disease of the aorta or aortic great vessels.

Treatment

1. **Surgery**: Indications for surgery include symptoms and degree of narrowing and peak systolic velocity (SV) of blood flow determined by arterial Duplex ultrasound imaging.

   In patients with *mild* or *moderate* CAS (Table 22.2) *without symptoms*, medical therapy and surveillance imaging are appropriate. In any patient with *symptomatic moderate* or *asymptomatic severe* CAS, referral to a vascular specialist is very important for consideration of intervention [5]. Patients with a TIA and

Table 22.2 Cut points for grading carotid diseae by Arterial Duplex imaging

	% Stenosis	Peak SV (cm/s)
Normal	None	<125
Mild	0–49	<125
Moderate	50–69	125–229
Severe	70+	>230

moderate or severe CAS benefits most from revascularization within 40 days. Asymptomatic severe CAS has an annual stroke risk of approximately 13% [6]. In patients >70 years of age, carotid endarterectomy is the most favorable according to most registries though trans-carotid placement of a stent by cutdown is a newer option, and, for patients <70 years, trans-aortic percutaneous placement of a carotid stent is a viable option if anatomically favorable.
2. **Lifestyle modifications**: Smoking cessation using pharmacologic agents if necessary is an important intervention in patients with CAS.
3. **Antiplatelet agents**: Either aspirin 81 mg or clopidogrel 75 mg daily for every patient with CAS for stroke prophylaxis. No significant benefit of aspirin + clopidogrel (no enhanced benefit, more bleeding) unless another clinical indication exists.
4. **Statin medications:** Intense-dose atorvastatin (40–80 mg) or rosuvastatin (20–40 mg), for every patient with significant PAD for myocardial infarction.

Aortic Disease

- Acute aortic syndromes (aortic dissection, AD; penetrating aortic ulcer, PAU; intramural hematoma, IMH) are medical emergencies that should prompt immediate consultation with a cardiothoracic or vascular specialist for management. Aortic disease is often silent, so information in this section focuses on screening for aneurysms which often precede AD, aneurysm surveillance and detection and pharmacological management of AD.

Screening for Aortic Aneurysms

1. Abdominal aortic aneurysms (AAA): Screening by duplex ultrasound or CT angiography is considered reasonable in *males between ages 65 and 75* who have smoked ≥100 cigarettes in their lifetime. At this time, there are no clear age ranges for screening asymptomatic males <65 years or for screening females, although some of the vascular societies do consider that it is reasonable to perform a one-time screen in any patient with a first-degree relative with aortic dissection [7–9]. This recognizes that many of the aortopathies are inherited in an autosomal recessive manner. Any abdominal aorta >3.5 cm is considered enlarged in most patients and should be followed at least annually. Any AAA ≥ 5.5 cm carries a clear indication for repair, though a delta growth of 0.5 cm over 6 months or a one-time measurement of 5.0–5.4 cm is considered reasonable to repair in most cases.
2. Thoracic aortic aneurysms (TAA): There are no guidelines for routine screening, though *ascending TAA* ≥ 5.5 cm or ≥ 5.0 cm if in a patient with Marfan's syndrome or congenital bicuspid aortic valve should be electively repaired. All other

TAA should be repaired if 5.5–6.0 cm or if >0.5 cm growth occurs over 6 months. Concomitant TAA and AAA are very rare, and routine screening for the other territory is not required.

Symptoms and Signs

Acute onset of sharp chest, back, or abdominal pain in a patient with either hypertension (concern for TAA rupture) or hypotension (concern for AAA rupture) warrants immediate imaging. TAA dissections can present with ST depressions or ST elevations in the inferior leads on a 12-lead ECG.

Physical Exam

Most physical exam findings in TAA and AAA aneurysms and dissection are extremely nonspecific. TAA dissection may manifest as unequal radial, brachial, or axillary pulses by palpation, but many older patients have unilateral subclavian stenosis which also manifests this way. Detecting an AAA by palpation alone is an insensitive test and can be affected significantly by the degree of obesity [10]. For this reason, most vascular societies discourage reliance solely on the physical exam in favor of age- and context-specific imaging.

Testing

CTA angiography in a stable patient or MRA in a stable patient with an iodinated contrast allergy is reasonable to assess for TAA and AAA dissections. TEE in a very unstable patient can visualize TAA dissection, though usually requires moderate sedation which may compromise hemodynamics.

Treatment

1. For any acute AD, IV infusion of beta-blockers *first*, followed by a vasodilator, is critical to decrease vascular wall dP/dt and further prevent dissection progression [11].
2. All TAA and dissections should be repaired surgically.
3. AAA can often be repaired surgically or by an endovascular approach. Endovascular stents should be evaluated at 1 month, 3 months, 6 months, and then annually for patency.

Chronic Venous Disease

- Chronic venous insufficiency (CVI) is notoriously underdiagnosed by cardiologists and primary care physicians. Patients will often complain of a swollen limb, and, as such, many patients with CVI who are in fact clinically euvolemic are erroneously misdiagnosed with a heart failure exacerbation and treated unnecessarily with diuretic medications. CVI is tenfold more common in the USA than arterial disease, affecting 25–75% of the adult population in their lifetime, one-third of whom are female one-fourth of whom will develop an associated lower extremity ulcer with advanced disease. CVI is often caused by obesity and the aging process as capillary hydrostatic pressure increases, remodeling veins and leading to interstitial edema and associated venous skin changes. The skin changes in advanced CVI are quite characteristic, and a major disservice to these patients is both a failure to recognize CVI on the physical exam and mistaking CVI for cellulitis. While advanced CVI can present with concomitant superimposed infection, misinterpreting skin changes associated with CVI as cellulitis often leads to unnecessary hospital admissions and erroneous prescription of antibiotics.

Screening for CVI

The major vascular societies do not endorse routine screening for CVI at this time by imaging. Careful attention must be paid to the physical examination in the context of the symptoms endorsed by the patient.

Symptoms and Signs

1. Tired, itchy, heavy legs
2. Swollen ankles
3. Pain in the calf muscles at rest and *relieved* by walking (venous claudication) which is the opposite of PAD
4. Changes in skin color and texture around the anterior tibial region and ulcers around the medial malleolus

Physical Exam

1. **Visible veins of varying caliber**: physical manifestations of CVI include the appearance of **reticular veins (<1 mm), spider veins (1–3 mm), and varicose veins (>3 mm).**

2. **Swelling:** generally patients will endorse persistent interstitial edema in the affected limb.
3. **Changes in skin color and texture**: there may be areas of a darkened area (stasis dermatitis and hemosiderosis) which may be raised and thickened (lipodermatosclerosis) (Fig. 22.2). There may be interpolated areas of white granulation tissue (atrophie blanche).
4. **Ulcers**: they are located close to the medial malleolus which is in the anatomic location of the greater saphenous vein (GSV) and are characteristic of the most advanced form of CVI.

Testing

CVI is a diagnosis based on clinical examination, but to qualify to certain percutaneous procedures to correct the issue, objective testing is sometimes needed.

1. Most institutions can perform a venous reflux study which involves using venous duplex ultrasound with the leg in the dependent position and a maneuver to augment venous return (right). If the resulting wave reversal as noted by continuous wave Doppler is >1000 ms in duration for a deep vein or > 500 ms in duration for a superficial vein, this is diagnostic for venous insufficiency (Fig. 22.3).
2. Photoplethysmography (PPG) is another technique some hospitals offer to assess CVI.

Treatment

1. **Conservative therapy**: in obese patients, weight loss is important, and leg elevation to decreased vascular hydrostatic pressure which progresses the disease.

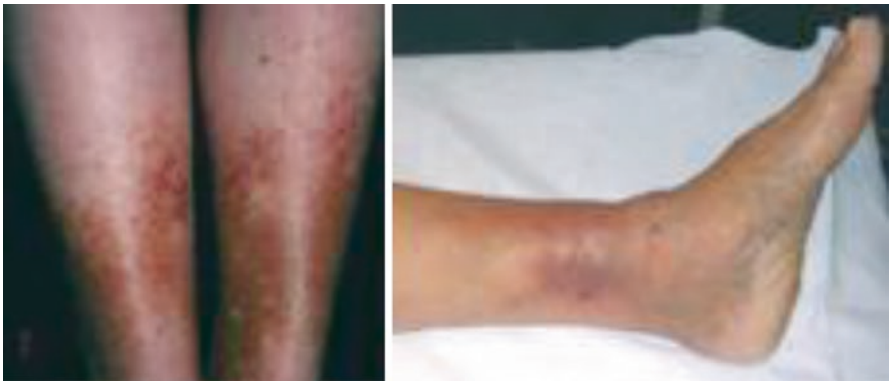

Fig. 22.2 Skin changes associated with advanced chronic venous insufficiency

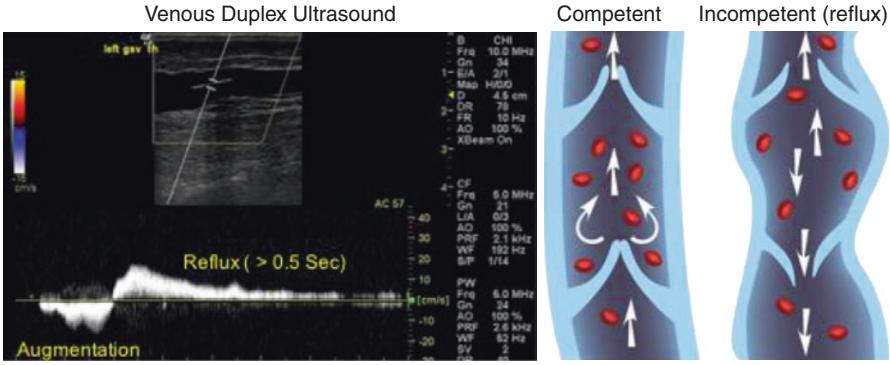

Fig. 22.3 Diagnosis of venous reflux (incompetent veins) by venous Duplex imaging

2. **Compression**: in patients with signs of advanced disease (skin changes, varicose veins, ulcers), compression therapy is the mainstay of treatment. Either ACE bandage wraps or 20–30 mmHg pressure compression stockings are needed and generally will require a prescription. Over-the-counter compression stockings are usually 15 mmHg pressure or less which is inadequate to treat most cases of CVI. 30 mmHg + compression stockings are needed for more advanced cases involving venous stasis ulcers.
3. **Pharmacological therapy**: pentoxifylline three times daily has been shown in some studies to lead to reverse remodeling of veins and improvement in skin discoloration. Horse chestnut seed extract (HCSE) which is an over-the-counter formulation is sometimes used to relieve symptoms of CVI. Several placebo-controlled studies reported a clear reduction of leg pain from CVI when HCSE was compared with placebo.
4. **Sclerotherapy**: in patients who fail compression therapy, reticular and spider veins can be treated locally by injecting a sclerosing agent.
5. **Endothermal venous ablation**: a percutaneous procedure using heat applied to the inside of the incompetent superficial veins. For reimbursement and according to guidelines by various vascular societies, demonstrating conservative treatment failure needs to be documented.
6. **Stab phlebectomy**: generally complated under moderate sedation, this procedure is reserved for very large varicose veins or with significant limb remodeling which has failed more conservative treatment.

Lymphatic Disease

- The lymphatic system forms the third network of the vasculature and is often overlooked. By definition, patients with lymphedema also have chronic venous insufficiency which leads to accumulation of interstitial edema with insufficient lymphatic drainage. Obesity is a common cause of lymphedema in the Western world, though one should stay attuned to inflammatory and paraneoplastic phenomena which lead to this disorder. As with CVI, the physical examination and

history are critical components to diagnosing disorders of the lymphatic system. Congenital lymphedema, 0–2 years; lymphedema praecox, usually females 2–35 years; lymphedema tarda, usually >35 years.

Physical Exam

1. Stemmer sign: this is a helpful physical exam finding. Try to pinch and lift the skinfold at the base of the second toe or middle finger. If you can pinch and lift the skin, **the Stemmer sign is negative**. If you can't and the skinfold is very thickened, **the Stemmer sign is positive**. False positives never occur so this is a very specific physical exam. On the other hand, a negative test doesn't necessarily rule out lymphedema.
2. Toe swelling.
3. No contour of calf.
4. Exaggerated (deep) skin creases.
5. Square toes.
6. Ski jump toenails.

Testing

1. *Always* consider occult malignancy in a patient with unexplained lower extremity lymphedema—especially if unilateral. Is the patient is current with their Papanicolaou smear, if age-appropriate, consider an ovarian mass.
2. If there is doubt based on the physical exam, you can consider performing a lymphatic scintigraphy study. Injection of a technetium-99m-labeled nanocolloid between the webbing of the first and second toe, on the resulting scan should look homogenous, with tracer accumulation if lymphatic obstruction is present.

Treatment

1. **Weight loss**: most lymphedema in the Western world is bilateral and related to obesity. Weight loss is therefore a very important but often overlooked part of the treatment plan.
2. **Lymphedema physical therapy**: is very effective, though most physical therapists require an additional credential to perform this procedure in which scheduled "milking" of the swollen limbs can decrease lymphatic accumulation.
3. **Pneumatic pumps**: There are commercially available pneumatic lymphatic pumps which tend to be expensive.
4. **Compression therapy**: 30–40 mmHg compression stockings are recommended or 40+ mm Hg for very severe cases.

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Chapter 23
Complications of Myocardial Infarction and Cardiovascular Emergencies

Nai-Lun Chang and Adam S. Budzikowski

Complications of Myocardial Infarction

1. Mortality rates due to complications of acute myocardial infarctions (AMIs) have been trending downward in recent years. With early reperfusion strategies and optimized medical therapy, early recognition and intervention are crucial [1, 2].
2. Complications can be separated into three main categories—arrhythmic, inflammatory, and mechanical.
3. Arrhythmic complications:
   (a) Common complications after acute MI.
   (b) Extensive MI with left ventricular (LV) failure.
      - Often improves with afterload reduction and treatment of pulmonary vascular congestion
   (c) Supraventricular tachyarrhythmias:
      - Triggered by excessive sympathetic activation.
      - Persistent sinus tachycardia.
   (d) Atrial fibrillation/atrial flutter:
      - The incidence rate of atrial fibrillation is 10–15% among patients who have AMIs.
      - Higher risk of heart failure (HF), stroke, shock, and mortality.

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H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7_23

- Rate versus rhythm control:
  - For patients with hemodynamic instability, immediate synchronized electrical cardioversion of 200 Joules is indicated. If AF does not respond to cardioversion, IV amiodarone can be used.
  - For patients who do not have hypotension, beta-blockers or calcium channel blockers can be used if no other contraindications.
  - Digoxin as an adjunct for rate control in patients with reduced LV systolic function or HF.
  - Indications/contraindications of anticoagulation should be considered.

(e) Bradyarrhythmias and intraventricular conduction defects:
- Transient.
- May occur immediately post reperfusion.
- High-degree atrioventricular (AV) block and persistent bundle branch block are strong predictors of cardiac death in the setting of MI [3].
- Extensive anterior and inferior MI may cause bundle branch block and AV blocks.
- Idioventricular rhythm is suggestive of reperfusion, albeit not sensitive or specific.
- Temporary transvenous pacemaker (TVP) needed, if:
  - Symptomatic bradycardia unresponsive in medical therapy (Class I).
  - High-grade AV blocks (second or third AVB), whether patient symptomatic or not.
  - New bundle branch (persistent or alternating) or bifascicular block for anterior or lateral MI [4].
  - Alternating BBB.
- Indications for permanent pacemaker:
  - Persistent high-degree AV block, with or without bundle branch block (Class I; LOE B, C) [4], even if patient is asymptomatic.

(f) Ventricular arrhythmias—ventricular fibrillation (VF) and ventricular tachycardia (VT) (see also Fig. 23.1):
- Most commonly occur during the first 48 h post-STEMI.
  - Polymorphic VT is associated with recurrent myocardial ischemia [5].
- VTs that occur post initial 48 h or in context of cardiogenic shock have poor prognosis:
  - Associated with depressed LV function and myocardial scar.
  - Need to rule out recurrent ischemia.
- Non-sustained VT:
  - Start beta-blocker, if no contraindications.
- Sustained VT is defined as three or more consecutive premature ventricular contractions (PVCs) at a rate > 100 bpm and lasting >30 s or PVCs causing hemodynamic compromise.
- Ventricular fibrillation:
  - Emergent defibrillation.

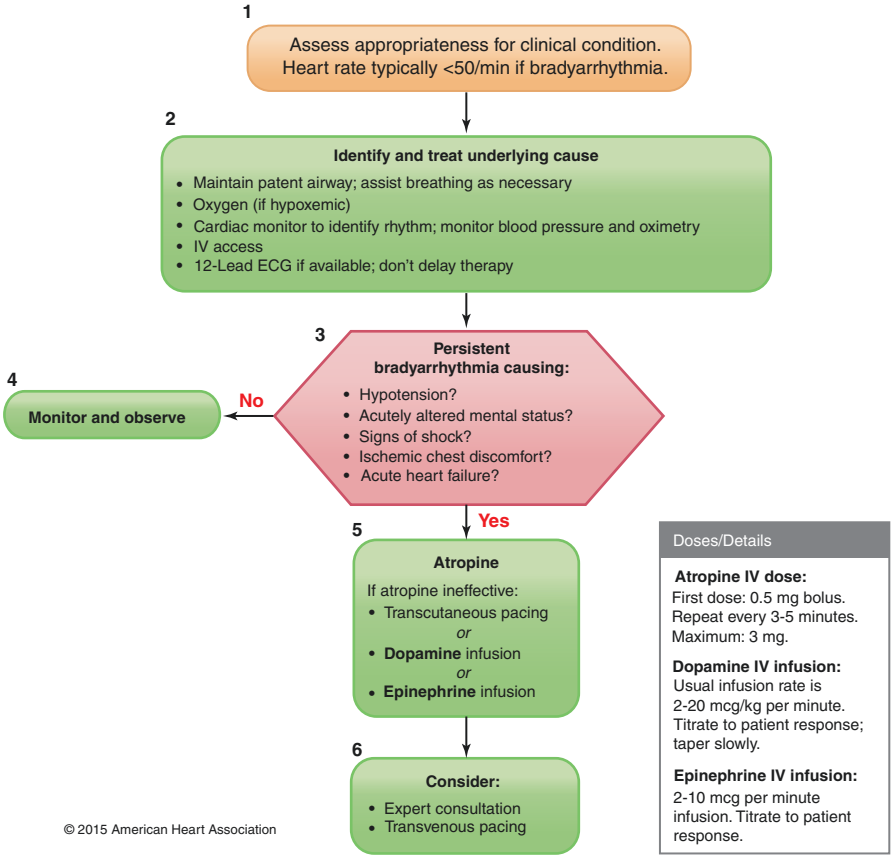


Fig. 23.1 Adult tachycardia (with pulse). Reprinted with permission from [34]

- Prevention of VF or VT is focused on electrolyte abnormality correction and revascularization for recurrent ischemia.
- Acute treatment in the setting of hemodynamic instability:
  - DCCV + IV amiodarone or lidocaine.
  - Revascularization if due to recurrent ischemia (recurrent angina ± new ECG changes).
  - Replete electrolytes (Keep K > 4 mEq/L and Mg > 2 mg/dL).
- Prophylactic suppression of premature ventricular contraction with lidocaine is not recommended, as it elevates risk of excess mortality by fatal bradycardia [4, 6, 7].
- Implantable cardioverter-defibrillator (ICD):
  - Not recommended in the setting of acute MI.
  - Current guidelines recommend deferring ICD implantation for at least 40 days following MI [8].

  - Overall mortality was not improved with early, prophylactic ICD therapy [9].
  - However, ICD therapy is indicated before discharge in patients who develop sustained VT/VF more than 48 h after STEMI, provided the arrhythmia is not due to transient or reversible ischemia, reinfarction, or metabolic abnormalities.
- LifeVest® (ZOLL, Pittsburgh, PA, USA) [10–13]:
  - Wearable external defibrillator that provides continuous protection for patients with elevated risk for sudden cardiac death
  - Indications:
    Serves as a bridge to cardiac transplantation or ICD placement.
    Early post-MI patients with markedly reduced LV function.
    Infected ICDs awaiting for device reimplantation.
    New-onset nonischemic cardiomyopathy with severe LV dysfunction during a trial of optimization of medical therapy.

4. Inflammatory:
   (a) Early pericarditis (2–4 days post MI):
   - Usually with extensive or anterior MI.
   - Pericardial rubs on physical exam.
   - EKG showing diffuse concave ST elevations with PR depressions.
   - Small pericardial effusion may be present on transthoracic echocardiogram (TTE).

   (b) Late pericarditis/Dressler's syndrome (weeks post MI):
   - Autoimmune reaction.

   (c) Treatment [4, 14]:
   - High-dose aspirin (Class I).
   - Adjunct colchicine, acetaminophen, or opioids may be useful (Class IIb).
   - Avoid NSAID and steroids (Class III).

   (d) Mechanical complications:
   - With early reperfusion strategy, the incidence of mechanical complications after acute myocardial infarction has declined. However, rapid deterioration of a patient's clinical status with new physiological exam findings should raise suspicion of mechanical complications and call for urgent diagnosis and surgical intervention [15].
   - Urgent echocardiography with color-flow Doppler is used as the initial diagnostic modality in the diagnosis and differentiation of the conditions.
   - Preoperative optimization, with an intra-aortic balloon pump and vasodilators, may help to reduce the afterload on the compromised ventricle following AMI. It may improve cardiac output in the short term but should not delay expedient surgical intervention in the setting of acute mitral regurgitation (MR).
   - Surgical intervention remains the mainstay of treatment in patients with mechanical complications of AMI, with dismal outcomes for patients treated medically.

(e) Rupture of LV free wall:
- A serious complication of ST-elevation myocardial infarction with very high mortality rate [16]. The SHOCK registry showed that mortality with free wall rupture was over 60% [17].
- It occurs in 0.5% of patients post MI.
- Occurs most often in anterior or transmural MI, elderly, and female patients.
- Signs and symptoms:
  - Recurrent chest pain with sudden hemodynamic collapse.
  - Patients may show signs of cardiac tamponade.
- Physical findings: diminished heart sounds, new murmurs, pulsus paradoxus, and jugular venous distention may be found.
- Diagnostics:
  - Urgent bedside echocardiography.
  - Right heart catheterization may show equalization of chamber pressures (right atrial, right ventricular diastolic, pulmonary wedge, and pulmonary arterial pressures) consistent with cardiac tamponade.
- Management: aggressive supportive care while waiting for cardiac surgery for emergent repair.

(f) Ventricular septum rupture (VSR):
- 1–2% of patients following AMI and usually between 3 and 5 days after AMI [15].
- Often in elderly, female, and hypertensive patients with poor collaterals to the infarcted area and in patients with delayed or lack of perfusion therapy.
- Sign, symptoms, and physical findings:
  - Sudden onset of heart failure or shock with new loud harsh holosystolic murmur, which is heard loudest at the left sternal edge, associated with a parasternal thrill.
  - The differential is acute mitral regurgitation secondary to papillary muscle rupture.
- Diagnostics:
  - ECG may show intra- or infranodal conduction abnormalities.
  - Transthoracic echocardiogram (TTE) to assess defect size and magnitude of shunt.
- Management:
  - Pressors, inotropes, and vasodilator agents.
  - Intra-aortic balloon pump (IABP) may be needed as a bridge to surgical repair [4].
  - Emergent surgical repair is necessary, even if patient is hemodynamically stable (Class I).

(g) Acute mitral regurgitation (MR) post MI:
- A life-threatening complication with a poor prognosis.
- High index of suspicion is needed if patient becomes hemodynamically unstable post MI.

- Incidence rate ranges from 3% [18] up to 39% [17].
- Occurs either from papillary muscle rupture or ischemic LV remodeling (functional ischemic MR) that restricts the posterior leaflet.
- Papillary muscle rupture resulting in MR occurs within 2–7 days of MI and occurs in 0.25% of patients following MI.
- The posteromedial muscle is affected more often than the anterolateral papillary muscle.
- Signs and symptoms:
  - Variable
  - May present as sudden pulmonary edema, with or without shock
- Physical findings: new systolic murmur. However, due to rapid equalization of pressure between the left atrium (LA) and left ventricle (LV), murmur may not be audible.
- Diagnostics:
  - CXR showing pulmonary edema.
  - TTE showing severe MR with flail leaflet.
- Management:
  - Medical therapy ± IABP support, to reduce afterload and increase forward volume and output, while waiting for urgent surgical repair.
  - Valve replacement, rather than repair, is necessary and required.

(h) Left ventricular aneurysm (LVA):

- Defined as a localized area of myocardium with abnormal outward bulging and deformation during both systole and diastole.
- The rate of LVA after AMI is approximately 3–15%.
- Signs and symptoms: severe LV dysfunction, leading to heart failure and cardiogenic shock if aneurysm is large.
- Diagnostics:
  - ECG showing persistent ST elevation after AMI that appears in the same leads as those showing the acute infarct.
  - TTE showing wide neck aneurysmal and dyskinetic segments, "smoke," and possible mural thrombus.
- Management:
  - IV vasodilators ± IABP for acute left ventricular failure.
  - Optimized medical therapy for chronic heart failure.
  - Surgical correction may be considered if heart failure is refractory to medical therapy or there is development of ventricular arrhythmia.

(i) LV pseudoaneurysm:

- Contained myocardial rupture or perforation.
- High mortality rate [19].
- Usually with inferior MI—proximal RCA occlusion with impaired flow to RV marginal branch.
- Signs and symptoms:
  - May be asymptomatic.
  - Variable (e.g., chest discomfort, dyspnea, etc.).

- Diagnostics:
  - ECG showing persistent ST elevations.
  - TTE showing a narrow neck pouching.
  - Ventriculogram on the left heart.
- Management:
  - Surgical correction recommended, despite symptomatology or size of the pseudoaneurysm, to prevent spontaneous rupture.

(j) Left ventricular mural thrombus (LVMT):
- Develops after anterior infarcts of the LV wall.
- Incidence ranges from 20 to 40% [20].
- Anticoagulation with warfarin for mural thrombus and embolization (Class I):
  - Target INR 2–3.
  - In addition to dual antiplatelet therapy (DAPT).

(k) Cardiogenic shock (CS):
- Cardiogenic shock remains a leading cause of mortality in the setting of an acute myocardial infarction, due to end organ failure [21].
  - Criteria:
    SBP <80–90 mmHg
    Pulmonary congestion
    Signs of low peripheral perfusion in the setting of severely depressed cardiac index <2.2 L/min (m^2) with support or <1.8 L/min (m^2) without support
    Elevated left ventricular filling pressures (pulmonary capillary wedge pressure >15–18 mmHg) [22, 23]
  - Risk factors:
    Elderly (>70 years of age)
    Female
    Multivessel coronary artery disease
    Extensive LV infarct, especially anterior MI
    ST elevation MI with new LBBB
    Prior history of CAD and HF
  - Causes [17]:
    Left (79%) or right ventricular failure (3%)
    Mechanical complications of acute MI (~12%)
    Iatrogenic (e.g., medication overdose)
    Ventricular outflow tract obstruction
    Cardiac tamponade
    Arrhythmia induced
  - Signs and symptoms:
    Variable (hypotension, altered mental status, dyspnea, oliguria, etc.)
    Right ventricle (RV)-related shock: high jugular venous pulse (JVP) and clear lungs
    Left ventricle-related shock: high JVP with pulmonary edema

  - Physical exam:
    Cold, mottled skin
    Faint and rapid peripheral pulses
    Jugular venous distension
    Rales
    Distant heart sounds
    Additional heart sounds (S3 or S4)
  - Diagnostics:
    Urgent echo to evaluate the cause of CS and to rule out tamponade and other mechanical complications of MI
    Pulmonary artery catheter (Swan-Ganz): diagnose and guide the shock therapy (monitor the pulmonary capillary pressure and the cardiac output)
- Management:
  - Early revascularization has survival benefit in patients with cardiogenic shock [24].
  - 2013 ACCF/AHA guidelines [4]:
    Emergent revascularization with either PCI or CABG is preferred (Class I).
    If patient is not a candidate for PCI or CABG, fibrinolytic therapy should be used if not contraindicated (Class I).
    Medical support with pressors and inotropes should be guided by hemodynamic monitoring and individualized as per clinical scenario.
    The use of mechanical hemodynamic support, such as intra-aortic balloon pump (IABP), may be helpful in patients who are unstable despite medical therapy (Class IIa). Alternative ventricular devices may also be considered (Class IIb).
  - 2016 ESC guidelines [25]:
    In contrast, the use of IABP as a routine management is not recommended (Class III).
    Volume support with bolus of normal saline or lactated Ringer's is first-line treatment, if patient has no signs of fluid overload (Class I).
    Norepinephrine is the preferred vasopressor over dopamine, in the setting of persistent hypotension (Class IIb).
    Dobutamine to augment cardiac output (Class IIb).
  - Medical therapy:
    Vasodilators (e.g., nitroprusside and nitroglycerin) have limited roles in cardiogenic shock due to their hypotensive effect.
    Vasopressors to maintain arterial pressure (mean arterial pressure 60–65 mmHg) for adequate end organ perfusion:
    Norepinephrine (0.2–3 μg/kg/min)
      First-line agent [26]
      Potent alpha and mild beta 1 agonist

Dopamine (3–20 mcg/kg/min)
- At low dose, acts on dopaminergic receptors producing renal vasodilation
- At higher dose, works on beta 1, dopaminergic, and alpha receptors
- High life ~2 min

Epinephrine (0.05–1 mcg/kg/min)
- Nonspecific adrenergic agonist
- Potent inotrope and chronotrope
- Associated with a higher rate of lactic acidosis, tachycardia, and arrhythmia [27]

Phenylephrine (0.5–15 mcg/kg/min)
- Alpha-adrenergic agonist
- Generally avoided in cardiogenic shock, since it increases afterload without augmenting cardiac contractility [27, 28]

Inotropes for severe LV dysfunction (low cardiac output):

Dobutamine (2.5–40 mcg/kg/min)
- Strong beta 1 and weaker beta 2 and alpha 1 agonist
- Has vasodilator and inotropic effect
- Half-life ~2 min

Milrinone (50 mcg/kg bolus followed by 0.375–0.75 mcg/kg/min infusion)
- Phosphodiesterase inhibitor
- Direct vasodilator and positive inotrope (weak chronotrope)
- Marked hypotensive effect
- Long half-life ~2.5 h
- Dose reduction by 50% in patients with renal failure
- Avoid when systolic pressure <90 mmHg

– Mechanical circulatory support (MCS) [23, 29]:

Early intervention with MCS may be considered in refractory shock.

Percutaneous circulatory assist devices, such as the Impella (Abiomed) and TandemHeart, are superior to medical therapy alone.

Consider venoarterial extracorporeal membrane oxygenation (ECMO) as preferred temporary MCS, for patients with defective gas exchange who will not rapidly improve with another MCS device.

Used as a bridge for heart transplant [30].

– The 2017 CULPRIT-SHOCK trial [31] showed that in patients with acute MI and cardiogenic shock showing multivessel disease on a cardiac angiogram, percutaneous coronary intervention to culprit lesion alone was superior to multivessel intervention.

This is in contrast to the current guideline [32], which recommends multivessel revascularization, if there is no contraindication (Class IIb).

In an older study from 2004, multivessel PCI in the setting of acute MI results in higher complication rate [33].

Bradycardia (Fig. 23.2)

1. Defined as heart rate < 60 bpm with symptoms (e.g., dyspnea, altered mental status, chest discomfort, etc.)
2. Evaluate for potential causes:

   (a) Iatrogenic
   - Medications (e.g., overdose of AV nodal block agents, digoxin toxicity, opioid overdose, etc.)
     - Digoxin/digitalis (cardiac glycoside).
     - AV node conduction suppression.
     - Increase of vagal tone.
     - Metabolized by the liver.
     - Half-life ~1–5 days.
     - Not dialyzable.
     - Toxicity associated with level > 2 ng/mL; however symptoms may occur at lower levels.

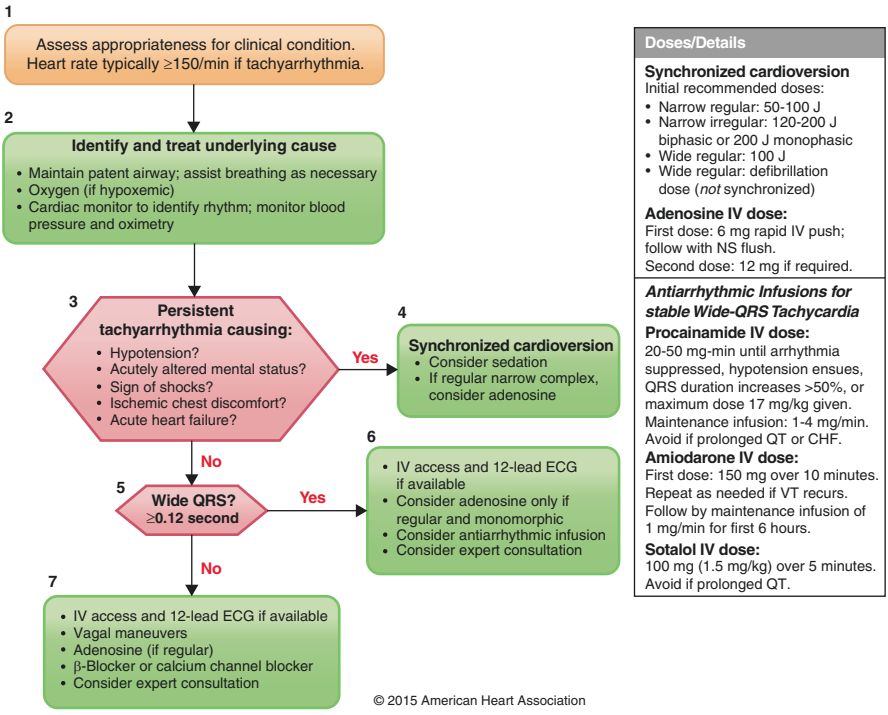


Fig. 23.2 ACLS treatment of bradycardia. Reprinted with permission from [34]

  - Variable symptoms: nausea, blurry vision, palpitations, altered mental status, GI distress, syncope.
  - EKG can show sagging ST depression and T wave (digoxin effect). It just indicates that patient is on digoxin and is not a marker of digoxin toxicity.
  - Multitude of ECG changes, such as bradyarrhythmias, AV blocks (first, second, or third), premature ventricular contractions, ventricular tachycardia (bidirectional), slow atrial fibrillation/flutter, paroxysmal atrial tachycardia with AV block, bidirectional ventricular tachycardia, etc.
- Management of digoxin toxicity:
  - Discontinuation of digoxin, correction of electrolyte imbalance.
  - Digoxin digoxin-specific antibody fragments are used to treat significant dysrhythmia from digitalis toxicity. The decision to use digoxin-specific antibody fragments is not dependent on the serum digoxin concentration.

(b) Electrolyte abnormalities:
- Hyperkalemia:
  - Hyperkalemia is defined as a potassium level >5.5 mEq/L.
  - Moderate hyperkalemia is a serum potassium >6.0 mEq/L.
  - Severe hyperkalemia is a serum potassium >7.0 mEq/L.
  - EKG changes: peaked T waves, widening and flattening of P wave, PR prolongation, QRS prolongation. With higher potassium level (>8.0 mEq/L), the progressively widened QRS eventually merges with the T wave, forming a sine wave pattern. Ventricular fibrillation or asystole follows.
- Treatment:
  - IV calcium.
  - IV insulin with glucose.
  - Consider beta-adrenergic agonist therapy (e.g., nebulized albuterol).
  - Therapy to remove excess potassium (diuretics, kayexalate, dialysis).

(c) Heart blocks:
- First-degree AV block = prolonged PR interval (>0.2 s)
  - Usually asymptomatic and does not cause hemodynamic instability
  - If isolated, does not require any specific treatment
- Second-degree AV block:
  - Mobitz I (Wenckebach) = progressive PR interval prolongation followed by non-conducted P wave
    Rarely causes hemodynamic instability.
    Low risk of progressing to complete heart block (provided QRS is narrow).

If asymptomatic, no specific treatment required. Decrease or avoid use of AV node-blocking drugs.

If symptomatic, there is usually improvement after addressing the underlying issue, and pacemaker may be indicated as well.

- Mobitz II = non-conducted P wave without progressive prolongation of PR interval

More likely to cause symptoms (most often syncope) and hemodynamic instability, which may occur spontaneously.

High risk of progression to complete heart block or sudden cardiac death.

Emergent need for pacing may be indicated if symptomatic and/or hemodynamically unstable.

Avoid drugs that can cause bradycardia, keep electrolyte levels within normal, and evaluate/treat any underlying disorder.

- Third-degree AV block = AV dissociation
  - Often, not always, accompanied by hemodynamic instability and/or symptoms, including syncope, altered mental status, hypotension, and sudden cardiac death.
  - Usually requires temporary pacing (particularly in patients with wide complex escape) (until permanent pacemaker can be placed or underlying condition is addressed).
  - Isoproterenol may be attempted to accelerate a ventricular escape rhythm, however with a low probability for efficacy.
  - In certain situations, a dopamine infusion may be a temporary alternative to improve the heart rate.
  - Evaluation and treatment of any underlying disorder are crucial (e.g., dialysis for hyperkalemia, antibiotics for Lyme disease, coronary reperfusion for MI).

Cardiac Arrest (Figs. 23.3, 23.4, and 23.5) [34, 35]

Ventricular fibrillation/pulseless ventricular tachycardia

- Sudden loss of mechanical activity in the heart
- May be multifactorial in etiology (cardiovascular, neurological, inflammatory, trauma, metabolic, etc.)
- Basic life support (BLS) and advanced cardiopulmonary life support (ACLS) algorithms

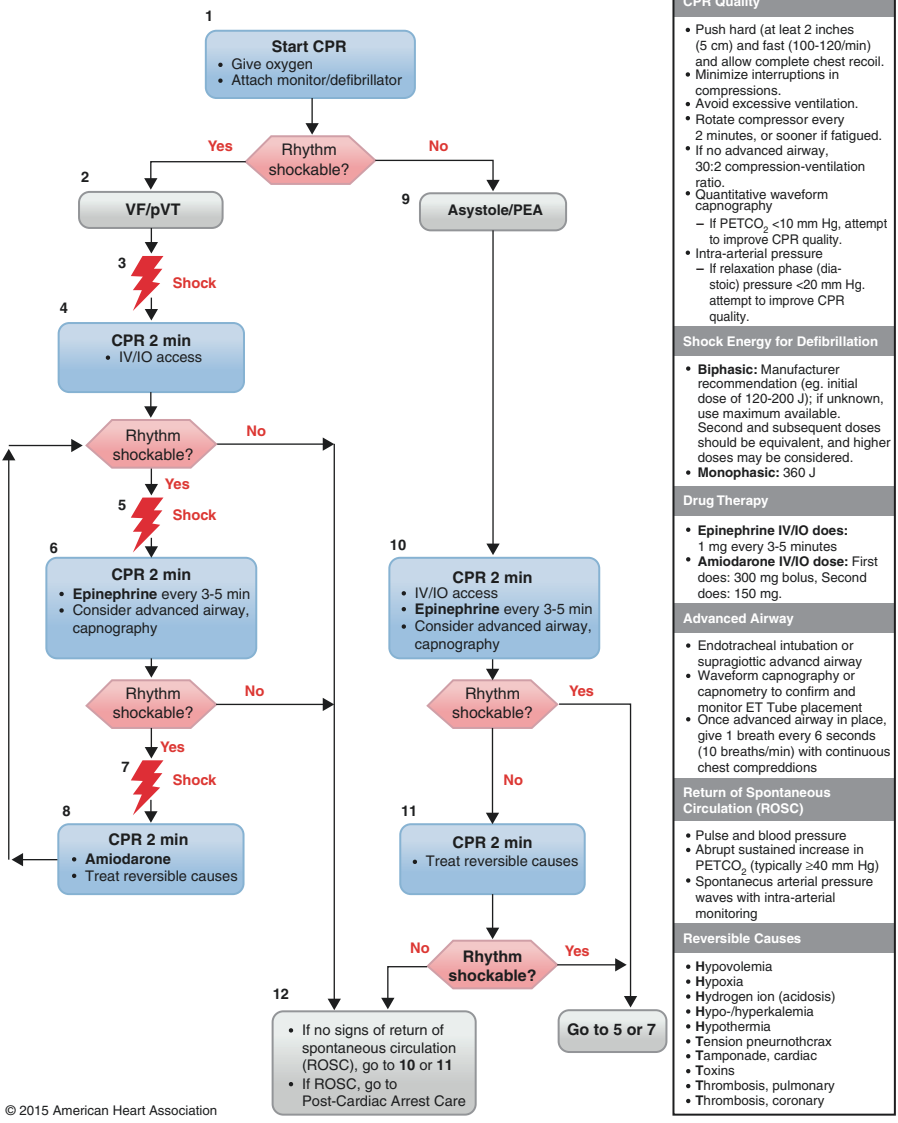
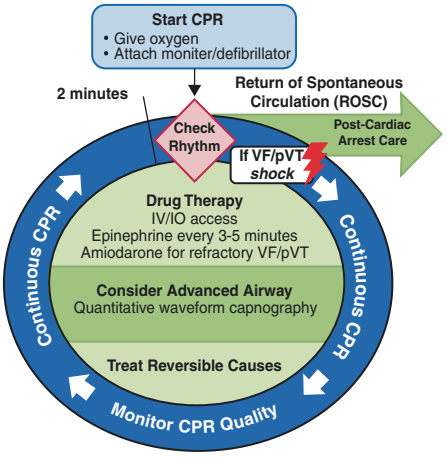


Fig. 23.3 Adult cardiac arrest algorithm—2015 update. Reprinted with permission from [34]



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CPR Quality

- Push hard (at least 2 inches (5 cm) and fast (100-120min) and allow complete chest receil.
- Minimize interruptions in compressions.
- Avoid excessive ventilation.
- Rotate compressor every 2 minutes, or sconer if fatigued.
- If no advanced airway, 30:2 compression-ventilation ratio.
- Quantitative waveform capnography
  - If $PETCO_2$ <10 mm Hg. attempt to improve CPR quality
- Intra-artenal pressure.
  - If relaxation phase (diastolic) pressure <20 mm Hg, attempt to improve CPR quality.

Shock Energy for Defibrillation

- **Biphasicc**: Manufacturer recommendation (eg. initial dose of 120-200 J); if unknown, use maximum available. Second and subsequent dose should be equivalent, and higher doses may be considered.
- **Monophasic**: 360 J

Drug Therapy

- **Epinephrine IV/IO dose**: 1 mg every 3-5 minutes
- **Amiodarene IV/IO dose**: First dose: 300 mg bolus, Second dose 150 mg.

Advanced Airway

- Endotracheal intubation or supragiottic advanced airway
- Waveform capnography or capnometry to confirm and monitor ET tube placement
- Once advanced airway in place, give 1 breath every 6 seconds (10 breaths/min) with continuous chest compressions

Return of Spontaneous Circulation (ROSC)

- Pulse and blood pressure
- Abrupt austained increase in $PETCO_2$ (typically ≥40 mm Hg)
- Spontaneous arterial pressure waves with intra-arterial monitoring

Reversible Causes

- **H**ypovolemia
- **H**ypoxia
- **H**ydrogen ion (acidosis)
- **H**ypo-/hyperkalemia
- **H**ypothermia
- **T**ension pneurnothorax
- **T**amponade, cardiac
- **T**oxins
- **T**hrombosis, pulmonary
- **T**hrombosis, coronary

Fig. 23.4 Adult cardiac arrest circular algorithm—2015 update. Reprinted with permission from [34]

Pulseless electrical activity

- Organized heart rhythm observed on ECG or telemonitor but without a detectable pulse
  - Check for underlying causes.
  - Mnemonic of 5 Hs and 5 Ts (hypo-/hyper-kalemia, hypothermia, hypoxemia, hypovolemia, hydrogen ion (acidosis) and toxins, tamponade, tension pneumothorax, thrombosis (coronary or pulmonary embolism (PE))).
- See AHA BLS/ACLS algorithms, (Figs. 23.3, 23.4, and 23.5) [34, 35].

Asystole

- Absence of any myocardial electrical activity.
- See AHA BLS/ACLS algorithms, (Figs. 23.3, 23.4, and 23.5) [34, 35].

Cardiac tamponade—please refer to Chap. 12 for more in-depth discussion.

Hypertensive emergency—please refer to Chap. 15 for more in-depth discussion.

Symptomatic tachyarrhythmia—please refer to Chaps. 17–19 and 21 for more in-depth discussion.

Aortic dissection—please refer to Chap. 22 for more in-depth discussion.

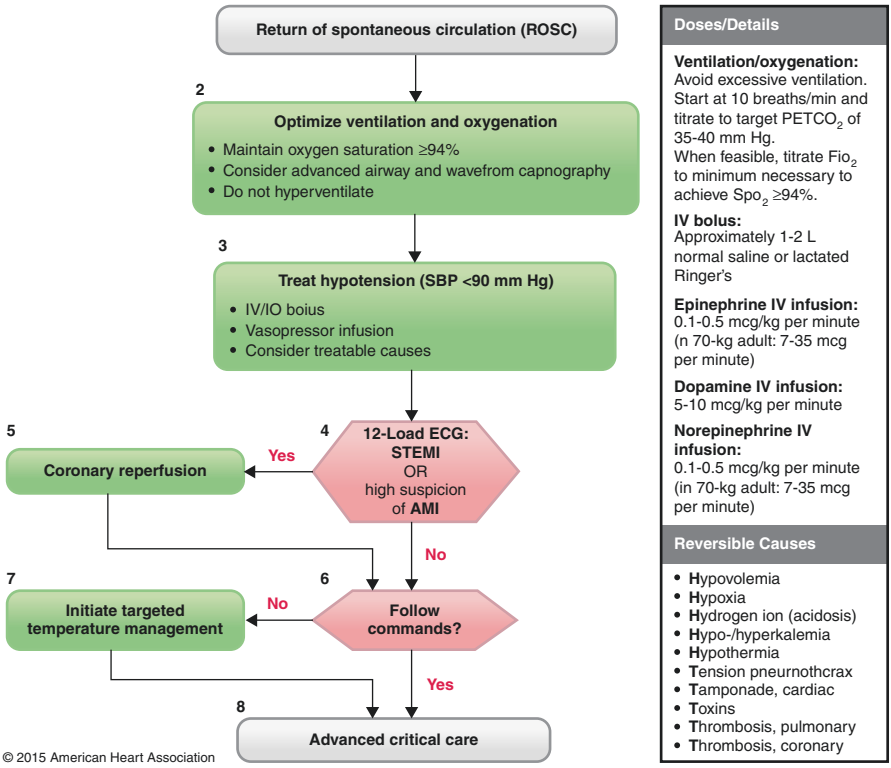

Fig. 23.5 Adult Immediate post-cardiac arrest care algorithm—2015 update. Reprinted with permission from [35]

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Chapter 24
Infective Endocarditis

Jonathan J. Ramalho and Adam S. Budzikowski

Definition

- Infective endocarditis (IE) is an infectious inflammation of the endocardial surface of the heart, which can encompass any endocardial structure including the heart valves, chordae tendineae, and papillary muscles.

Epidemiology

- There are between 10,000 and 15,000 cases of IE each year in the United States.
- A vast majority of those inflicted with IE are between the ages of 45 and 65, and roughly half of those affected are >60 years old [1].
- Men are 2.5 times more likely to be affected than women [1].

Pathophysiology

- Typically, the endothelial lining of the heart is resistant to various bacteria and fungi. Therefore, in order for an infectious vegitation to form, there must be damange to a previously normal valve allowing an organism to intiate the vegita-

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H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7_24

tion process or a highly virulent organism must be involved to affect a structurally normal heart valve.

- In most cases, the initiating event is endothelial injury. Turbulent blood flow can lead to damage of the endothelium/valve resulting in the adherence of platelets and fibrin, as per the primary clotting cascade.
- Microorganisms from a distant focal infection or from a transient bacteremia then have a nidus to which they can adhere on the endocardial surface. These pathogens then proliferate, resulting in further stimulation of the coagulation cascade and attraction of white blood cells, including monocytes to the site of injury.
- Monocytes are responsible for the release of various cytokines, which allow for additional platelets and fibrin to adhere to the developing lesion and perpetuate this cycle. It is believed that bacterial-platelet and neutrophil-platelet interactions act as extracellular traps and may be responsible for the enlargement of a vegetation.

Classification

- There is no definitive classification system of IE; however, a few different types of classification can be used to help organize endocarditis in reference to the different causative agents [2].
- Classification of IE can be based on acuity and related organisms, as well as valve type and related organisms.

1. Acuity:
   (a) Acute IE: High-virulence organisms that affect previously normal valves in a relatively rapid manner, resulting in larger-sized vegetation and death within 6 weeks if left untreated
      - Coagulase + *Staphylococcus* (*aureus*): most common cause of IE in IV drug users
      - Streptococcal species, Group A–G
      - *Streptococcus pneumoniae*
      - *Haemophilus influenzae*

   (b) Subacute IE: Low-virulence organisms that affect previously damaged valves (e.g., rheumatic HD, MVP, bicuspid aortic valve) in a relatively insidious manner, resulting in smaller-sized vegetations
      - Viridans streptococci: most common cause of IE overall
      - *Streptococcus* bovis: associated with GI malignancy (seen in ~15% of pts)
      - Enterococci

   (c) IV drug user IE:
      - *Staphylococcus aureus*: most common cause in IV drug users and most commonly affects the tricuspid valve

- *Pseudomonas* aeruginosa
- Enterococci
- *Candida* spp. and *Aspergillus*

(d) Nosocomial IE:

- *Staphylococcus aureus*: most common cause in patients with IV catheters
- Enterococci: most common cause in patients with indwelling foley catheters

(e) HACEK organisms IE:

- *Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella* are all Gram-negative organisms.

(f) Other Gram-negative IE:

- *Chlamydia* spp., *Coxiella* spp., *Bartonella* spp., *Brucella* spp., and *Legionella* spp.

(g) Fungal IE:

- Most common causative agents include *Candida* and *Aspergillus*.
- Most common in those with prosthetic valves, those who are immunocompromised, and those who use IV drugs.
- Mortality is >50%.

2. Valve type:

(a) Native valve endocarditis (NVE): infection of a native heart valve

- Viridans streptococci: the primary cause of native valve IE. Typically penicillin sensitive
- *Staphylococcus*: MSSA and MRSA
- Group D *Streptococcus* (*Enterococcus*): Typically penicillin resistant

(b) Prosthetic valve endocarditis (PVE): 10–30% of all IE cases

- Viridans streptococci: most common cause of IE of a prosthetic valve
- *Staphylococcus aureus*: mortality rate of >45% if IE of a prosthetic heart valve
- Group D *Streptococcus* (*Enterococcus*): Typically penicillin resistant
- *Streptococcus faecalis*: vancomycin-resistant *faecium* recently emerged, requiring treatment with linezolid or daptomycin
- Early PVE: IE that occurs within 1 year of heart valve replacement.
  - Typically caused by *S. aureus* and coagulase – *Staphylococcus* (*epidermidis*)
- Late PVE: IE that occurs >1 year since heart valve replacement
  - Typically caused by the same organisms that cause NVE

Approach to the Patient

- The clinical presentation of IE is highly variable, as some patients may present with typical signs and symptoms and others may not.
- IE may present as an acute disease with rapidly developing symptoms, or it may present as a subacute/chronic disease with a more insidious and less severe presentation.
- Symptoms:
  - Constitutional symptoms: fever (the most common clinical sign seen in up to 90% of pts), chills, anorexia, fatigue, malaise, weight loss, myalgias, arthralgias, dyspnea, and headache [2]
- Signs:
  - Heart murmur (85% of cases) [1]
  - Osler nodes: tender subcutaneous nodules on pads of fingers and toes (10–23% of cases) [1]
  - Janeway lesions: non-tender hemorrhages on the palms and soles (10% of cases) [1]
  - Roth spots: round retinal hemorrhages
  - Splinter hemorrhages: non-blanching subungual petechiae due to septic emboli (15% of cases) [1]
  - Petechiae: usually found on the conjunctiva and buccal and palatal mucosa
  - Focal neurological deficits: due to septic emboli (associated with increased mortality)
  - Splenic enlargement
  - Congestive heart failure
  - Bradycardia or irregular rhythm suggestive of heart block

Osler nodes and Roth spots are rheumatologic sequelae of vascular microthrombi and likely occur as a result of immune-mediated vasculitis.

- Laboratory findings:
  - A CBC may show a leukocytosis ±, the presence of bands.
  - Inflammatory markers (ESR and CRP) may be elevated.

Diagnosis

Echocardiogram

- Echocardiogram is the imaging technique of choice when IE is suspected.
- The decision on whether to obtain a transthoracic echo (TTE) or a transesophageal echo (TEE) is a difficult one but in general you may start with a TTE (Table 24.1).

Table 24.1 Sensitivity and specificity of transthoracic and transesophageal echo

	Transthoracic echo (TTE)	Transesophageal echo (TEE)
Sensitivity	60%	90–95%
Specificity	90–95%	90–95%

- If a patient has a native valve, it is reasonable to begin with a TTE and then proceed to a TEE if the TTE was negative for a vegetation and clinical suspicion remains high.
- In patients with a prosthetic valve, a TEE is preferred.
- TEE may be repeated if the initial TEE was negative, but clinical suspicion remains significantly high.
- TEE may also be obtained when TTE is positive but there is suspicion for a complication of IE (such as an abscess) and before cardiac surgery.

- Duke criteria: a set of criteria established to assist in the diagnosis of IE [3].
- The Duke criteria was first established in 1994 to help the physician make a diagnosis of infective endocarditis given its clinical difficulty.
- This criterion was modified slightly in 2000, after additional review of the Duke IE database and the modified Duke criteria was established (Table 24.2).
- The modified Duke criteria has a high sensitivity and high negative predicative value for the diagnosis of IE [4, 5].
- There are three criteria categories: pathologic criteria, major criteria, and minor criteria [3].
- The use of these different criteria helps assist the physician to establish a definitive diagnosis to investigate a possible diagnosis or to reject the diagnosis of IE.

Other Types of Endocarditis

- Other types of endocarditis, such as those listed below, are usually associated with inflammation and are thought to be the result of mucin production and subsequent embolic phenomena. They are not associated with bacteremia and destruction of the involved valves, such as in IE [4].

1. Libman-Sacks endocarditis:

   Seen in patients with systemic lupus erythematosus (SLE).
   TEE shows vegetations on both sides of the valve involved.
   Patients may have positive antiphospholipid antibodies with a reported history of miscarriages, venous thrombosis, or thrombocytopenia.

2. Marantic (non-bacterial thrombotic) endocarditis:

   Endocarditis in which sterile vegetations are seen
   Can be associated with tumors: pancreatic (most common), lung, and colon cancer or other chronic diseases such as SLE, tuberculosis, or AIDS

Table 24.2 Modified Duke criteria for IE

Pathologic criteria

1. Microorganisms: Positive culture or histology of a cardiac vegetation, a vegetation that has embolized to elsewhere, or in an intracardiac abscess
2. Histology: Vegetation or intracardiac abscess confirmed by histology which shows active endocarditis

Major criteria

1. Blood cultures positive for endocarditis
   - Typical microorganism consistent with IE from two separate blood cultures
     - Viridans streptococcus species or *Streptococcus bovis*
     - HACEK organism
     - *Staphylococcus aureus*
     - Community-acquired enterococci in the absence of another focus
   - Persistently positive blood cultures from an organism not mentioned above
     - Two blood cultures drawn 12 h apart
     - Three of four blood cultures positive even if drawn together
   - One positive blood culture for *Coxiella burnetii* or antiphase I IgG Ab titers > 1:800
2. Evidence of endocardial involvement
   - Echocardiogram positive for IE, an abscess, a new partial dehiscence of a prosthetic valve, or a new valvular regurgitation

Minor criteria

1. Fever (>100.4 °F)
2. Predisposing heart condition or IV drug use
3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, Janeway lesions
4. Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor
5. Microbiologic evidence: positive blood cultures that do not meet criterion as above or serological evidence of active infection with organisms consistent with IE

Definite	**Possible**	**Rejected**
One or more pathologic criteria Two major criteria One major and three minor criteria Five minor criteria	One major and one minor criterion Three minor criteria	Does not meet criteria for "definite" or "possible" Resolution of IE symptoms with antibiotic therapy for <4 days No pathological evidence of IE at surgery or autopsy with antibiotic therapy for <4 days

Adapted from [5]
Definite: Start antibiotic treatment based on treatment section below, and identify those who need surgical intervention.
Possible: Clinical judgment guides the physician's next step in management, but consider TEE and treatment option if clinical suspicion remains high.
Rejected: Continue workup for other causes of the patient's presentation.

Complications of IE

- Heart failure: the most common cause of death due to IE as a result of valve damage
- Perivalvular abscess: occurs in 30–40% of cases (aortic > mitral)
- Septic embolization: may result in stroke, blindness, limb ischemia, splenic/renal infarction, pulmonary embolism, and acute myocardial infarction
- Pericarditis and cardiac tamponade

- Mycotic aneurysm: typically occurs at points of vessel bifurcation
- Renal involvement: renal infarction, acute renal failure, and glomerulonephritis
- Musculoskeletal involvement: vertebral osteomyelitis and septic arthritis
- Pulmonary complications: bacterial pneumonia, lung abscess, pleural effusions, and pneumothorax
- Neurologic complications: embolic stroke, brain abscess, meningitis, meningoencephalitis, cerebral hemorrhage, or seizures
- Heart block

Treatment

- For acutely ill patients in whom clinical suspicion for IE is high, early empiric treatment is imperative; however, treatment should be delayed until at least two sets of blood cultures are drawn from two separate venipuncture sites [4].
- In acutely ill patients, it is reasonable to draw blood cultures first, start empiric coverage second, and obtain TTE/TEE third.
- *Response to treatment*:
  - Should be assessed by repeating blood cultures 48 h after antimicrobial therapy has been started and by monitoring the patient's clinical response
- *Duration of treatment*:
  - In general, patients will require 6 weeks of antimicrobial therapy, beginning from the first day that the first set of negative blood cultures are obtained.
- *Empiric treatment* should cover the most likely pathogens, which vary based on the following:
  - Patients with native valves

    Vancomycin 15–30 mg/kg IV q 12 h (renally adjusted)
  - Patients with prosthetic valves (<60 days old)

    Vancomycin 15–30 mg/kg IV q 12 h (renally adjusted) and gentamicin 3 mg/kg IV q daily
    Cefepime 2 g IV q 8 h
  - Patients with prosthetic valves (between 60 and 360 days old)

    Vancomycin 15–30 mg/kg IV q 12 h (renally adjusted) and gentamicin 3 mg/kg IV q daily
  - Patients with prosthetic valves (>360 days old)

    Vancomycin 15–30 mg/kg IV q 12 (renally adjusted) and gentamicin 3 mg/kg IV q daily
    Ceftriaxone 2 g q IV daily

- It is a Class I recommendation to obtain an infectious disease consultation at the time of initiation of empiric antimicrobial therapy (*Circulation, 2015;132:1435–1486)*
- Of note, it is important to be aware of your institution's antibiotic resistance when considering empiric coverage.
- Empiric treatment for fungi and Gram-negative organisms is not necessary given their low likelihood in IE.
- Tables 24.3 and 24.4 contain the approach to *confirmed treatment* of IE based upon culture results.
- In those patients who do have a true penicillin allergy, third-generation cephalosporins in those with NVE due to *S. aureus* and vancomycin/daptomycin are both adequate alternatives.
- Guidelines regarding those patients that need prophylaxis for IE have changed. Refer to Table 24.5 for a list of those that need prophylactic antibiotics.

The following procedures are often thought by some to require prophylaxis for IE, but they *do not*:

- Dental fillings
- OB/GYN procedures
- Urinary procedures including cystoscopy
- Patients with aortic stenosis or regurgitation, mitral stenosis or regurgitation, pacemakers or implantable defibrillators, mitral valve prolapse, hypertrophic cardiomyopathy, ASD, and VSD

Indications and Timing of Surgery

Decision about timing of surgical intervention should be made by a multidisciplinary heart valve team (cardiology, cardiothoracic surgery, and infectious disease) [6].

Class I Indictions for Surgery in patients with IE:

1. Early surgery (during initial hospitalization before completion of a full therapeutic course of antibiotics) is indicated in patients with IE who present with valve dysfunction resulting in symptoms of HF. (Level of Evidence: B)
2. Early surgery (during initial hospitalization before completion of a full therapeutic course of antibiotics) is indicated in patients with left-sided IE caused by Staphylococcal aureus, fungal, or other highly resistant organisms. (Level of Evidence: B)
3. Early surgery (during initial hospitalization before completion of a full therapeutic course of antibiotics) is indicated in patients with IE complicated by heart block, annular or aortic abscess, or destructive penetrating lesions. (Level of Evidence: B)
4. Early surgery (during initial hospitalization before completion of a full therapeutic course of antibiotics) for IE is indicated in patients with evidence of persistent

Table 24.3 Native valve endocarditis treatment

Organism	First-line agents	Second-line agents
Penicillin-susceptible viridans streptococci or *S. bovis*	Penicillin G 12–18 million U/day IV in divided doses q 4–6 h Ampicillin 2 g IV q 4 h Ceftriaxone 2 g IV q daily	Vancomycin 15–30 mg/kg IV q 12 h (renally adjusted)
Penicillin-resistant strep	Penicillin G 24 million U/day IV in divided doses q 4–6 h Ampicillin 2 g IV q 4 h Ceftriaxone 2 g IV q daily	Vancomycin 15–30 mg/kg IV q 12 h (renally adjusted)
Methicillin-sensitive staphylococci	Oxacillin 12 g/day IV divided in doses q 4–6 h Nafcillin 12 g/day IV divided in doses q 4–6 h	Cefazolin 6 g/day IV in divided doses q 8 h Vancomycin 15–30 mg/kg IV q 12 h (renally adjusted) Daptomycin 8–10 mg/kg IV q daily
Methicillin-resistant staphylococci	Vancomycin 15–30 mg/kg IV q 12 h (renally adjusted)	Daptomycin 8–10 mg/kg IV q daily Bactrim 960 mg/day IV divided into doses q 4–6 h plus clindamycin 1800 mg/day divided into doses q 8 h
Penicillin-sensitive enterococci	Ampicillin 2 g IV q 4 Penicillin 18–30 million U/day IV divided into doses q 4 h Amoxicillin 200 mg/kg/day divided in doses q 4–6 h plus gentamicin 3 mg/kg/day IV divided in doses q 8–12 h Ampicillin 2 g IV q 4 h plus ceftriaxone 2 g IV q 12 h	Vancomycin 15–30 mg/kg IV q 12 h (renally adjusted) plus gentamicin 3 mg/kg/day IV divided in two doses 12 h apart
Penicillin-resistant enterococci	Ampicillin/sulbactam 3 g IV q 6 h plus gentamicin 3 mg/kg/day IV divided in doses q 8–12 h	Vancomycin 15–30 mg/kg IV q 12 h (renally adjusted) plus gentamicin 3 mg/kg/day IV divided in doses q 8 h
Vancomycin-resistant *Enterococcus faecium* (VREF)	Linezolid 600 mg IV q 12 h Daptomycin 10–12 mg/kg IV q daily	
HACEK pathogens	Ceftriaxone 2 g IV q daily Ampicillin/sulbactam 3 g IV q 6 h	Ciprofloxacin 400 mg IV q 12 h; 1000 mg PO q daily
Fungal pathogens	Surgery + amphotericin B 3–5 mg/kg IV q daily plus flucytosine 25 mg/kg/day divided in doses q 6 h (only in those with normal renal function)	Caspofungin 150 mg IV q daily Micafungin 150 mg IV q daily Anidulafungin200 mg IV q daily

Table 24.4 Prosthetic valve endocarditis treatment

Organism	First-line agents	Second-line agents
Penicillin-susceptible viridans strep or *S. bovis*	Penicillin G 24 million U/day IV divided into doses q 4–6 h Ampicillin 2 g IV q 4 Ceftriaxone 2 g IV q daily	Vancomycin 15–30 mg/kg IV q 12 h (renally adjusted)
Penicillin-resistant strep	Penicillin G 24 million U/day IV divided into doses q 4–6 h Ampicillin 2 g IV q 4 h Ceftriaxone 2 g IV q daily plus gentamicin 3 mg/kg/day IV q daily	Vancomycin 15–30 mg/kg IV q 12 h (renally adjusted) plus gentamicin 3 mg/kg/day IV q daily
Methicillin-sensitive staphylococci	Nafcillin 12 g/day divided in doses q 4 h Oxacillin 12 g/day IV divided in doses q 4 h Cefazolin 6 g/day IV divided in doses q 4 h plus rifampin 900 mg/day PO or IV divided in doses q 8 h plus gentamicin 3 mg/kg/day IV q daily	Vancomycin 15–30 mg/kg IV q 12 h (renally adjusted) plus rifampin 900 mg/day PO or IV divided in doses q 8 h plus gentamicin 3 mg/kg/day IV q daily
Methicillin-resistant staphylococci	Vancomycin 15–30 mg/kg IV q 12 h (renally adjusted) plus rifampin 900 mg/day PO or IV divided in doses q 8 h plus gentamicin 3 mg/kg/day IV q daily	
Penicillin-sensitive enterococci	Ampicillin 2 g IV q 4 h Penicillin 18–30 million U/day divided in doses q 4 h Amoxicillin 200 mg/kg/day IV divided in doses q 4 h plus gentamicin 3 mg/kg/day IV q daily	Vancomycin 15–30 mg/kg IV q 12 h (renally adjusted) plus gentamicin 3 mg/kg/day IV q daily
Penicillin-resistant enterococci	Ampicillin/sulbactam 3 g IV q 6 plus gentamicin 3 mg/kg/day IV in divided doses q 8	
Vancomycin-resistant *Enterococcus faecium* (VREF)	Linezolid 600 mg IV/PO q 12 h Daptomycin 10–12 mg/kg q daily	
HACEK pathogens	Ceftriaxone 400 mg IV q 12 h Ampicillin/sulbactam 3 g IV q 6 h	Ciprofloxacin 400 mg IV q 12 h; 1000 mg PO q daily Ampicillin/sulbactam 3 g IV q 6 h and gentamicin 3 mg/kg/day IV divided in doses q 8 h
Fungal pathogens	Surgery + amphotericin B 3–5 mg/kg IV q daily plus flucytosine 25 mg/kg/day divided in doses q 6 h (only in those with normal renal function)	Caspofungin 150 mg IV q daily Micafungin 150 mg IV q daily Anidulafungin 200 mg IV q daily

Table 24.5 Infective endocarditis prophylaxis [6]

	Need prophylaxis	PPX antibiotic
Cardiac defects (CDs)	Patients with CDs, prosthetic valves, transcatheter implanted prostheses [TAVR], homografts, and for patients with prosthetic material used in valve repair (including annuloplasty ring or artificial chords) Patients with unrepaired CDs or repaired CD with residual shunts or valvular regurgitation, at the site or adjacent to the site of a prosthetic patch or prosthetic device Patients with previous history of IE Patients with CDs who are transplant recipients and have previously developed valve disease	
Procedures	Dental procedures that cause bleeding	Amoxicillin or Ampicillin (PO or IV) Allergy to penicillin or ampicillin: clindamycin 600 mg PO or IV

infection as manifested by persistent bacteremia or fevers lasting longer than 5 to 7 days after onset of appropriate antimicrobial therapy (Level of Evidence: B)

5. Surgery is recommended for patients with prosthetic valve endocarditis and relapsing infection (defined as recurrence of bacteremia after a complete course of appropriate antibiotics and subsequently negative blood cultures) without other identifiable source for portal of infection. (Level of Evidence: C)

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Chapter 25
Pregnancy and Heart Disease for the Consulting Physician

Priscilla Givens and Gladys Velarde

Epidemiology [1]

- Pregnancy-related deaths, defined as death occurring within 12 months of giving birth, have risen over the last decade thought in part to be from the increasing number of women in the USA becoming pregnant with underlying chronic diseases.
- Cardiovascular disease (CVD) affects about 8% of all pregnancies, and significant disease is seen in approximately 2% of pregnancies.
- From 2011 to 2013, CVD was noted to be the number one cause of pregnancy-related deaths in 15.5%, cardiomyopathy noted to be the cause in 11.0%, and hypertensive disorders in 7.4% of pregnancy-related deaths in the USA.
- Among pregnant women with CVD, congenital heart disease (CHD) is the predominant form of heart disease in developed countries, whereas rheumatic heart disease predominates in developing countries.
- Pregnancy in heart disease does not necessarily preclude a successful pregnancy in many cases. It is important to keep in mind the increase in risk to both the mother and the fetus and utilize appropriate treatment with a team approach.

Risk Factors [1, 2]

- Advanced maternal age usually considered >35 y/o at time of delivery
- Cyanosis (oxygen saturation at rest <90%)

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H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7_25

- Right ventricular systolic dysfunction and/or severe pulmonary regurgitation
- Moderate or severe systemic atrioventricular valve regurgitation
- Moderate or severe pulmonary atrioventricular valve regurgitation
- Mechanical valves

CARPREG and WHO [2]

- The Cardiac Disease in Pregnancy (CARPREG) risk score is based on the presence of the risk factors listed below and can be calculated to estimate a woman's cardiac risk during pregnancy:
  - History of cardiac events prior to pregnancy (arrhythmia, pulmonary edema, or stroke)
  - Poor functional status, e.g., New York Heart Association functional class II or greater
  - Reduced LV systolic function (left ventricular ejection fraction <40%)
  - Left heart obstruction (mitral valve area of <2 cm^2, aortic valve area <1.5 cm^2, peak left ventricular outflow tract gradient >30 mmHg by transthoracic echocardiogram)
- One point is assigned for each of risk factors denoted above and risk is calculated.
- For 0 points, the risk of maternal complications is 5%; for 1 point, it rises to 27%, and for 2 points and above, it rises to 75%.

The modified World Health Organization (WHO) classification is recommended for the assessment of maternal risk in women with cardiovascular disease and includes contraindications for pregnancy not incorporated in other risk score calculations.

General Principles of WHO [3]

- Risk for complication is low for women who fall into the WHO class I, and routine follow-up is recommended. It includes uncomplicated small/mild pulmonary stenosis, mitral valve prolapse, and PDA. Successfully repaired simple lesions: atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA). Isolated PACs and PVCs.
- Risk for complication is low or moderate for women who fall into the WHO class II, and follow-up every 3 months is recommended. It includes unoperated ASD (if patient is doing well), repaired tetralogy of Fallot, and most arrhythmias.
- Risk for complication is moderate for women who fall into the WHO class II–III depending on the patient: mild LV dysfunction, hypertrophic cardiomyopathy,

heart transplant, Marfan syndrome without aortic dilation, aortic dilation <45 mm in bicuspid valve aortopathy, tissue prosthetic valve, or native valvular heart disease not WHO IV.

- Risk for complication is high for women who fall into WHO class III, and monthly follow-up is recommended. It includes mechanical prosthetic valve, aortic dilation 40–45 mm in Marfan syndrome or 45–50 mm in bicuspid aortopathy, systemic right ventricle, post-Fontan operation, cyanotic heart disease, and other complex CHD.
- For women who fall into WHO class IV, pregnancy is very high risk and is not recommended. Women should be counseled on termination. However, if patients elect to continue the pregnancy, they should be monitored with monthly follow-up.

Contraindications to Pregnancy (Conditions in Which Pregnancy Risk Is WHO 4) [1, 4]

- Dilated aortic root (>45 mm) in Marfan syndrome
- Dilated aortic root >50 mm in bicuspid valve aortopathy
- Pulmonary hypertension (pulmonary vascular resistance, >6 Wood units)
- Moderate-to-severe left ventricular outflow tract obstruction (≥30 mmHg), severe symptomatic aortic stenosis, or severe mitral valve stenosis
- NYHA class III or IV or LVEF <30%
- Previous peripartum cardiomyopathy with any residual LV dysfunction

- If a woman with one of these conditions becomes pregnant, early consultation with a maternal-fetal medicine specialist and a cardiologist should be done in order to evaluate the patient's risk and develop the plan of care.
- Pulmonary hypertension confers a prohibitively high cardiac risk and carries a combined maternal and fetal mortality rate that approaches 50%. Termination of pregnancy should be considered in this condition.

Indications for Cesarean Section

- Obstetrical reasons.
- Preterm labor in patient on oral anticoagulation.
- Fixed cardiac obstructive lesions (e.g., severe aortic stenosis).
- Pulmonary hypertension/Eisenmenger syndrome.
- With few exceptions, vaginal delivery w/ facilitated second stage is preferred for women with heart disease.

Hemodynamic Changes of Pregnancy [1, 5–7]

- Cardiac output (CO) begins to increase from conception and increases in the order of 30–50% which peaks around 20–24 weeks into pregnancy [1, 5, 6].
- Heart rate (HR) increases an average of 15–20 bpm starting at 2 weeks into pregnancy.
- Preload increases as a result of increased plasma volume on average around 45% during pregnancy which continues to rise into the third trimester [1, 5].
- Stroke volume (SV) is increased to around 40% peak in the second trimester of pregnancy with a slight decline at 38 weeks [1, 5, 6].
- There is a substantial reduction in systemic vascular resistance (SVR) and a concomitant decrease in blood pressure (BP) [1, 6].
- The decline in blood pressure is mitigated by increased activity of the renin-angiotensin-aldosterone system which causes water retention.

Hemodynamic Changes During Labor and Postpartum [1]

- During labor the CO increases further during uterine contractions due to increased stroke volume.
- Immediately after delivery, the filling pressures may increase with the decompression of the vena cava and return of the uterine blood to the systemic circulation.
- The changes acquired during pregnancy regress at 6 weeks postpartum but may be longer.

Symptoms and physical exam findings with pregnancy are listed in Table 25.1.

Table 25.1 Symptoms and physical exam

Symptoms	Signs
Normal findings with pregnancy	
Decrease in exercise tolerance (fatigability)	Peripheral edema
Tiredness	Hyperventilation
Dyspnea	Distended neck veins
Orthopnea	Prominent a and v wave and x and y descent
Light-headedness	Diffuse apical impulse
Syncope	Palpable RV
Abnormal findings with pregnancy	
Severe or progressive dyspnea	Cyanosis
Progressive orthopnea	Clubbing
Syncope (with exertion)	Persistent neck vein distention
Chest pain (effort related)	Hemoptysis
	Cardiomegaly (general or localized)
	Sustained arrhythmias
	Parasternal lift

Normal Heart Sounds in Pregnancy

- Increased S1 may show exaggerated splitting (pre-closure of the mitral valve).
- No significant change in S2 prior to 30th week gestation; may be persistently split in lateral decubitus position.
- S3 may be easily heard in up to 80% of pregnant patients, usually more at 20–30th week.
- S4 generally represents disease.

Murmurs in Pregnancy (Table 25.2)

Systolic murmurs are common, usually grade <3/6, more detectable at 16–20th week gestation.

- The majority disappear shortly after delivery (about 1 week postpartum).
- Examples: (1) Mammary souffle (*soplare*, to blow) heard over the breasts late in pregnancy but especially in the postpartum period in lactating women. The mammary souffle is influenced by local compression and position and disappears after lactation. (2) Arteriovenous fistula murmur can be attenuated by pressure and can persist post lactation. (3) Cervical venous hum is present in almost all pregnant women and more common than the mammary souffle. It is most prominent on the right side and radiates only rarely below the clavicle in pregnant patients; when it does, it may be confused with the PDA murmur. It is reduced or abolished by digital compression of the ipsilateral internal jugular vein.

Diastolic murmurs are uncommon and warrant closer attention.

Diagnostic Testing

- When heart disease is present, each patient and each condition should be considered individually.

Table 25.2 Summary of murmurs

Normal murmurs of pregnancy	Abnormal murmurs of pregnancy
Mammary souffle[a]	Systolic murmurs grade > 3/6 in intensity
Cervical venous hum[a]	An accompanying palpable thrill
Supraclavicular systolic murmur	Occur later or throughout systole
Pulmonic systolic murmur (innocent)	Diastolic murmurs are uncommon and warrant a closer evaluation

[a]Continuous murmurs commonly have diastolic component

Specific Conditions

Hypertension and Pregnancy [1, 9, 10]

Etiology and Risk Factors

- Hypertension in pregnancy is sorted into four categories: preeclampsia-eclampsia, chronic or preexisting hypertension, preeclampsia-eclampsia superimposed upon chronic hypertension, and gestational hypertension [1, 9] (Tables 25.3 and 25.4).
- Prevalence of preeclampsia is highest in women with preeclampsia during prior pregnancy.
- Preeclampsia-eclampsia can also be superimposed on chronic hypertension.

Diagnostic Testing

- Diagnosis is made with measurement of elevated blood pressures on two separate occasions.

Table 25.3 Classification of HTN in pregnancy

Classification	Systolic BP (mmHg)	Diastolic BP (mmHg)
Mild	140–149	90–99
Moderate	150–159	100–109
Severe	≥160	≥110

Table 25.4 Hypertension and pregnancy

Category	Time period	Findings
Preeclampsia-eclampsia	After 20 weeks gestation Complicates 5–7% of pregnancies	Preeclampsia: proteinuria ± end organ damage[a] Eclampsia: preeclampsia with seizures
Chronic (preexisting) hypertension	Before 20 weeks gestation; persists after 12 weeks' postpartum Complicates 1–5% of pregnancies	BP ≥ 140/90 mmHg
Preeclampsia-eclampsia w/ chronic hypertension	Before 20 weeks gestation	Worsening of chronic hypertension with new development of features of preeclampsia
Gestational hypertension	After 20 weeks gestation Complicates 6–7% of pregnancies	Elevated BP without features of preeclampsia

[a]New onset of significant proteinuria 0.3 g/24 h or other end organ dysfunctions such as low platelet count (<100,000/μL), serum creatinine >1.1 mg/dL, transaminitis twice the upper limit of normal, pulmonary edema, new-onset headaches, or visual disturbance [9, 10]

- Once the diagnosis is made, further evaluation with basic labs and urinalysis is recommended to evaluate for preeclampsia.
- In a pregnant patient with hypertension, it is recommended that the patient check her BP daily, with a bi-weekly check by a clinician according to the American College of Obstetricians and Gynecologists [9].

Treatment [16–19]

- Treatment is recommended for those with severe hypertension, defined as BP ≥ 160/110 as it can reduce the incidence of maternal intracranial hemorrhage [1, 9].
- Target treatment with goal mean arterial pressure <125 mmHg.
- Lifestyle modification is difficult in pregnancy as lowering salt intake may cause low intravascular volume in the mother, and weight loss is not recommended [1, 9].
- Bed rest has not provided significant benefit.
- For treatment of hypertension in pregnancy, the drug of choice is methyldopa or labetalol [1].
- For severe hypertension, IV metoprolol or IV labetalol can be used.
- If preeclampsia is complicated by pulmonary edema, IV nitroglycerin can be administered.
- Drugs to avoid during pregnancy are listed in Table 25.5.
- Evidence is limited for indications on the treatment of mild to moderate hypertension given the increased risk of harm to the fetus from side effects of treatment [1, 9–11].
- Aggressive hypertensive management was associated with placental hypoperfusion, compromising the fetus [10].
- In cases of emergent or refractory hypertension, induction of labor is recommended between 38 and 39 weeks gestation to balance lowest maternal and fetal risks [14, 15, 20, 21].
- The only treatment for preeclampsia is delivery of the fetus.
- If earlier induction is necessary, pretreatment with steroids for fetal lung maturity is recommended.

Table 25.5 Drugs to Avoid in Pregnancy and its Teratogenic Effects

Drugs to avoid	Teratogenicity
ACE inhibitors, ARBs, direct renin inhibitors	Teratogenic: oligohydramnios [8, 11]
Mineralocorticoid receptor antagonists	Antiandrogen effects cause feminization of male fetus
Nitroprusside	Fetal cyanide poisoning
Atenolol	Intrauterine growth retardation, preterm delivery [12]

Hypertension and preeclampsia in pregnancy have been recognized as important risk factor for cardiovascular disease (CVD) in women in the future.

Cardiomyopathies, Heart Failure, and Pregnancy [22–28]

- Assessing a patient for heart failure in pregnancy should be approached similarly to the non-gravid patient.
- Hemodynamic changes of pregnancy should be kept in mind given the changes in volume status involved, as it may precipitate an acute exacerbation.

Peripartum Cardiomyopathy [29–34]

Etiology and Risk Factors

- Defined as idiopathic cardiomyopathy (LVEF <45%) first identified in the last month of pregnancy up to 6 months postpartum.
- Etiology is still unknown, though many are postulated and thought to be multifactorial.
- In patients with peripartum cardiomyopathy in a prior pregnancy, there is up to 30–50% risk of recurrence in subsequent pregnancies.
- Prognosis is variable, and >50% will see partial or complete recovery of LV function (LVEF >50%) in 6 months.
- If no improvement in EF is seen after first 6 months, prognosis is poor.
- Patients with peripartum cardiomyopathy should be advised against future pregnancies (contraceptive methods need to be discussed with GYN/OB team).

Risk Factors

- Modifiable
  - Obesity
  - Smoking
  - Poor nourishment
  - Alcoholism
  - Hypertension
- Non-modifiable
  - Older age (>30 years old)
  - African-American race
  - Multiparity
  - Multiple pregnancy (i.e., twins)
  - Low socioeconomic status

- Risk factors for persistent LV dysfunction
  - Fractional shortening <20%
  - Left ventricular end-diastolic dimension ≥6 cm
  - LVEF ≤30%
  - African-American race
  - Elevated cardiac troponin T
  - Diagnosed early in pregnancy

Diagnostic Testing

- Baseline clinical status should be established with evaluation through history, echocardiography, electrocardiogram, and lab work.

Treatment (Tables 25.6 and 25.7)

- Treatment is similar for those with chronic heart failure in pregnancy and for peripartum cardiomyopathy.

Table 25.6 Treatment of chronic heart failure in pregnancy

Treatment regimen for chronic heart failure in pregnancy [35]			Drugs to avoid in pregnancy [9, 12, 13]	
Drugs	Name	Indication	Drugs	Teratogenicity
Beta-blockers	Metoprolol (preferred), carvedilol	Chronic treatment for beta-adrenergic blocking. Beta-1 selective preferred because it does not interfere with beta-2-mediated uterine relaxation and peripheral vasodilation	Atenolol [14]	Intrauterine fetal growth retardation
Diuretics	Loop diuretics (preferred), thiazides	Volume overload with peripheral edema, pulmonary edema		
Vasodilators	Isosorbide dinitrate	HTN with HF	ACE inhibitors, ARBs, direct renin inhibitors	Oligohydramnios
Miscellaneous	Digoxin	Persistent symptoms despite treatment with standard therapy, control of HR in patient with concomitant AFib	Ivabradine	Lacking evidence for safety
			Aldosterone antagonist	Antiandrogen effects cause feminization of male fetus

Ischemic Heart Disease

Etiology and Risk Factors (*Tables 25.8 and 25.9*)

- Given the gender and age of the pregnant population, acute myocardial infarction and ischemic disease are rare, but the incidence is increasing.
- Most cases occur late in pregnancy, from the third trimester to 6 weeks postpartum, most likely related to the hemodynamic changes of pregnancy increasing myocardial oxygen demand [36, 37].
- Atherosclerotic heart disease, with or without thromboembolic disease, accounts for about half of the acute coronary syndrome cases; however the pregnant population has a higher prevalence of coronary dissection compared to their nonpregnant counterparts (about 30%) [37].
- Mortality is higher in patients who suffer acute myocardial infarction (AMI) during pregnancy; complication rates are higher with reports of heart failure postpartum. Premature delivery of the fetus was also seen, without known explanation [36].

Table 25.7 Treatment of acute decompensated heart failure in pregnancy

Treatment of acute decompensated heart failure in pregnancy
Oxygen therapy
Diuretics
Blood pressure management
Beta-blockers
IV ionotropic therapy in selected cases
Mechanical support[a]

[a]There are only limited case reports regarding mechanical support/LVADs in pregnancy and delivery, though there seem to be improved outcomes with their use

Table 25.8 Common causes of ischemic heart disease in pregnancy

Coronary dissection
Thromboembolic disease
Atherosclerosis/stenosis
Other (unknown cause, spasm)

Table 25.9 Risk factors of ischemic heart disease in pregnancy

Advanced maternal age	Thrombophilia associated with pregnancy
Hypertension/preeclampsia/eclampsia	Anemia
Diabetes mellitus	Postpartum infections
Obesity	Migraine headaches (vasospasm)
Smoking and drug use (i.e., cocaine)	Multiparity
Dyslipidemia	Family history

Diagnostic Testing

- Signs and symptoms of ischemic disease are similar to their nonpregnant counterparts, and chest pain is a common reported symptom of ACS.
- Evaluate with electrocardiogram. Can consider imaging modalities depending on acuity of the patient.

Treatment

Medical Management (Table 25.10)

Surgical Management

- Invasive procedures during pregnancy can be considered, and the best time for percutaneous intervention is considered to be after 16th week of gestation (organogenesis complete).
- Exposure to radiation should be minimized for the fetus by using appropriate shield over the uterus and minimizing time of fluoroscopy/cineangiography [38].

Spontaneous Coronary Artery Dissection (SCAD) [37, 39]

Etiology and Risk Factors

- Women with SCAD may not have many or any CV risk factors.

Table 25.10 Medical management of ACS in pregnancy [1]

Medication	Pregnancy class	Adverse effects
Nitroglycerine	B	Maternal hypotension and uterine hypoperfusion
Low-molecular-weight heparin	B	Hemorrhage; should be stopped prior to delivery
Unfractionated heparin	C	Hemorrhage; should be stopped prior to delivery
Beta-blockers (excluding atenolol)	C	Intrauterine growth restriction with atenolol; interfere with beta-2-mediated uterine relaxation and peripheral vasodilation
Aspirin (low dose)	C	Teratogenicity reported in high doses, increases fetal hemorrhage, intrauterine growth restriction
Clopidogrel	B	Limited data available; should be stopped 1 week prior to delivery
ACE inhibitors, ARBs	X	Teratogenic (renal dysgenesis), oligohydramnios
Statin	X	Likely teratogenic, placental growth disruption

[a]Glycoprotein IIb/IIIa inhibitors have not been studied in pregnancies

- Spontaneous coronary artery dissection (SCAD) is the presence of coronary artery dissection without evidence of atherosclerotic disease.
- This entity is more common in the pregnant population and is implicated in about a third of the acute coronary syndrome (ACS) cases.
- It is a rare but presumed underdiagnosed disease.
- Hormonal changes have been implicated in the weakening of the endothelial wall of the coronary arteries, increasing the incidence of coronary artery dissection.
- There is an association between patients with SCAD and fibromuscular dysplasia.

Diagnostic Testing

- Signs and symptoms of ischemic disease are similar to their nonpregnant counterparts, and chest pain is a common reported symptom of ACS.
- Evaluate with electrocardiogram (ECG). Can consider imaging modalities depending on acuity of the patient.

Treatment

Medical Management

- Conservative management without PCI is recommended for management with dual-antiplatelet therapy (aspirin and clopidogrel) and a beta-blocker, though no randomized studies on therapy exist.
- Medical management often resulted in spontaneous healing confirmed by angiography.

Surgical Management

Ongoing ischemia, hemodynamic compromise, or left main coronary artery dissection would require consideration for percutaneous intervention or coronary artery bypass graft.

Valvular Heart Disease [1, 40–44]

- Patients with severe valve pathology should be routinely followed by a cardiologist throughout their pregnancy.
- In general, valvular regurgitation is tolerated better in pregnant patients compared to patients with stenosis.

- The risks and benefits of proceeding with pregnancy must be fully discussed with the patient.

General points to keep in mind:

- Patients with valve regurgitation tolerate pregnancy relatively well due to the decreased left ventricular afterload from decreased systemic vascular resistance [40].
- Patients with severe valve stenosis (especially aortic and mitral valve stenosis) have a poor tolerance of the hemodynamic changes of pregnancy.
- Increased cardiac output from increased volume and increased maternal heart rate (especially in the presence of A. fibrillation) can decrease diastolic filling time and worsen symptoms of congestive heart failure.
- In patients with mitral valve stenosis (MS) with symptoms, maximal medical management is recommended as first-line therapy. In symptomatic patients or with pulmonary hypertension, restriction of activity and selective beta-blockers can be used. Diuretics can be used when congestive symptoms persist despite beta-blockers.
  - If, despite max medical therapy, patients with MS continue to have moderate to severe symptoms and reduced exercise tolerance, then percutaneous mitral valve balloon valvuloplasty dilation (PBMV) may be indicated.
  - Moderate to severe MS patients with symptoms should be managed with PBMV prior to considering pregnancy. However, even asymptomatic patients with severe MS should be counseled against pregnancy, and intervention should be performed prepregnancy.
- Poor maternal functional capacity is associated with increased fetal mortality (30% when NYHA class IV disease in the mother).
- Valve surgery during pregnancy is high risk (30–40% fetal mortality rate and up to 9% maternal mortality rate reported). Reserved for severely symptomatic patients unresponsive to bed rest and medical therapy.

Diagnostic Testing

- Pregnant patients with valvular heart disease or suspected valve disease should undergo evaluation with a transthoracic echocardiogram (Table 25.11).

Table 25.11 Valvular lesions associated high maternal and/or fetal risk during pregnancy [41]

Severe aortic stenosis (with or without symptoms)
Aortic regurgitation with NYHA functional class II–IV symptoms
Mitral stenosis with NYHA functional class II–IV symptoms
Mitral regurgitation with NYHA functional class III–IV symptoms
Severe pulmonary hypertension (resulting from valve disease)
Severe LV dysfunction (LVEF <40%) (resulting from valve disease)
Mechanical prosthetic valve requiring anticoagulation
Marfan syndrome with or without aortic regurgitation

Treatment

Native Valve Stenosis/Regurgitation

Medical Management

- Decrease heart rate with use of beta-blockers to allow for longer diastolic filling time.
- Judicious use of diuretics primarily in regurgitant lesions for management of heart failure symptoms.

Surgical Management

- Patients with severe mitral or aortic valve stenosis or regurgitation who are symptomatic should be counseled, and intervention is recommended prior to pregnancy.
- When at all possible repair/replace prior to pregnancy with balloon valvuloplasty or pulmonary autograft (Ross operation) for mitral and aortic stenosis, respectively.
- Data on TAVR in pregnant patients with severe aortic stenosis (AS) is very limited.
- Goal is to eliminate obstruction and decrease risks during gestation, labor, and delivery.
- If stenosis is discovered during pregnancy, or if there is hemodynamic compromise due to volume changes of pregnancy, then intervention during pregnancy can be considered.
- In the absence of severe heart failure symptoms or hemodynamic compromise, valve surgery is not recommended.
- Prophylactic antibiotic therapy during delivery is not recommended in most women with valvular heart disease (class III).

Prosthetic Valves

- In pregnant patients with mechanical valves, the maternal and fetal risks associated with anticoagulation should be discussed and counseling provided [39].
- Pregnant patients are characteristically pro-coagulable, and data on anticoagulation from the nonpregnant population cannot be extrapolated.
- Bioprosthetic valves are less pro-coagulable compared to mechanical valves and do not require anticoagulation unless there are other indications.

Anticoagulation in Pregnant Patients with Mechanical Prosthetic Valves (Fig. 25.1)

- The optimal anticoagulant used during the first trimester in pregnant patients with mechanical prosthetic valve remains controversial [40, 44, 45].
- While warfarin is safer for the mother, low-molecular-weight heparin (LMWH) is safer for the fetus.

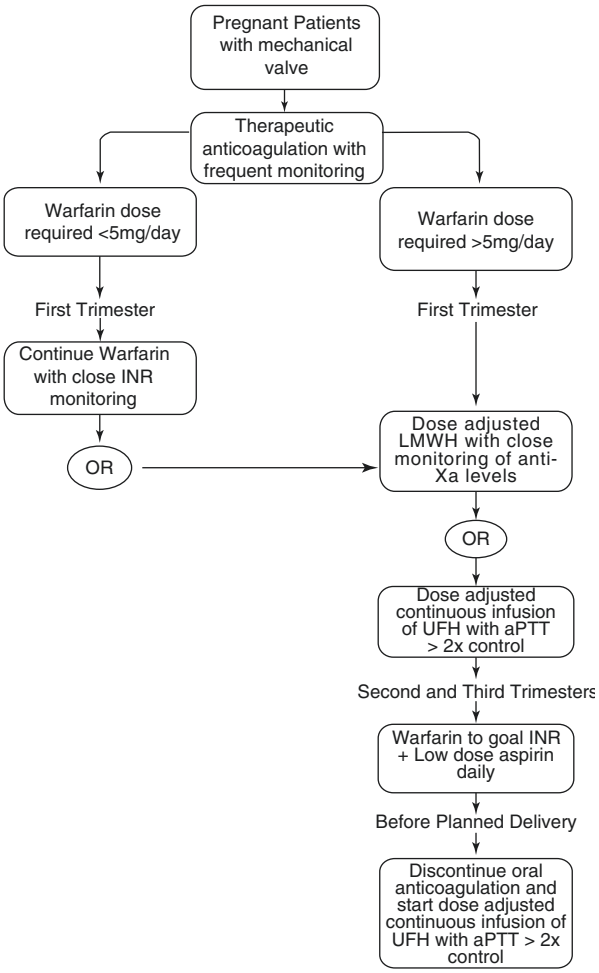

Fig. 25.1 Algorithm for anticoagulation management in pregnant patients with mechanical valves. Adapted from 2014 AHA/ACC Guidelines for the Management of Patients with Valvular Heart Disease [41]

- Though heparin does not cross the placenta, treatment with heparin during the first trimester does not eliminate fetal risk.
- Warfarin can be used throughout pregnancy if therapeutic INR is achieved with a dose of 5 mg/day or less.
- The importance of therapeutic anticoagulation throughout pregnancy and the maternal risks and fetal risks associated with each anticoagulant regimen needs to be discussed with patients.
- Anticoagulation in the first trimester
  - Use of oral vitamin K antagonist (warfarin) for anticoagulation for mechanical valve prosthesis is emphasized by guidelines as long as the total dose

remains <5 mg/day with close monitoring of international normalized ratio (INR) throughout pregnancy.
  - Women with an increased risk of prosthetic valve thrombosis (multiple mechanical valves, small or aged mechanical valve, atrial fibrillation/flutter, or previous complications from thromboembolism) should continue with warfarin along with aspirin, which reduces maternal risk. Patients should be counseled on the increased risk to the fetus.
  - In women without one or more of the risk factors for prosthetic valve thrombosis, warfarin dose ≤5 mg/day is recommended with close INR monitoring. Women, who wish to decrease the fetal risk of low-dose warfarin during the first trimester, may elect to switch to dose-adjusted low-molecular-weight heparin SC twice daily from 5 to 12 weeks.
  - Women who require >5 mg/day of warfarin should be switched to low-molecular-weight heparin (LMWH) subcutaneously (SC) twice daily throughout the first trimester (target anti-Xa activity 1.0–1.2 units/mL for mitral valve prosthesis and 0.8–1.0 units/mL for aortic valve prosthesis at 4–6 h post-dose). Checking trough activity (proposed minimum trough level of 0.6 units/mL) is also advised.
  - If LMWH is unavailable, dose-adjusted continuous inpatient intravenous (IV) infusion of unfractionated heparin (UFH; with targeted activated partial thromboplastin time [aPTT] 2–2.5 times control) is an option. However, the efficacy and safety of this treatment are uncertain.
- Second/third trimester
  - Warfarin (adjusted to INR goal) along with aspirin (75–100 mg daily) until 36 weeks provides the best thromboembolic protection for the mother.
  - If the patient elects to decrease fetal risk associated with warfarin, then therapeutic low-molecular-weight heparin SC twice daily can be used adjusted to achieve target anti-Xa activity (as above).
  - If LMWH is unavailable, warfarin is the preferred anticoagulant. If the mother declines to take warfarin, then dose-adjusted SC UFH (with regular monitoring to ensure the 6-h post-dose aPTT is at least twice baseline) can be offered as an alternative option (last resort). However, use of SC UFH in this setting is controversial and not endorsed by some experts.
- Delivery
  - Warfarin should be switched to dose-adjusted low-molecular-weight heparin (LMWH) subcutaneously (SC) administered twice per day to achieve target anti-Xa activity (as above).
  - If LMWH is unavailable, then unfractionated heparin (UFH) IV can be used (maintaining the activated partial thromboplastin time [aPTT] at 2–2.5 times control).
  - Low-dose aspirin is recommended to be continued up until planned delivery (this should be discussed with the multidisciplinary team).

- Switch to unfractionated heparin (target aPTT at least twice control) should be planned 24 h prior to planned vaginal or surgical delivery in order to minimize the risk of bleeding at delivery.
- It should be discontinued 4–6 h prior to initiation of neuraxial anesthesia or analgesia.

Arrhythmias in Pregnancy [1, 46–49]

Etiology and Risk Factors

- Increased incidence of arrhythmias in pregnancy is unclear, though it is attributed to hemodynamic changes including intrinsic increase in the heart rate and the stretching of the atria from increase in fluid volume.
- There may also be contribution from increased adrenergic tone in pregnancy.

Diagnostic Testing

- For evaluation, consider getting a baseline ECG, Holter, or event monitor.

Treatment

Medical Management

- Supraventricular tachycardia [47]
  - Class I recommendations
    Initial management should include vagal maneuvers followed by adenosine.
    In any patient with hemodynamic instability, electric cardioversion is safe at any stage of pregnancy and should be used if pharmacotherapy has been unsuccessful or contraindicated.
  - Class II recommendations
    Acute management can be accomplished with IV metoprolol, propranolol (class IIa), or verapamil (class IIb).
    Chronic management should first include beta-blocking agents and digoxin and then, in highly symptomatic agents, oral sotalol or flecainide (class IIa) or propafenone or procainamide, followed by amiodarone, and oral verapamil could be considered (class IIb).

- Ventricular tachycardia
  - Most frequent cause of VT in healthy pregnant women is idiopathic RVOT tachycardia.
  - Class I recommendations:
    In any patient with hemodynamic instability, electric cardioversion is safe at any stage of pregnancy.
    For congenital long QT syndrome, beta-blockers are first-line agents for medical management.
    Idiopathic sustained ventricular tachycardia can be controlled using oral metoprolol, propranolol, or verapamil.
  - Class II recommendations:
    For hemodynamically stable, monomorphic sustained VT, IV sotalol or procainamide can be used for acute conversion (class IIa).
    For hemodynamically unstable monomorphic sustained VT which is refractory to cardioversion and other pharmacologic therapies, amiodarone can be used (class IIa).
    Chronic management can include oral sotalol, flecainide, and propafenone if other agents are unsuccessful in controlling the VT.
    Catheter ablation can be considered if other management options fail.
- Sinus bradycardia is likely transient; however if symptomatic, a temporary pacemaker can be placed [1].
- Atrioventricular blocks [1]
  - First-degree AV block generally does not require treatment.
  - Second-degree AV block does not require treatment if type I (Wenckebach) and asymptomatic.
  - Complete heart block may require the use of temporary pacing for support.

Surgical Management

- Catheter ablation should only be reserved in patients with intolerable arrhythmias refractory to medical therapy. Fetal radiation exposure is a major concern; however if necessary, procedures should not be performed until after 20 weeks of gestation [49].

General Recommendations

Class I:

- Women with known or suspected congenital or acquired cardiovascular and aortic disease should be evaluated prepregnancy and have counseling regarding maternal and fetal risks of pregnancy.

- High-risk patients should be treated in specialized centers by a multidisciplinary team.
- Pregnant patients with unexplained or new cardiovascular signs or symptoms should have echocardiogram done for evaluation.

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Chapter 26
Chemotherapy, Cardiovascular Disease, and Cardiac Tumors

Jims Jean-Jacques and Eugene Storozynsky

Cardiotoxicity of Common Chemotherapy (Anthracyclines, Trastuzumab, and Anti-VEGF Treatments)

Background: New treatment strategies in oncology have greatly improved prognosis and survival of cancer patients [1–3]. As the utility of these chemotherapeutic drugs increases, the possible cardiotoxic effects of these agents become more apparent [4]. Chemotherapeutic agents can cause acute and chronic cardiovascular toxicity including hypertension, thromboembolism, pericarditis, coronary artery disease resulting in early and late myocardial ischemia, cardiomyocyte damage (immune and non-immune mediated) leading to cardiomyopathy, myocarditis, early and late conduction abnormalities, and valvular abnormalities [5–10] (Figure 26.1 showing an overview of the cardiovascular side effects of chemotherapy and radiation).

Anthracyclines: Highly effective antibiotic-based chemotherapeutic agents commonly used in the treatment of solid-tumor and hematologic malignancies including leukemias, lymphomas, and sarcomas [11]

- Initially discovered in the late 1950s from *Streptomyces* bacterium species (*Streptomyces peucetius* var. *caesius*)
- Anti-tumor effects [12]
  - Occur by preventing DNA and RNA synthesis by intercalating between nucleic acid base pairs, thereby inhibiting replication of rapidly proliferating cancer cells

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H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7_26

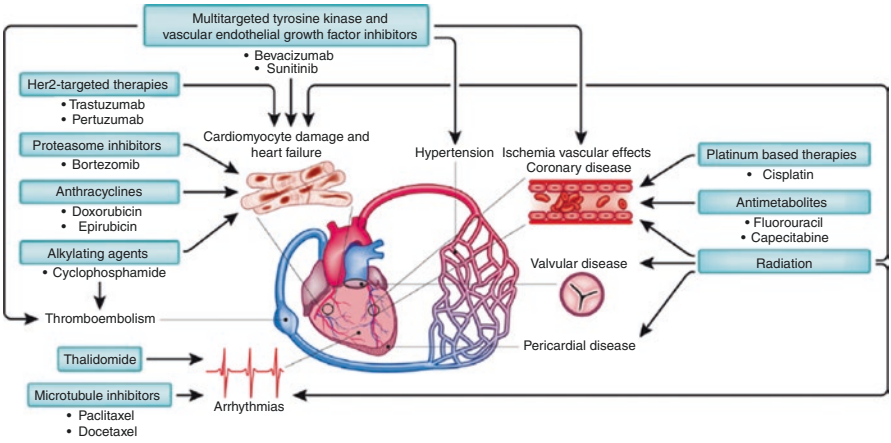

Fig. 26.1 An overview of the cardiovascular side effects of chemotherapy and radiation. Reproduced with permission from Carrie GL [13] Circ Res. 2016 Mar 18;118(6):1008–20, Copyright © Wolters Kluwer Health, Inc.

  - May inhibit the action of topoisomerase II enzyme, which in turn prevents relaxation of supercoiled double-helix DNA, thus blocking DNA transcription and replication
  - Seem to generate free oxygen radicals that may damage DNA, proteins, and cell membranes

- Possible mechanisms of anthracycline-induced cardiotoxicity [13]
  - May impair removal of cytosolic calcium
  - Reduce loading of the sarcoplasmic reticulum
  - Induce defective calcium release leading to impaired myocyte contraction and relaxation
  - Alteration of SERCA2 pump—leading to calcium mishandling
  - Promotion of free radicals leading to apoptosis (Fig. 26.2a–c)

Cardiotoxicity remains the major limitation for use of anthracyclines.

1. **Epidemiology of anthracycline-induced cardiotoxicity** [14, 15]**:**
   (a) 5–23% of patients expose to anthracycline will develop short- and/or long-term left ventricular dysfunction and heart failure.
   (b) The risk for cardiotoxicity and subsequently heart failure depends on the cumulative exposure dose.
      - 5% risk of heart failure at 400 mg/m [2]
      - 25% risk of heart failure at 700 mg/m [2]
   (c) Other risk factors for cardiac toxicity:
      - Both extreme of age (<18 or >60)
      - HTN
      - LVH

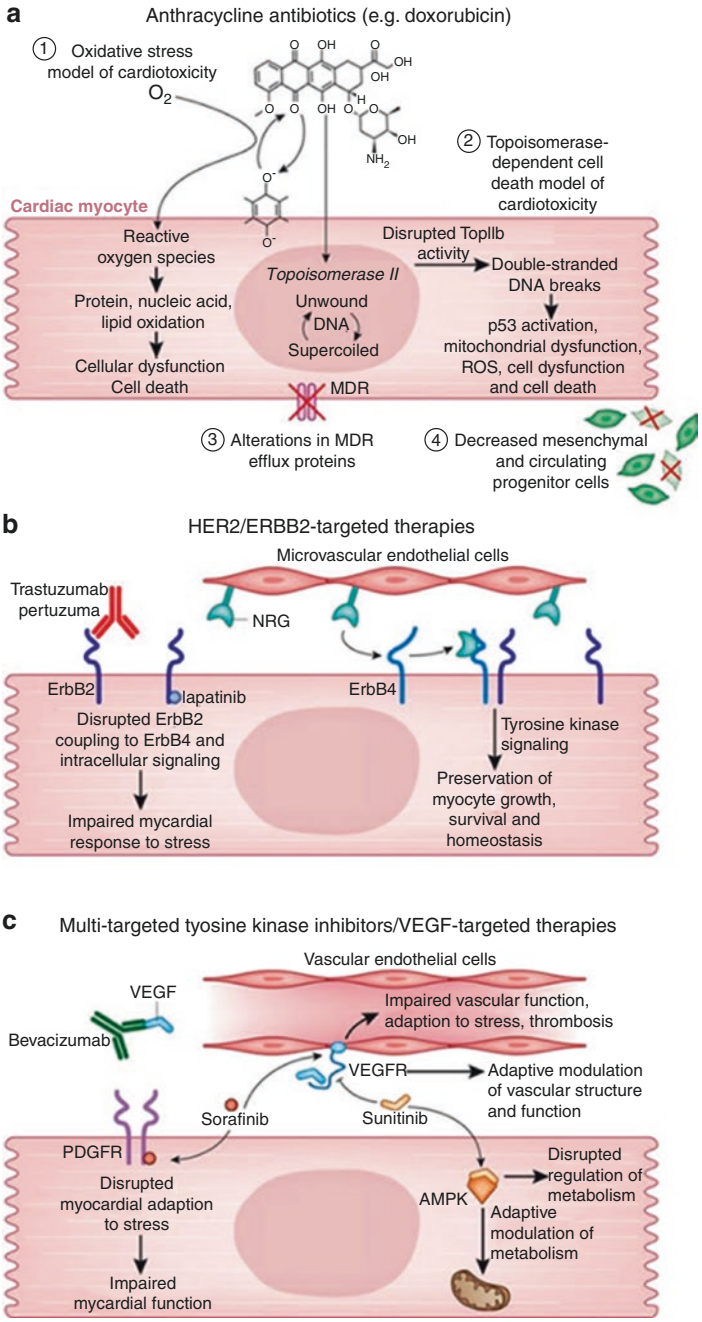

Fig. 26.2 Molecular pathways involved in cardiotoxicity related to anthracyclines and HER2-targeted and tyrosine kinase inhibitors/vascular endothelial growth factor (VEGF) inhibitors. Reproduced with permission from Carrie GL [13] Circ Res. 2016 Mar 18;118(6):1008–20, Copyright © Wolters Kluwer Health, Inc.

- Type II DM
- Prior or concomitant chemo/XRT
- Hematopoietic cell transplantation
- Tobacco habituation

(d) Timing:
- Acute cardiotoxicity: occurs at the time of infusion
- Early cardiotoxicity: occurs within 1 year of exposure
- Late cardiotoxicity: occurs within 1–20 years of exposure

2. Examples of anthracyclines and tumors they treat [11]:
   (a) *Doxorubicin and epirubicin*: breast cancer, pediatric solid tumors, sarcomas, and lymphomas
   (b) *Daunorubicin*: acute lymphoblastic or myeloblastic leukemias
   (c) *Idarubicin*: multiple myeloma, non-Hodgkin's lymphomas, and breast cancer
   (d) *Nemorubicin*: hepatocellular carcinoma
   (e) *Pixantrone*: non-Hodgkin's lymphomas
   (f) *Sabarubicin*: non-small cell lung cancer, metastatic prostate cancer, and ovarian cancer
   (g) *Valrubicin*: bladder cancer

Molecularly Targeted Chemotherapeutic Agents

Her-2 Receptor [16]

- A receptor kinase involved in normal cell growth.
  - Also called ERBB2, human EGF receptor 2, and human epidermal growth factor receptor 2.
  - Overexpressed in subset of breast, ovarian, and possibly colon cancers.
  - May be a target for cancer treatment.
  - Inhibition of ERBB2 in cardiomyocytes interferes with growth, repair, and survival of cardiomyocytes.
    May result in ATP depletion and contractile dysfunction
- A signaling pathway independent of ERBB2 signaling may also exist in which there is immune-mediated destruction of cardiomyocytes (see Figure 26.3 showing ERBB2 signaling and inhibition in breast cancer and cardiomyocytes).

Epidemiology

1. Close to 30% of women treated initially with anthracyclines and subsequently with HER-2 neu-targeted agents have developed cardiotoxicity.
2. Patients identified as at increased risk for developing cardiotoxicity include:
   (a) Standard risk factors for developing structural heart disease

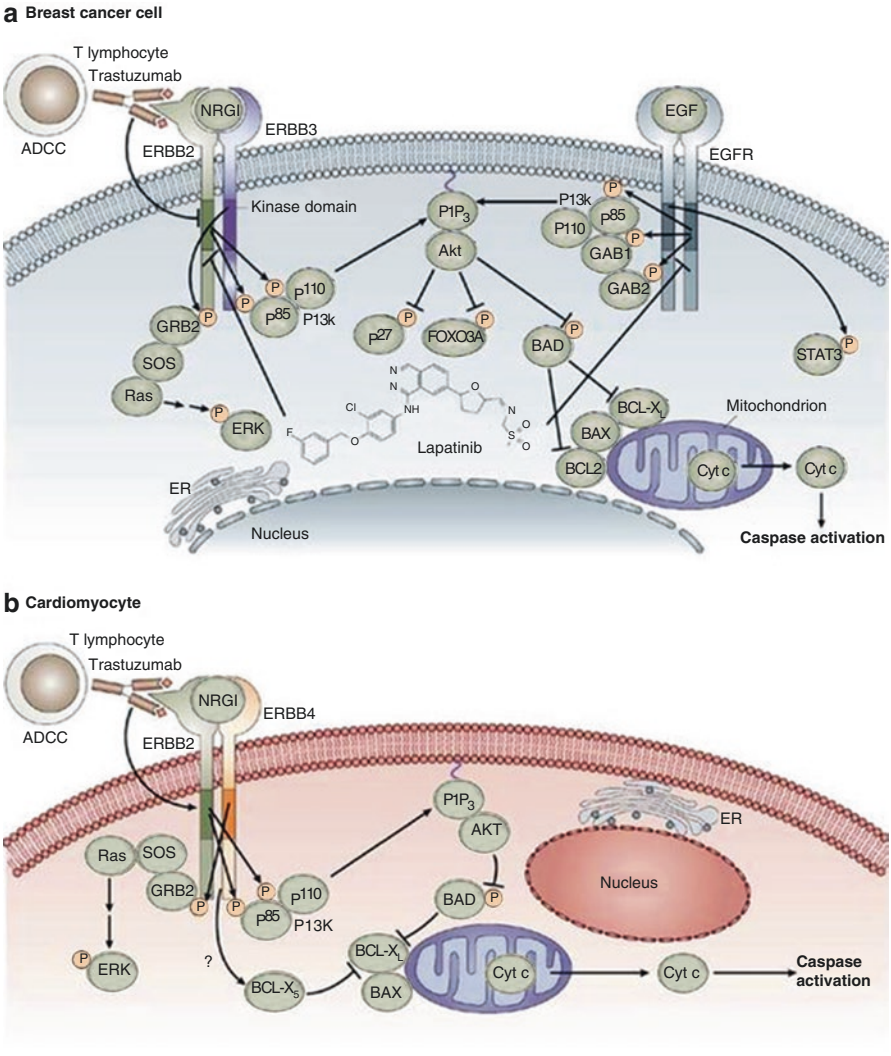

Fig. 26.3 ERBB2 signaling and inhibition in breast cancer and cardiomyocytes. Reproduced with permission from Force, T. et al. Nature Reviews Cancer 7, 332–44 (May 2007), Copyright ©

(b) Previous doxorubicin exposure
(c) Previous chest wall irradiation
(d) Obesity

3. Reversibility—largely possible but not necessarily 100%

Inhibition of Vascular Endothelial Growth Factor (VEGF) Signaling Pathways [17]

1. VEGF is expressed in endothelin cells and within the kidney and plays a role in producing nitric oxide and prostacyclin and decreasing production of endothelin-1, a potent vasoconstrictor.
2. VEGF is secreted by tumors and plays a key role in angiogenesis by binding to VEGF receptors and activating VEGF signaling pathways.
   (a) Chemotherapeutic agents that inhibit VEGF (monoclonal antibodies or small molecules) appear to downregulate nitric oxide and prostacyclin production and increase endothelin production (see Fig. 26.4, mechanisms of VEGF-/VEGFR-mediated protection of cardiomyocytes).
3. Cardiovascular side effects of VEGF signaling inhibitors:
   (b) Hypertension
   - Appears to occur within 1 week of initiation and seems to occur in a dose-dependent and transient manner.
   - The overall incidence of HTN ranges from 20 to 25% with bevacizumab and sunitinib to >50% with newer agents.

   (c) Vascular thrombosis
   (d) Cardiomyopathy
   - **Detection** [18–21]: At present, there are no consensus guidelines for early detection for adults undergoing chemotherapy. However, there are surveillance strategies being developed to identify patients at risk for developing

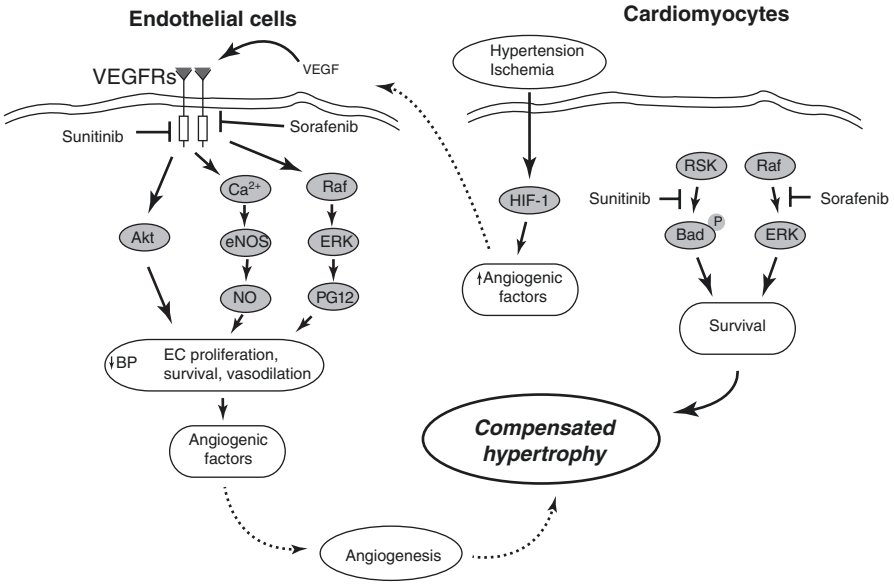

Fig. 26.4 Mechanisms of VEGF-/VEGFR-mediated protection of cardiomyocytes from pressure stress and ischemia and potential interactions of sunitinib and sorafenib. Reprinted with permission Circulation. 2008;118:84–95, Copyright ©

subclinical cardiotoxicity. These include ECG, multimodality imaging strategies, and novel biomarkers that may be useful in the early identification of patients developing subclinical chemotherapy-induced cardiotoxicity.

- **Electrocardiography:**
  - Early predictor of drug-induced cardiomyopathy
  - Limb lead QRS voltage decrease by ≥30%
- **Imaging:**

  Echocardiogram:
  - The preferred imaging modality to monitor LVEF pre- and postexposure to cardiotoxic chemotherapy agents.
    - Widespread availability and absence of radiation exposure
  - 3D echo produces additional benefit over 2D.
    - Improved accuracy and reproducibility
  - Tissue Doppler and Strain:
    - Global longitudinal strain may provide early detection of myocardial dysfunction by measuring the degree of myocardial deformity.
    - Measurement of left ventricular systolic function not left ventricular ejection fraction

  Nuclear imaging:
  - An alternative to echocardiography especially when results are suboptimal.
  - MUGA scans provide a more precise measure of LVEF compared with an echocardiogram.

  Cardiac MRI:
  - Indicated when echocardiography or nuclear results are inconclusive or inconsistent

- **Biomarkers:** may provide earlier detection of cardiac damage before LV dysfunctions take place. Serum troponin release is a marker of cardiac microscopic and/or macroscopic injury with some correlation with the dose of chemotherapy. It has been monitored in high-risk patients undergoing doxorubicin treatment and shown to potentially identify patient at risk for developing subsequent LV dysfunction. BNP is an established biomarker of LV dysfunction/heart failure and may be followed serially prior to development of LV dysfunction on less-sensitive modalities such as cardiac imaging. Once left ventricular dysfunction occurs, the compensatory mechanism of the myocardium has already been compromised. Biomarkers may provide earlier detection of cardiac damage before LV dysfunctions take place.

  Serum troponins:
  - Marker of cardiac injury that may have some correlation with the dose of doxorubicin used
  - If troponins remain positive, may predict long-term development of left ventricular dysfunction

  BNP:
  - Although an established biomarker of heart failure, its use in identifying asymptomatic left ventricular dysfunction is controversial.

- **Treatment:** Currently, there are no guidelines from the ACC, AHA, and HFSA regarding the treatment and management of chemo-induced cardiotoxicity. The general consensus from experts is the initiation of angiotensin-converting enzyme inhibitor, beta blocker, and statin for patients who develop left ventricular dysfunction or to prophylactically treat patients that are deemed to be at high risk of developing cardiotoxicity. Classes of medications that may increase SERCA2 expression/function include angiotensin-converting enzymes and beta blockers.
  - **ACEi:**
    - Showed in prospective studies to improve LVEF in women treated with epirubicin for metastatic breast cancer
  - **Beta blocker:**
    - Small randomized trials have suggested the use of carvedilol or nebivolol that may have a protective effect.
      - Carvedilol
        - May be important in upregulating mitochondrial SERCA2 expression and function thereby preventing intracellular calcium mishandling
        - May prevent mitochondrial dysfunction and alleviate oxidative stress
  - **Statins:**
    - Appear to exert their effects by decreasing oxidative stress and inflammation
    - May have cardioprotective effects against chemotherapy induced cardiotoxicity
  - **Dexrazoxane (Zinecard)**
    - A derivative of EDTA found to be a potent intracellular chelating agent
    - The only drug approved by the FDA to prevent cardiotoxic effect of anthracycline
    - May help prevent cardiotoxicity in selected cardiovascular high-risk breast cancer patients treated with doxorubicin

Take-Home Message: Cardioprotective strategies include general cardiovascular risk factor modifications (treatment of hypertension, diabetes, hyperlipidemia, coronary artery disease).

ASCO Guidelines Cardiotoxicity

Adapted from the American Society of Clinical Oncology, All rights reserved [21].

American Society of Clinical Oncology Clinical Practice Guideline recommendations for prevention and monitoring of cardiac dysfunction before, during, and after treatment with potentially cardiotoxic agents:

1. Minimize risk before therapy (ASCO *Clinical Practice Guideline* **Recommendation 2**)
   - Avoid or minimize potentially cardiotoxic therapies if alternative therapy exists and that would not compromise outcomes.

- Perform a comprehensive assessment with a history and physical examination, screening for cardiovascular disease, and an echocardiogram before initiating therapy.

2. Minimize risk during therapy (ASCO *Clinical Practice Guideline* **Recommendation 3**)
   - Screen for and actively manage cardiovascular risk factors.
   - Incorporate strategies, including the use of dexrazoxane, continuous infusion, or liposomal formulation of doxorubicin, for prevention of cardiotoxicity in patients planning to receive high dose of anthracyclines.
   - Select lower radiation doses when clinically appropriate and exclude as much of the heart as possible for patients who require mediastinal radiation therapy.
3. Surveillance and monitoring during treatment (ASCO *Clinical Practice Guideline* **Recommendation 4**)
   - Complete a careful history and physical examination in patients who are receiving potentially cardiotoxic treatments.
   - If patients develop clinical signs or symptoms that are concerning for cardiac dysfunction during treatment, perform a diagnostic echocardiogram.
   - Cardiac magnetic resonance imaging (MRI) or multigated acquisition (MUGA) scan if echocardiogram is not available or technically feasible (preference given to cardiac MRI).
   - Serum cardiac biomarkers (troponins, natriuretic peptides) or echocardiography-derived strain imaging in conjunction with routine diagnostic imaging.
   - Referral to a cardiologist.
4. Surveillance and monitoring after treatment (ASCO *Clinical Practice Guideline* **Recommendation 5**)
   - Complete history and physical examination on cancer patient who were previously treated with cardiotoxic therapies.
   - If patients develop clinical signs or symptoms that are concerning for cardiac dysfunction after treatment, perform a diagnostic echocardiogram.
   - Cardiac magnetic resonance imaging (MRI) or multigated acquisition (MUGA) scan if echocardiogram is not available or technically feasible.
   - Serum cardiac biomarkers (troponins, natriuretic peptides) or echocardiography-derived strain imaging in conjunction with routine diagnostic imaging.
   - Referral to a cardiologist.
   - Cardiac MRI or MUGA may be offered for surveillance in asymptomatic individuals if an echocardiogram is available or technically feasible (preference given to cardiac MRI).

Cardiac Tumors

- **Background and Epidemiology** [22–24]
  - Occur in 1 per 300–100,000 autopsies.
  - In adults, ~75% of all primary cardiac tumors are benign.
  - In children, ~90% of the primary cardiac tumors are benign.

  - Most common in adults:
    - Myxoma (40% of all primary cardiac tumors)
    - Papillary fibroelastoma (8%)
    - Rhabdomyoma
    - Lipomatous hypertrophy
  - Most common in pediatric:
    - Rhabdomyoma
    - Fibroma
    - Teratoma
  - Secondary cardiac tumors:
    - 20–40 times more common than primary tumors.
    - Occurs mainly with extensive metastatic cancer.
    - See Fig. 26.5 for common distribution of cardiac masses.
    - See Fig. 26.6 for a diagnostic algorithm for evaluation of a cardiac mass.
- **Clinical Presentation** [25–27]
  - Determined by location rather than histopathology
  - Can present with both cardiac and non-cardiac manifestations
  - Obstruction (valvular), embolic (TIA/CVA), and constitutional (weight loss, fever, fatigue, dyspnea, and malaise)

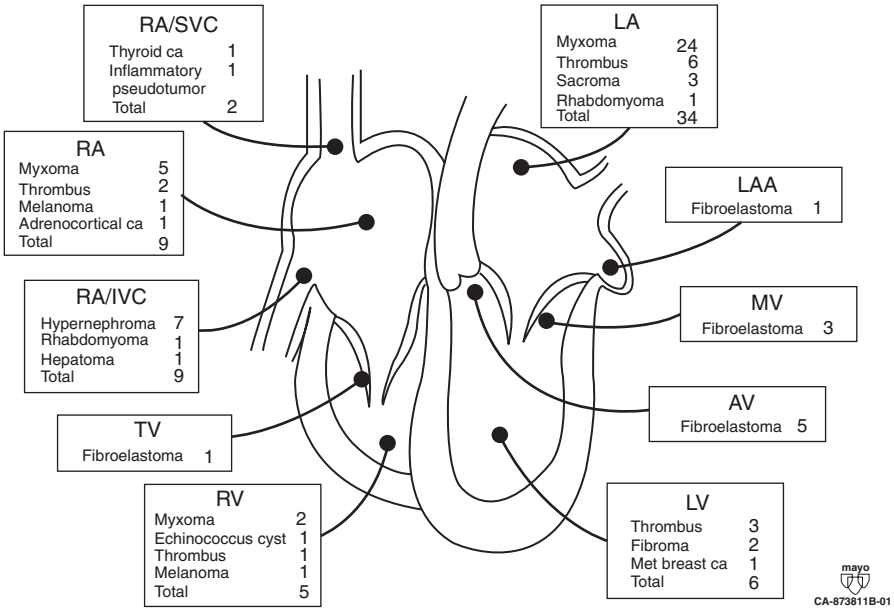

Fig. 26.5 Distribution of cardiac masses. Reprinted from Dujardin KS, Click RL & Oh TK, The role of intraoperative transesophageal echocardiography in patients undergoing cardiac mass removal, J Am Soc Echocardiogr 13: 12, 1080–1083, Copyright © (2000), with permission from Elsevier

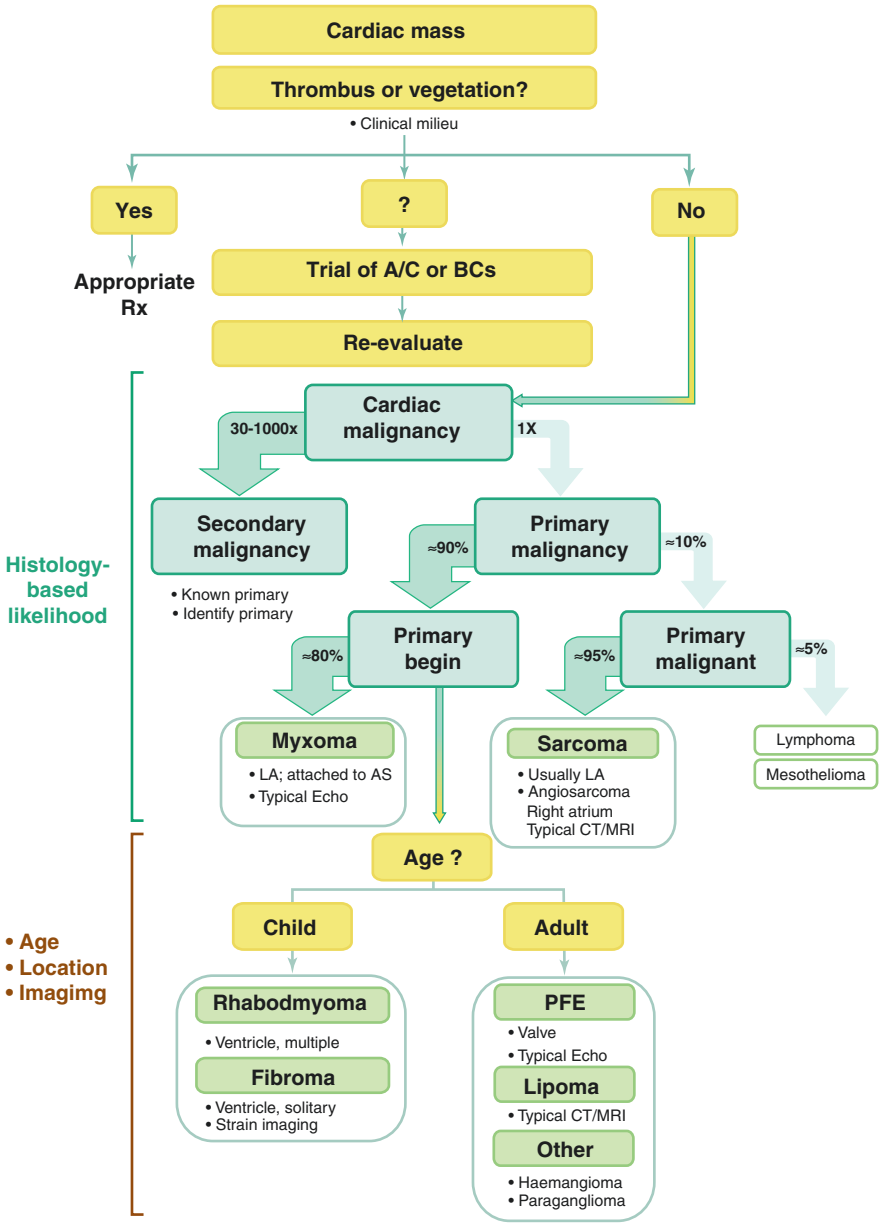

Fig. 26.6 Diagnostic algorithm for evaluation of a cardiac mass. Reproduced from Cardiac tumours: diagnosis and management, Charles JB, Heart 2011; 97:151–160, Copyright © 2011 with permission from BMJ Publishing Group Ltd. [22]

- **Detection**
  - **Echocardiography** [28, 29]
    - Initial imaging method of choice
    - Noninvasive, inexpensive, simple, and widely used
  - **CT** [30–34]
    - When MRI is not available
  - **MRI** [32]
    - ECG-gated MR is the imaging modality of choice.
    - Can offer clues as to the type of tumors.
    - Provides high temporal resolution and excellent soft-tissue contrast.
- **Primary Benign Cardiac Tumors** [22]
  - **Myxoma**
    - Most common primary tumor
    - Sporadic: 90% occur in atria, 80% on left side
    - Pedunculated tumors
    - Usual symptoms: due to obstruction, emboli, and constitutional
    - Familial with Carney syndrome: 10% of the cases, autosomal dominant with extra-cardiac manifestation (blue nevus, schwannomas, skin pigmentation, and endocrine dysfunction)
    - Treatment: excision
  - **Lipomatous hypertrophy**
    - Rare cardiac tumors.
    - Usually confined to atrium with sparing of the fossa ovalis.
    - Septal thickness is 2–7 cm.
    - Usual symptoms: congestive heart failure, atrial fibrillation, supraventricular tachycardia, syncope, dysthymias, and sudden cardiac death.
    - Treatment: none.
  - **Lambl excrescence**
    - Filamentous strands seen originating from the aortic valve.
    - Also called valvular strands.
    - Usually in the elderly population.
    - Associated with stroke.
    - Looks very fragile and delicate.
    - Generally, there is absence of any clinical evidence of valvular dysfunction.
    - Treatment:
      - If no history of TIA/CVA, conservative management
      - If TIA/CVA (no anticoagulation), warfarin, or ASA and clopidogrel
      - If TIA/CVA (on anticoagulation), surgical debridement
  - **Fibroma**
    - Rare in adults but very common in the pediatric population
    - Found in 10% of Gorlin syndrome patients (nevoid-basal cell carcinoma syndrome)
    - Treatment: excision or possibly transplant

  - **Rhabdomyoma**
    - 50–90% of primary tumors in the pediatric population
    - May present with valvular obstruction or sudden cardiac death
    - Treatment: Usually regresses spontaneously, surgical intervention only if outflow obstruction or dysrhythmia
- **Primary Malignant Cardiac Tumors** [22]
  - Constitute 15% of primary cardiac tumors; most common are the sarcomas.
  - **Angiosarcoma**
    - Most common primary malignancy in adults
    - Mostly atrium (right more than left)
    - Male predominance
    - Treatment: very poor prognosis and death usually within months
  - **Rhabdomyosarcoma**
    - Most common cardiac malignancy in infants and children
    - Usually metastases to the lung, GI tract, and kidney
    - Treatment: surgical resection and chemotherapy
  - **Leiomyosarcoma**
    - Usually very poor prognosis
    - Arises from the pulmonary veins and arteries
    - Associated with EBV in cardiac transplantation
  - **Lymphoma:**
    - Associated with immunocompromised states
    - Usually diffuse large B cell lymphoma
    - Poor prognosis
  - **Posttransplant lymphoproliferative disorder**
    - Lymphoid proliferations that occur in the setting of organ transplantation as a result of immunosuppression
    - Mostly related to B cell proliferation secondary to infection with Epstein-Barr virus
    - Treatment: antiviral prophylaxis and early tapering immunosuppressive therapy
- **Secondary Cardiac Tumors** [22]
  - Metastatic involvement of the heart is relatively common.
  - Reflects the aggressiveness of the individual malignancy.
  - Virtually any primary malignancy may metastasize to the heart, however, the most often encountered primaries comprise:
  - They may arise from:
    - Lung, breast, kidney, and thyroid carcinomas and malignant melanomas.
    - Other common sources are lymphomyeloproliferative types, lymphoma, and leukemia.

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Chapter 27
Pulmonary Embolism

Hanna Z. Mieszczanska and Scott J. Cameron

Epidemiology

- Acute pulmonary embolism (PE) represents a true thrombotic emergency and is the third leading cause of death (after myocardial infarction (MI) and cerebrovascular accident (CVA)).
- The epidemiology of PE is difficult to determine because PE often is asymptomatic and therefore undiagnosed.
- The incidence of PE is estimated to be approximately 1–2 cases per 1000 each year in the United States.
- Sudden death is the first finding in about one quarter (25%) of people who have a PE [1, 2].

Definitions

- Low-risk PE: segmental, subsegmental, and no hemodynamic changes or right ventricular (RV) strain
- Intermediate-risk PE ("submassive"), evidence of RV strain (CT, Echo, MRI, etc.) with or without positive plasma cardiac biomarkers (troponin, BNP, NT-proBNP >500 pg/mL), 90-day mortality around 25%
- High-risk PE ("massive"): SBP <90 mmHg for at least 15 min and/or pressor/inotrope dependence to keep SBP >90 mmHg. 90-day mortality around 50%

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H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7_27

Diagnosis: Is This Really a PE?

Modified Well's score for diagnosing PE [3]

Clinical evaluation for predicting pretest probability of pulmonary embolism:

- Prior history of deep vein thrombosis (DVT) or pulmonary embolism (1.5 points)
- Symptoms of DVT (3 points)
- Alternative diagnosis less likely than PE (3 points)
- Immobilization (≥3 days) or recent surgery (within last 30 days) (1.5 points)
- Presence of hemoptysis (1 point)
- Tachycardia with pulse >100 bpm (1.5 points)
- Presence of malignancy (treated within last 6 months) (1 point)

Pulmonary Embolism Risk Score interpretation

Clinical probability of pulmonary embolism:

Score 0–1, low; 2–6, intermediate; 7 or more, high probability

The value of clinical judgment has been confirmed in several large series, including the Prospective Investigation Of Pulmonary Embolism Diagnosis (PIOPED) [4].

The PIOPED II study listed the following indicators for pulmonary embolism:

- Travel of 4 h or more in the past month
- Surgery within the last 3 months
- Malignancy, especially lung cancer
- Current or past history of thrombophlebitis
- Trauma to the lower extremities and pelvis during the past 3 months
- Smoking
- Central venous instrumentation within the past 3 months
- Stroke
- Prior pulmonary embolism
- Heart failure
- Chronic obstructive pulmonary disease

Signs and symptoms of PE:

- The classic presentation of pulmonary embolism is sudden-onset pleuritic chest pain, dyspnea, and hypoxia.
- Symptoms may vary from gradually progressive dyspnea to sudden hemodynamic collapse.
- However, many patients with pulmonary embolism can be asymptomatic at presentation.
- The diagnosis of pulmonary embolism should be suspected in patients with respiratory symptoms unexplained by an alternative diagnosis (e.g., dyspnea, cough, hemoptysis).

Practical considerations at the bedside:

- Respiratory distress but clear lung fields by auscultation.
- Unexplained hypotension + jugular venous distention.
- Unexplained large A-a O_2 gradient: ABG can be helpful in the diagnosis of PE.

Other physical exam findings in patients with pulmonary embolism:

- Tachypnea (respiratory rate > 16/min)
- Tachycardia (heart rate > 100/min)
- S_3 or S_4 gallop
- Clinical signs and symptoms suggesting thrombophlebitis
- Tricuspid regurgitation murmur
- Accentuated pulmonic component of S2

Risk Stratification of Patients with Acute PE to Determine the Severity [5]

- The Pulmonary Embolism Severity Index (PESI) score estimates the risk of 30-day mortality in patients with acute pulmonary embolism (PE) and is useful for risk stratifying low-risk PE but can underestimate the true risk in submassive and massive PE [6].
- The main clinical determinants of the outcome of patients with PE are listed below. The following variables are assigned one point each [7]:
  - Advanced age (>80 years)
  - Male sex
  - History of cancer
  - History of heart failure or chronic lung disease
  - Altered mental status
  - Temperature <36 °C
  - Clinical signs of right ventricular dysfunction (tachycardia ≥110 bpm, hypotension with SBP <100 mmHg, respiratory rate ≥ 30 bpm, and hypoxia with oxygen saturation <90% on room air)
- If none of the above clinical variables are present (i.e., total score of 0), patients are considered as low risk and have mortality- and pulmonary embolism-related complication rates significantly lower than those with a score ≥ 1 [8].
- Assuming that patient is *not* extremely hypotensive, there is no right heart strain (RV/LV ratio < 0.9) on CT angiography or echocardiography.
  - Hemodynamically unstable patients with shock or hypotension with clinical suspicion of PE should immediately be identified as high-risk patients.
  - Normotensive patients in Pulmonary Embolism Severity Index (PESI) Class III are in the intermediate-risk group. Of these, patients who have both evidence of right ventricular (RV) dysfunction (assessed by echocardiography or CT angiography) and elevated cardiac biomarkers (including brain natriuretic peptide (BNP), N-terminal pro-BNP (NT-proBNP), and troponin) are classified into an intermediate-high-risk category and need to be monitored for early detection of hemodynamic decompensation.
  - Right ventricular dysfunction (RVD) and elevated biomarkers including troponin (indicates right ventricular (RV) microinfarction), pro-B-type natri-

uretic peptide, and B-type natriuretic peptide (can be a marker of RV overload) have a prognostic value and have been associated with an increased mortality or PE-related complications including cardiogenic shock and recurrent PE in patients with normal blood pressure [7, 9].

The presence of RVD is indicated by at least 1 of the following [10]:

- Echocardiography showing RV systolic dysfunction or RV dilation (apical four-chamber RV diameter divided by LV diameter 0.9)
- Computed tomography angiography showing RV dilation (four-chamber RV diameter divided by LV diameter 0.9)
- B-type natriuretic peptide (BNP) >90 pg/mL or N-terminal pro-BNP >500 pg/mL
- ECG changes (see below)
- Elevated plasma troponin (evidence for myocardial necrosis)

How Bad Is the PE?

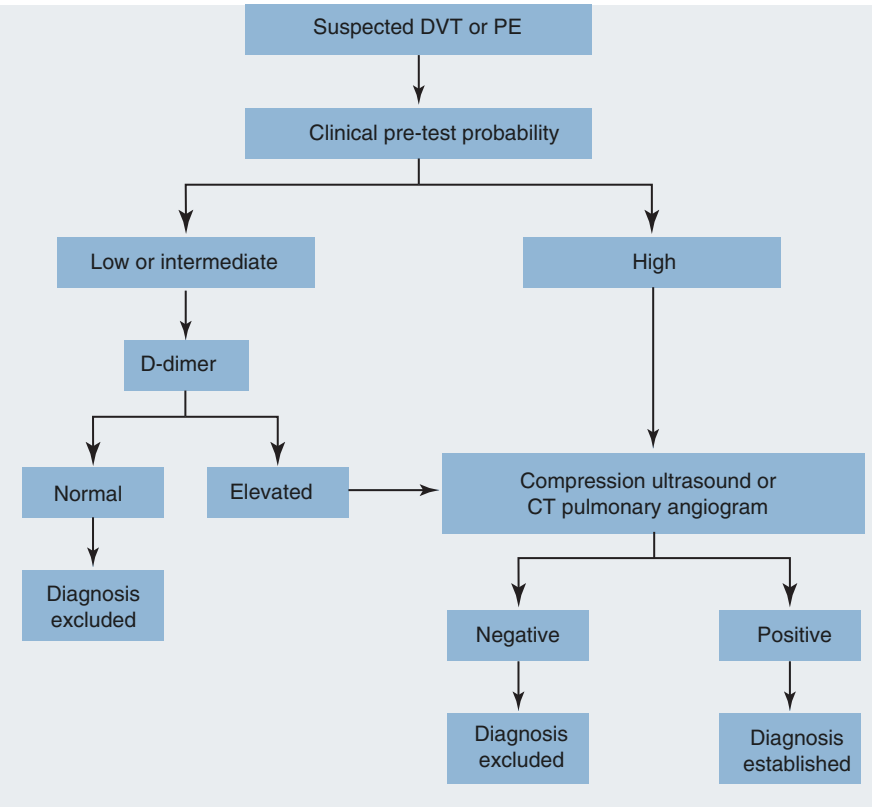
- A PESI Class I or II, or a PESI of 0, indicates a low risk of an early adverse outcome.
- If PESI score is very low (≤65) or low risk (66–85), outpatient management of PE can be considered if clinically appropriate. However, findings which could point toward clinically significant PE should not be overlooked in the setting of a low PESI score.
- If PESI score is intermediate (86–105) or high risk (106–125), higher level of care (e.g., inpatient or ICU) should be considered.

The pretest probability is higher if there are risk factors for VTE, such as active cancer or recent surgery or immobilization, and if the symptoms and signs are typical, particularly if they are severe. Using such scores, clinical pretest probability is categorized as likely or unlikely or as high, intermediate, or low.

- Plasma D dimer, the end product of plasmin-mediated fibrin degradation, is a highly sensitive marker for detection of thrombosis but lacks specificity. D-dimer is recommended to reduce the need for unnecessary imaging and irradiation. Increasing the D-dimer cut point for patients >50 years using the following formula decreases unnecessary CT angiograms: patient age × 10 = new D-dimer cutoff (in μg/L) suggesting imaging for PE is needed (Fig. 27.1).

Electrocardiogram (ECG) (can be helpful but lack of findings does not rule out PE)

Most common abnormalities occur predominantly with a massive embolism than with smaller emboli, but these findings are also nonspecific.



D-dimer quantification aids clinical decision making for patients with low or intermediate pre-test probability of DVT or PE.CT = computed tomography; DVT = deep-vein thrombosis; PE = pulmonary embolism.

Fig. 27.1 Algorithm for diagnosis of DVT or PE using D-dimer. D-dimer quantification adis clinical decision making for patients with low or intermediate pre-test probability of DVT or PE. *CT* computed tomography, *DVT* deep-vein thrombosis, *PE* pulmonary embolism. Reproduced with permission from JACC 2017 [11]

- Unexplained sinus tachycardia and nonspecific ST-T wave abnormalities
- Anteroseptal T-wave inversion (common)
- ST segment elevation in aVR (prevalent in ~1/3 of cases and often missed)
- ECG manifestations of acute cor pulmonale, such as an S1, Q3, and T3 pattern (Fig. 27.2)
- New complete or incomplete right bundle-branch block
- P-pulmonale or right axis deviation

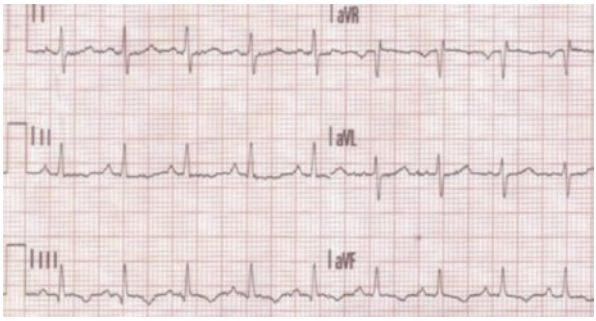


Fig. 27.2 ECG manifestations of acute cor pulmonale, with an S1, Q3, and T3 pattern

Imaging studies [12]:

- Chest radiography: usually nondiagnostic.
- Computed tomography angiography (CTA) is the standard test for diagnosing pulmonary embolism. A normal CTA safely excludes PE in patients with low or intermediate clinical probability, or PE unlikely, while CT angiography showing a segmental or more proximal thrombus confirms PE.
- V/Q scanning: Can be obtained if CT scanning is not available or is contraindicated. A normal perfusion lung scan excludes PE, and a high-probability ventilation-perfusion (V/Q) scan confirms PE; in case of a nondiagnostic V/Q lung scan, PE may be excluded if proximal compression venous ultrasonography is negative and the clinical probability is low or PE unlikely. V/Q scanning is the gold standard to diagnose chronic thromboembolic pulmonary hypertension in which this chronic PE manifestation is often undetected by CTA.
- Pulmonary angiography: criterion standard for diagnosing pulmonary embolism when MDCTA is not available.
- MRI: Using standard or gated spin-echo techniques, pulmonary emboli demonstrate increased signal intensity within the pulmonary artery.
- The echocardiogram is a low-yield diagnostic tool in patients with PE, because it will usually be normal. However, it can identify enlarged RV with RV dysfunction (RV strain) typical for PE. Regional wall motion abnormalities with right ventricular dysfunction and with akinesia of the mid-free wall sparing the right ventricular apex (McConnell's sign) are particularly suggestive of PE [13]. RV strain can be misleading around or following cardiac arrest as the RV dilates nonspecifically, not necessarily secondary to pressure overload from PE. RV dilation in this setting should NEVER be used as the sole reason for administering systemic thrombolysis.
- Echocardiogram in acutely sick patients can also help to exclude other catastrophic illnesses, such as pericardial tamponade, dissection of the aorta, and acute myocardial infarction [9].
- Duplex ultrasonography: Noninvasive diagnosis of pulmonary embolism by demonstrating the presence of a DVT at any site. A DVT at or above the popliteal fossa are highest risk for embolizing. DVTs distal to the popliteal fossa don't often embolize and, while treated with anticoagulants most often, can also be followed by serial venous duplex studies to assess for proximal migration.

Treatment of PE [7, 10]

Anticoagulation and thrombolysis

- Immediate full anticoagulation is mandatory for all patients suspected of having DVT or pulmonary embolism. Diagnostic investigations should not delay empirical anticoagulant therapy.
- For most cases of acute PE without hemodynamic compromise, initial regimens of acute-phase treatment consist of parenteral anticoagulation (intravenous unfractionated heparin, subcutaneous low-molecular-weight heparin, or fondaparinux) over the first 5–10 days, overlapping and followed by a vitamin K antagonist (warfarin), which is adjusted to obtain a therapeutic (2.0–3.0) international normalized ratio.
- The new oral anticoagulants (NOACs; direct inhibitors of factor Xa or thrombin, e.g., dabigatran, apixaban, edoxaban, and rivaroxaban) are non-inferior in terms of efficacy and possibly safer, particularly in terms of major bleeding, than the standard anticoagulation regimen consisting of heparin followed by a vitamin K antagonist (VKA). However, dabigatran and rivaroxaban are contraindicated in patients with creatinine clearance (CrCl <30 mL/min). Apixaban and edoxaban are contraindicated in patients with CrCl <15 mL/min and moderate to severe hepatic impairment or hepatic disease with coagulopathy.
- Systemic thrombolysis is not routinely recommended as primary treatment for patients with intermediate-high-risk PE. Dabigatran and edoxaban require a 5-day lead-in period with parenteral heparin prior to their initiation for VTE/PE management.
- Low-risk patients in the PESI Class I or II, and probably those with sPESI of 0, should be considered for early discharge and outpatient treatment, if this appears feasible based on the patient's anticipated compliance, as well as his/her family and social background.

Duration of Anticoagulation [14]

- In patients with acute *provoked* VTE (including proximal DVT or provoked PE), the duration of oral anticoagulation should be at least 3–6 months.
- In the extended treatment of VTE, NOAC's are both effective (in terms of prevention of symptomatic or fatal VTE recurrence) and safe (particularly in terms of major bleeding), probably safer than standard VKA regimens.
- In patients with an *unprovoked* episode of venous thromboembolism and low or moderate risk of bleeding, extended anticoagulant therapy is recommended (no scheduled stop date).
- Patients who have PE and preexisting irreversible risk factors, such as deficiency of antithrombin III, protein S and C, factor V Leiden mutation, or the presence of

antiphospholipid antibodies, should be placed on long-term anticoagulation. In INR goal for each is 2–3 except for antiphospholipid syndrome which carries an INR target of 2.5–3.0.

Management of High-Risk PE

- If patient has massive or submassive PE, an institutional multidisciplinary Pulmonary Embolism Response Team (PERT) should be activated if one is available. PERTs streamline care for high-risk PE [15].
- Primary reperfusion therapy with systemic thrombolytic therapy should be considered in patients with acute pulmonary embolism associated with hypotension (systolic blood pressure <90 mmHg), who do not have a high bleeding risk (age >65 is the strongest risk for bleeding), and in selected patients with initial clinical presentation or clinical course suggesting a high risk of developing hypotension. Alteplase is the approved agent by the FDA for this indication; all others including tenecteplase are considered off-label.
- Unfractionated heparin with aPTT monitoring is the preferred anticoagulation regimen in such patients [14, 16, 17].
- Absolute contraindications to systemic thrombolysis:
  - H/o of hemorrhagic stroke
  - Ischemic stroke within 3 months
  - Suspected aortic dissection
  - Intracranial or intraspinal surgery within 3 months
  - Intracranial masses
  - Known structural intracranial cerebrovascular disease (e.g., arteriovenous malformation)
  - Active hemorrhage: intraperitoneal, retroperitoneal, pulmonary, uterine, and bladder
  - Already given thrombolytics or known allergy to a fibrinolytic
  - GI bleed previous 30 days
  - Head trauma causing loss of consciousness within previous 7 days
- Percutaneous catheter-directed techniques are an option for patients with hemodynamic decompensation and high bleeding risk [17].
- Surgical pulmonary embolectomy can be used for central PE and contraindications to thrombolytics or hemodynamically unstable patients with RV dysfunction after receiving thrombolytic therapy.
- Other options for PE + severe RV dysfunction: VA-ECMO, Flolan, and pressors for RV support.

Inferior vena cava (IVC) filters in patients with DVT or acute PE:

- The only indication for placement of the IVC filter according to established guidelines is an absolute contraindication to anticoagulation with VTE, in patients experiencing major bleeding events during the acute phase and patients

with objectively confirmed recurrent PE, despite adequate anticoagulation treatment.
- IVC filters are not free of complications, and its use should be limited to these strict indications. The research does not support the use of this type of filter in patients who can be treated with anticoagulation [7, 17].

Chronic Thromboembolic Pulmonary Hypertension (CTEPH) [18]

– V/Q scanning is the gold standard. Many cases of CTEPH are not detected by CTA.
– A mean pulmonary artery pressure ≥25 mmHg with normal capillary wedge pressure persisting 6 months after acute PE.
– Presence of organized persistent thrombi and pulmonary vascular remodeling can lead to progressive right ventricular failure and poor outcome in CTEPH.
– Prevalence is reported to be approximately 4% after PE.
– Angiographic signs of typical pulmonary bed obstruction.
– Life-long anticoagulation (warfarin; goal INR of 2–3) is recommended for all patients with CTEPH.
– Surgical pulmonary endarterectomy is an option. However, it is performed in only selected centers.
– Emerging treatment alternatives with pharmacotherapy thromboendarterectomy and pulmonary angioplasty exist for non-operable patients, as well as for those with pulmonary hypertension persisting after intervention.

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Description of Recommendations Used in the Guidelines

Indications:

Class I	Intervention/treatment should be performed
Class IIa	Intervention/treatment is reasonable
Class IIb	Intervention/treatment may be beneficial
Class III	Intervention/treatment should not be performed

Levels of evidence:

Level A: Decision support is derived from multiple randomized trials or meta-analyses.

Level B: Decision support is derived from single randomized trial or non-randomized studies.

Level C: Decision support is derived from either limited populations or consensus expert opinion.

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H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7

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H. Z. Mieszczanska, A. S. Budzikowski (eds.), *Cardiology Consult Manual*,
https://doi.org/10.1007/978-3-319-89725-7