Cardiovascular Anatomy and Pharmacology

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Key Points

1. The major determinants of myocardial O_2 *supply* are coronary blood flow and arterial O_2 content. Coronary blood flow is determined by the patency of the coronaries, coronary perfusion pressure, and coronary vascular resistance.
2. The major determinants of myocardial O_2 *demand* are heart rate, inotropic state, and wall tension (which is the function of intracavitary pressure, radius and wall thickness, preload and afterload).
3. Critical O_2 delivery is the point at which the extraction ratio is maximized, and any further incongruence between demand and supply will lead to tissue hypoxia.
4. In the perioperative setting, continuation of long-standing beta blocker therapy is recommended.
5. Beta blockers should not be started on the day of surgery in beta blocker naïve patients.
6. Patients with coronary artery disease undergoing surgical coronary revascularization should be administered a beta blocker before surgery.
7. Although recent perioperative guidelines suggested continuing angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) before non-cardiac surgery, adverse circulatory effects during anesthesia in patients chronically treated with ACE inhibitors/ARBs has led to the recommendation that these drugs be discontinued 24 h before surgery.
8. Epinephrine inhibits uterine contractions especially during the second stage of labor.

11.1 Part 1: Cardiac Anatomy

11.1.1 Development and Anatomy of the Heart

The heart is a conical hollow muscular organ located between the lungs in the mid-mediastinal portion of the thorax, suspended in the pericardial sac. As a dual pump, it maintains unidirectional blood flow to the body and the lungs by its rhythmical torsion and untwisting throughout the series of cardiac cycles. Its receiving chambers (the left and right atrium, composed of 2 myocardial layers), and its pumping chambers (the left and right ventricle, composed of 3 layers of myocardium building up the 2 separate vortices each ventricle) are structurally separated by their respective interchamber septa corresponding with the long axis of the heart, and are electrically isolated by the left and right fibrous rings comprising the fibrous cardiac skeleton in the short axis of the heart, perpendicular to the long axis.

A Brief Review of Cardiogenesis

The development of the cardiovascular system begins on day 17 of gestation, when mesoderm-derived blood islands, consisting of endothelial cells and hemoblasts, begin to form. These blood islands coalesce to form a pair of endothelial heart tubes, which on day 21 fuse into a single primitive heart tube with a cranial inflow (arterial) and a caudal outflow (venous) end. This primitive heart tube is divided into 5 regions: truncus arteriosus, bulbus cordis, primitive ventricle, primitive atrium, and sinus venosus. Initial contractions occur on day 21–22, and unidirectional circulation is established by week 4. From weeks 4–7, folding and septation of the heart and the great vessels takes place, critical to the development of the 4 chambers and the normal embryonic vascular circuit. In the developed heart, the atrial chambers lie cephalad and to the right of their corresponding ventricles, and the right-sided chambers lie anterior to their corresponding left-sided chambers. The atrial and ventricular septation is summarized later.

A Review of the Gross Anatomy of the Heart

Fibrous Skeleton

The fibrous skeleton of the heart is a framework of 4 dense collagen rings around the atrioventricular (AV) and semilunar valves, as well as the left and right fibrous trigones (also known as the central fibrous body), and the membranous portion of the interatrial and interventricular septum. Its main component is the central fibrous body, where the leaflets of all 4 cardiac valves converge. The fibrous skeleton reinforces the ostia of the valves and prevents the annuli from overdistension by resisting forces of pressure developing through the cardiac cycle. It provides attachment for the valvular leaflets and cusps, as well as for some of the musculature of the atrial and ventricular wall. It is electrically impermeable, only allowing electrical propagation from the atrioventricular node across the right fibrous trigone to the bundle of His. Chronic degenerative changes and calcium deposition into the collagen skeleton results in delayed conduction and depolarization, arrhythmias, rigidity of the valvular ostia, restricted leaflet opening and/or leaflet malcoaptation.

Interatrial Septum

The interatrial septum is a blade-shaped wall between the left and right atrium. Its development begins during the fifth gestational week with the septum primum growing from the posterior wall of the primary atrium toward the endocardial cushion, formed within the atrioventricular canal. With the incomplete fusion of the septum primum and the endocardial cushion, a progressively diminishing space above the endocardial cushion, the ostium (also known as foramen) primum remains. During this process, small coalescing perforations in the upper portion of the septum primum create the ostium (or foramen) secundum. Concurrently, a second septum, the septum secundum begins to form to the *right* of the septum primum, growing from the anterior wall, partially covering the foramen primum. Its growth stops at the seventh week of gestation, leaving a gap known as the foramen ovale. This is essential in reducing pulmonary blood flow through the inactive fetal lungs.

The foramen ovale is continuous with the ostium secundum, and is covered by the septum secundum on its *left* side. As a result of normal adaptive changes in the neonatal circulation, the decreasing pulmonary vascular resistance (PVR) and the resultant reversal of interatrial pressure gradient results in the permanent functional closure of the foramen ovale. In one-third of the population incomplete fusion between the septum primum and the septum secundum results in a residual flap valve and a probe patent foramen ovale (PFO).

Excessive apoptosis within the septum primum, or incomplete development of the septum secundum results in an atrial septal defect (ASD), the most common congenital heart defect to manifest in adulthood:

- There are 4 types of ASD, the most common being the secundum type ASD, accounting for 80–90% of all ASDs. The secundum type ASD is located centrally, it is larger than a PFO, and it is commonly associated with mitral valve prolapse.
- The primum type ASD is less common, it represents 2–3% of ASDs. It is located in the lower portion of the interatrial septum, and it is associated with endocardial cushion defects, AV-valve abnormalities, or ventricular septal defects such as in Down syndrome.
- The sinus venosus ASD represents 2–10% of ASDs. It is associated with abnormal pulmonary venous return.
- The fourth type, the coronary sinus ASD or unroofed coronary sinus is the least common. It results from incomplete septation between the inferior portion of the left atrium and the coronary sinus, and is commonly associated with a persistent left superior vena cava.

ASDs often remain clinically silent with preserved normal left atrial size, however, longstanding left-to-right shunting and resultant dilatation of the right-sided chambers along with persistent pulmonary hypertension may reverse the direction of the shunt, resulting in hypoxemia and Eisenmenger physiology.

Interventricular Septum

The interventricular septum (IVS) separates the left and right ventricles from one another. Under physiological pressure and filling conditions its convexity is bowing into the right ventricle. Its margins are marked externally by the anterior and posterior interventricular grooves. The upper, posterior part of the interventricular septum is thin, and constitutes the membranous interventricular septum. The greater, anterior portion is the muscular interventricular septum.

During cardiogenesis, along with the atrial septation a concurrent ventricular septation is also taking place. With the development of the endocardial cushions and the atrioventricular separation, there is tissue growth between the left and the right sides of the developing atrioventricular canal. This is the muscular portion of the interventricular septum, growing from the inferior portion of the ventricle toward the endocardial cushion. As the muscular IVS reaches the endocardial cushion, a small interventricular foramen remains. This is closed by tissue growth from the endocardial cushion, connective tissue from the muscular IVS, as well as tissue from the septation of the truncus pulmonalis and the conus arteriosus. Inadequate contribution from either component results in different types of ventricular septal defects.

Chambers and Valves of the Right Heart

Right Atrium

The right atrium is the cardiac chamber receiving the systemic and cardiac venous return via the superior and inferior venae cavae (SVC and IVC) and the coronary sinus. It is divided into 3 components.

The venous component receives deoxygenated blood from the SVC and the IVC. At the inferior cavoatrial junction lies the Eustachian valve, important before birth in directing blood from the IVC to the left atrium across the foramen ovale. A network of fine filamentous strands, the Chiari network, may be seen in this region. The variably sized Eustachian valve and Chiari network are normal variants within the right atrium.

The second component is the vestibule, which converges into the leaflets of the tricuspid valve, and the third is the appendage (also known as auricle). The right atrial appendage has a wide junction with both the vestibule and the venous component. The vestibuloauricular junction is identified by the terminal groove, the external marking of the prominent terminal crest on the internal surface. A consistent feature of the right atrial anatomy is the extension of the auricular pectinate muscles beyond the appendage to the atrioventricular junction.

The sinus node, a cluster of specialized myocardial cells capable of spontaneous electrical impulse generation, lies at the superior cavoatrial junction at the terminal groove. It is supplied by the nodal artery, arising from the right coronary artery in 55% of cases, or the proximal left circumflex artery in the remaining 45%. The atrioventricular node is located in the floor of the right atrium, near the opening of the coronary sinus. Preserving blood flow to the sinus node and other conductive tissues is key to avoiding arrhythmias and other conduction abnormalities.

Tricuspid Valve

The tricuspid valve is located nearly vertically behind the aortic valve. With a valve area of 4–6 cm^2, it is the largest of the 4 valves in the heart. Its annular plane is saddle-shaped and is apically displaced relative to that of the mitral valve. A displacement index greater than 8 mm/m^2 (body surface area) suggests the presence of Ebstein's anomaly. Its 3 leaflets are the septal, anterior, and posterior tricuspid valve leaflets, attached by their chordae tendineae to the right ventricular papillary muscles (true chords), or, not uncommonly, directly to the septum (false chords). The subvalvular apparatus of the tricuspid valve is variable. Most commonly, the chordae tendineae originate from 2 or 3 papillary muscles, the anterior being the most prominent; the posterior, which is usually less prominent and may have several subdivisions; and the septal, which is the least prominent or may be entirely absent.

Right Ventricle

The right ventricle is the most anterior of the 4 chambers of the heart, located immediately behind the sternum. Its geometry is complex: The right ventricle is crescent shaped when viewed in the short axis, and triangular when viewed longitudinally. Current guidelines identify its walls as anterior, inferior, and lateral free wall. Medially, the right ventricle shares the septum with its left-sided counterpart. For purposes of functional quantification, these walls are further divided into basal, mid, and apical segments.

Anatomically and functionally, the right ventricle is composed of 3 portions: the smooth muscular right ventricular inflow tract, the apical trabecular, and the right ventricular outflow tract. The inlet portion encircles the tricuspid valve. The trabecular portion of the right ventricle extends into the apical region. The wall of the ventricle is thin here, making it vulnerable to perforation by catheters and electrodes.

The most prominent of the trabeculae is the septomarginal trabecula. It carries part of the right bundle branch of the conduction system. It was once wrongly thought to prevent the right ventricle from overdistending, hence the name "moderator band." The septomarginal trabecula originates from the base of the septum, it divides into an anterior limb that supports the pulmonic valve cusps, and a posterior limb, from which the medial papillary muscle arises. Its main mass extends from the base of the septum to the apex and divides into smaller muscle ridges. Two of these are particularly prominent, one giving rise to the anterior papillary muscle, and the other crossing the right ventricular cavity as the moderator band.

The outlet portion consists of the circumferential muscular infundibulum that supports the pulmonic valve, which is the only one of the cardiac valves with no single ringlike annulus. It is supplied by the conus branch of the right coronary artery.

Pulmonic Valve

The pulmonic valve separates the right ventricular outflow tract from the pulmonary artery. It is located anteriorly and to the left of the aortic valve. It is a semilunar valve formed by 3 cusps, labeled as anterior (nonseptal), left, and right, each with a fibrous nodule at the midpoint of their free edges. The leaflets coapt via their crescent-shaped surfaces. The cusps of the pulmonic valve are formed by endocardial folds that are supported by internal dense collagenous plates as well as elastic connective tissue, continuous with the fibrous skeleton of the heart. They are thinner than the cusps of the aortic valve, and, lacking fibrous continuity with the septal leaflet of the tricuspid valve, are supported only by a prominent ridge of the posterior subpulmonary infundibular musculature. This is the supraventricular crest that separates the pulmonic and tricuspid valves from one another, and supports the semilunar attachments of the pulmonic valve. Surgical incisions made through this crest may run toward the interventricular septum, and jeopardize the right coronary artery.

Chambers and Valves of the Left Heart

Left Atrium

Oxygen-rich blood returning from the lungs via the 4 pulmonary veins is received first by the left atrium. The left atrium has 3 basic components: first, the largest, smooth-walled pulmonary venous component; second, the vestibule; and third, the left atrial appendage. The wall of the vestibule is continuous with both the venous component and the posterior (mural) leaflet of the mitral valve, and may affect normal valvular function when left atrial dilation is present. Pectinate muscles are confined almost exclusively to the appendage in the left atrium. The flap valve of the fossa ovalis is found on the left atrial side of the interatrial septum.

Recurrent, symptomatic, drug-refractory atrial fibrillation most often originates from the pulmonary veins or their pulmonary venous ostia. Circumferential or segmental ablation of potential triggers is considered effective means to control refractory atrial fibrillation, as scar forming is thought to prevent propagation of abnormal signals to the rest of the atrial musculature. The ablation and mapping catheters are inserted via the femoral or jugular veins, and are placed through separate transseptal punctures. Most often, radiofrequency energy is used to make ablation lesions around the pulmonary vein ostia. In the presence of a left atrial appendage thrombus, or inability to anticoagulate in the 30-day peri- and post-procedural period, pulmonary vein isolation for atrial fibrillation ablation is contraindicated. A rare, frequently disabling, sometimes fatal complication of the procedure is an atrio-esophageal fistula resulting from thermal damage. Other potential complications are cardiac tamponade, arrhythmias or atrioventricular block, embolic events, valvular complications, or peripheral vascular damage.

Mitral Valve

The bileaflet mitral valve is located between the left atrium and left ventricle, embedded into the saddle-shaped mitral valve annulus. It serves as a unidirectional valve directing blood from the atrium toward the ventricle by passively opening during diastole and closing in systole, as determined by the pressure gradient between the chambers.

The mitral valve apparatus consists of the left atrial wall, the annulus, the anterior leaflet attached to the aortic root, the posterior leaflet attached to the left atrial myocardium, the chordae tendineae attached to the ventricular side of the mitral valve leaflets, and the anteromedial and posterolateral papillary muscles.

The anterior leaflet of the mitral valve is wide. It occupies about one-third of the annular circumference, and forms the anterior portion of the left ventricular outflow tract. In contrast with the posterior leaflet, its free edge has no indentations. The posterior (mural) leaflet is narrower, it occupies about two-thirds of the annular circumference, and it is further divided into 3 scallops by 2 clefts. Because the posterior aspect of the mitral valve annulus contains little fibrous tissue, the posterior leaflet, especially the middle scallop, is

more prone to prolapse than the anterior. The circumflex artery courses near the left half of the posterior leaflet, whereas the right half is in close proximity to the coronary sinus and the arterial branch supplying the AV node.

The mitral valve leaflets are supported by a dense collagen annulus. The most vulnerable portion of the mitral valve annulus is its aspect continuous with the right fibrous trigone, due to the proximity of the atrioventricular node and the penetrating bundle of His.

The muscular components of the mitral valve apparatus are the anteromedial and posterolateral papillary muscles. The anteromedial papillary muscle is more prominent and is supplied by the left coronary system. The posteromedial papillary muscle is smaller, and is supplied by the right coronary artery. The mitral valve closes with the contraction of the papillary muscles, and open when they relax. Papillary rupture, as a result of ischemia, will result in acute mitral regurgitation. Because the anterolateral papillary muscle is supplied by both the left anterior descending (LAD) artery and the left circumflex artery, its ischemic dysfunction is relatively uncommon. In about 60–65% of individuals, the posteromedial papillary muscle was found to be perfused by a single vessel, most commonly by the right coronary artery.

Left Ventricle

The left ventricle (LV) is the largest and thickest chamber of the heart. It receives oxygenated blood from the left atrium during diastole, to transfer it to the body during across the aortic valve during systole. Relative to the right ventricle, it is located laterally and posteriorly. Its superior, widest aspect is termed the base, leaning upward and toward the right shoulder, opposing its apex, pointing down and to the left. By consensus, its 4 walls are termed septal, and the free anterior, inferior, and lateral walls. For purposes of functional quantification, these are further divided into basal, mid, and apical segments.

Morphologically, the left ventricle also has an inlet, a fine trabecular and an outlet component. The inlet portion extends from the mitral valve annulus to the origins of the papillary muscles, and contains the mitral valve apparatus. In contrast to the coarsely trabeculated right ventricle, the left ventricular free wall is finely trabeculated. The trabeculation extends to the apex, where, due to the progressively decreasing number of myocardial fibers, the wall thickness is thin. Its outflow tract differs from that of the right ventricle in that it is anatomically and functionally contiguous with the inlet via the aortic-mitral continuity. The left ventricular outflow tract supports the aortic valve, and its septal portion, in contrast with the primarily muscular right ventricular infundibulum, includes the membranous interventricular septum. The left bundle branch of the conduction system courses posteriorly to the membranous septum between the right and noncoronary cusps of the aortic valve.

The interventricular septum is formed by subendocardial myocardial fibers of both the left and the right ventricle, intermingled with circumferentially arranged fibers derived from the left ventricle. For this reason, in a normally functioning heart, the septum thickens toward the left ventricle during systole. During contraction, the high left ventricular pressure along with the septum provides a "splint" against which the right ventricle is able to shorten, hereby contributing to the emptying of the right ventricle (systolic ventricular interdependence). Under pathologic conditions, for example, during acute right ventricular volume or pressure overload, or due to conduction abnormalities or pacemaker activation, the septum may appear flat, or move paradoxically toward the right ventricle during systole. Blood flow to the anterior 2/3 of the septum is supplied by the septal perforators of the left anterior descending artery. The posterior 1/3 is supplied by the distal branches of the right coronary artery.

The 2 papillary muscles of the left ventricle arise from the anterolateral and posteromedial portions of the left ventricular free wall. Their arrangement ensures parallel alignment of the chordae tendineae with the LV axis during systole, allowing for complete leaflet coaptation and closure of the mitral valve in the normally functioning heart.

All 3 coronary branches contribute to the blood supply of the left ventricle, acute ischemic events therefore predictably manifest as regional wall motion abnormalities based on the coronary distribution. The left anterior descending artery and its branches, the septal perforators and the diagonals perfuse the anterior wall, the anterior two-thirds of the septum, and the apex. The obtuse marginal branches of the left circumflex artery supply the lateral wall. The right coronary artery perfuses the medial portions of the inferior wall, as well as the posterior one-third of the interventricular septum. Anastomotic connections between the left and the right coronary system allows for preserved myocardial perfusion distal to a significant obstruction or total coronary occlusion.

Aortic Valve

The aortic valve is part of the aortic root consisting of the annulus, the aortic valve cusps, the sinuses of Valsalva, the junction between the sinuses and the proximal ascending aorta (the sinotubular junction), and the proximal ascending aorta. It is located at the left ventricular outlet, separating the aorta and the ventricle. Owing to its central location, it is the only valve in the heart that is related to all 4 chambers and each of the valves. As a trileaflet semilunar valve, it consists of 3 cusps: the left and right coronary cusps giving rise to their respective coronary arteries, as well as the non-coronary cusp, which faces the interatrial septum. The right coronary cusp is the most anterior and is adjacent to the right ventricular outflow tract. The left coronary cusp is located posteriorly relative to the other 2. Histologically, its cusps are composed of dense collagenous plates, which are in continuity with the fibrous skeleton of the heart, covered by endocardium. Each cusp has its attachment to the aorta and the left ventricle. Immediately behind the cusps, the wall of the proximal ascending aorta bulges outward to form the aortic sinuses of Valsalva. The function of these sinuses is to prevent coronary ostial occlusion by creating eddy currents of blood flow during rapid ejection. As with the pulmonic valve, each cusp has a fibrous nodule at the midpoint of their free edges, forming

the nodule of Arantius. The leaflets coapt via their crescent-shaped surfaces. Incomplete coaptation of the valve leaflets during diastole results in aortic regurgitation, whereas limited systolic leaflet excursion due to excessive leaflet thickening resulting from degenerative or rheumatic disease process suggests the presence of aortic stenosis. The severity of aortic stenosis can be assessed by various methods. A peak transaortic velocity of greater than 4 m/second, a peak transaortic gradient of at least 70 mm Hg and a mean gradient of at least 40–50 mm Hg, as well as an aortic valve area of less than 1 cm^2 is consistent with severe aortic stenosis.

Coronary Circulation

The first pair of arteries branching off the proximal ascending aorta are the left and right coronaries, originating from their respective sinus of Valsalva in the aortic root. While there is some variability in their point of origin and their distribution, the right coronary artery (RCA) almost always supplies the right ventricle (RV), whereas the left coronary artery (LCA) supplies the anterior and lateral wall of the left ventricle (LV), as well as the anterior portion of the interventricular septum. Blood supply to the remainder of the left ventricle is determined by the coronary dominance. This refers to the artery that supplies the posterior descending artery (PDA) and the posterior lateral branch (PLB). Right dominance (when the right coronary artery gives off the PDA and the PLB) occurs in 80–90% of normal individuals. Left dominance (the PDA and the PLB originating from the left circumflex artery) is slightly more common in men than in women. If the PDA is supplied by the RCA and the PLB branches off the left circumflex artery, the system is codominant.

The Left Coronary System

The left coronary artery arises from the left coronary sinus as the left main stem, which then bifurcates into 2 segments: the left anterior descending (LAD) and the circumflex (LCx) artery. The relatively short left main stem courses between the left atrial appendage and the pulmonary trunk before giving off the LAD and the LCx, and, in 15–30% of cases the variant coronary ramus intermedius, the branch supplying the anterior aspect of the heart.

The left anterior descending artery traverses the anterior interventricular groove and perfuses the anterior wall via the diagonal branches, as well as the anterior two-third of the interventricular septum via its septal perforators coursing along the anterolateral wall, and a small portion of the anterior wall of the right ventricle, adjacent to the interventricular groove, via the right ventricular branches.

The circumflex artery courses in the left atrioventricular groove. Its primary branches are the obtuse marginals, supplying the lateral aspect of the left ventricle, including the posteromedial papillary muscle. In 10% to 15% of individuals, it gives off the posterior descending artery (left dominance). Further branches of the left circumflex artery supply the left atrium, and, in 45% of the cases, the sinus node. A left dominant coronary system also supplies the atrioventricular node.

The Right Coronary System

The right coronary artery emerges from the right sinus of Valsalva and is carried by the right atrioventricular groove. In about half of the cases it gives off the conus branch that supplies the right ventricular outflow tract. The RCA perfuses the anterior free wall of the right ventricle via its acute marginal branches, the sinus node via the nodal artery in 55% of individuals, and the atrioventricular node in patients with right-dominant coronary circulation. It bifurcates into the posterior descending artery and the posterolateral branch at the posterior interventricular groove. The posterior descending artery gives off the posterior septal perforators that supply the posterior one-third of the interventricular septum. The posterolateral branch supplies the inferoposterior wall of the left ventricle along with the acute marginal branches of the RCA and/or the circumflex artery. The Kugel's artery is an anastomotic branch between the RCA and the LCx that may give off a branch that supplies collateral circulation to the atrioventricular node.

The Coronary Veins

Of the cardiac veins, the great cardiac vein courses in the anterior interventricular groove upward from the apex, alongside the LAD. It drains into the coronary sinus. The middle cardiac vein courses in the inferior interventricular groove, upward from the apex, accompanying the PDA.

The coronary sinus courses in the posterior atrioventricular groove, alongside the left circumflex artery. It receives the great cardiac vein proximally and the middle cardiac vein distally, and drains into the right atrium. Its orifice is guarded by the Thebesian valve.

The anterior right ventricular veins course on the anterior surface of the right ventricle, where they may drain directly into the right atrium, or coalesce to form the small cardiac vein. The small coronary vein runs posteriorly through the right AV groove.

The Thebesian veins are small veins draining directly into the cardiac chambers, primarily into the right atrium and the right ventricle.

11.2 Part 2: Cardiovascular Pharmacology

11.2.1 An Overview of Subcellular Mechanisms: Ion Channels and Receptors

Patients in the perioperative period often receive agents that affect hemodynamic variables such as heart rhythm and rate, blood pressure, or cardiac output. The effect of these agents is governed predominantly by transmembrane ion fluxes. Drugs used for rhythm and rate control act by modulating Na^+, K^+, and Ca^{2+} currents. Intracellular calcium is a key mediator in coupling electrical excitation to mechanical contraction, and is an important determinant of the contractile state of the myocardium. The vascular tone of resistance vessels is regulated by ion fluxes via different types of K^+, Ca^{2+} and Cl^- channels.

Much of human physiology (for example, responses to stimuli by hormones, neurotransmitters, ions, or photons) is regulated by GTP binding (G) protein-linked signal transduction. G-proteins serve as points of communication between the extracellular and intracellular environment.

Adrenergic receptors are membrane-spanning molecules coupled to adenylate cyclase via a G-protein located on the inner membrane of the cell. Their activation ultimately leads to the modulation of downstream effectors. G-proteins consist of 3 (α, β and γ) subunits. The binding of an agonist to the adrenergic receptor replaces guanosine diphosphate (GDP) by guanosine triphosphate (GTP), and causes the α-subunit of the G-protein to break free from the β-γ complex, and act as a primary messenger: in beta receptors, it stimulates adenylate cyclase and triggers cyclic adenosine monophosphate (cAMP) production, which, as a second messenger in the process of signal transduction, activates its target kinases that phosphorylate regulator proteins and ultimately increases intracellular calcium levels.

Pure alpha-adrenergic agonists also increase intracellular calcium levels by stimulating phospholipase C, an enzyme that catalyzes hydrolysis of phosphatidyl inositol to diacyl glycerol and inositol triphosphate. Inositol triphosphate stimulates the release of calcium from the sarcoplasmic reticulum, and both molecules act as myofilamental calcium sensitizers.

11.2.2 Antiarrhythmic Agents

A Review of Electrophysiology and the Anatomy of the Cardiac Conduction System

Under physiologic conditions, electrical impulse generation, conduction, and propagation occurs in specialized excitatory and conductive tissues within the myocardium, and is driven by a sequence of ion fluxes through sarcolemmal ion channels. The pacemaker of the normal cardiac muscle is the sinoatrial (SA) node, located in the right atrium, below and lateral to the ostium of superior vena cava, supplied by the nodal branch of the right coronary artery (RCA). Its intrinsic rate (60–100 beats per minute) is determined by the resting transmembrane potential, the threshold potential, and the rate of phase 4 spontaneous diastolic depolarization. The SA node has the steepest slope of phase 4 depolarization. For this reason, its intrinsic rate is the highest, therefore this is the dominant, primary pacemaker of the heart.

Rhythmical, automatic impulses generated by the sinus node spread directly to the right atrium via its own noncontractile sinus fibers that fuse with excitable and contractile atrial fibers, as well as anteriorly to the left atrium via the Bachmann's bundle. Electrical impulse from the right atrium propagates via 3 other internodal tracts, including the posterior (Thorel's) and median (Wenkebach's) pathways to the atrioventricular (AV) node. The AV node, supplied by the AV nodal branch of the distal RCA and the septal perforators of the left anterior descending (LAD) coronary artery, and located in the right atrial side of the interatrial septum behind the tricuspid valve and superior to the coronary sinus, delays impulses from the atria by approximately 70–100 ms before allowing them to pass to the bundle of His. These slow conduction velocities allow the atria to empty before ventricular contraction begins. The AV node is the primary regulator of ventricular rate in atrial fibrillation and flutter. Its intrinsic rate is 40–60 beats per minute, and it is considered a latent intrinsic pacemaker.

The bundle of His is located just above the interventricular septum (IVS) and is supplied by the septal perforators of the LAD, as well as the posterior descending artery. As a latent pacemaker, its intrinsic rate is 20–40 beats per minute. From the bundle of His, impulses rapidly travel down the bundle branches on either side of the membranous portion of the interventricular septum, to depolarize the left (left bundle branch, LBB, which also depolarizes the IVS) and the right (right bundle branch, RBB) ventricles. The left bundle branch further divides into the anterior and posterior fascicles. Both bundles terminate in the Purkinje fibers that penetrate the ventricular myocardium, initiating its contraction from the endocardium toward the epicardium. An organized sequence of impulse generation and conduction is required for the cardiomyocytes to synchronously contract, and, by coordinated chamber contraction, to maintain cardiac output.

Understanding normal cardiac electrophysiology is the foundation for understanding the basic principles of disease mechanisms and antiarrhythmic pharmacotherapy. The following is a brief review.

Cardiac Action Potential

In the normal resting myocardium, transmembrane potential is determined primarily by potassium conductance, and is maintained by the Na^+/K^+ ATPase. The resting transmembrane potential is stable around −90 mV (the intracellular compartment being more negative relative to the outside of the cell), approaching the potassium equilibrium potential.

An action potential is triggered by either the cardiac pacemaker cells, or by the surrounding cardiomyocytes. This results in a transient increase in Na^+ conductance, which in turn initiates an increase in Na^+-influx through fast sodium channels. When the threshold potential is reached at around −70 mV, a large enough number of sodium channels have been opened to generate a self-sustaining sodium influx. Above −40 mV, long-opening (L-type) Ca^{2+}-channels open with resultant Ca^{2+}-influx down its concentration gradient. At around 0 mV, fast Na^+-channels start to close. This is Phase 0 (early rapid depolarization), peaking at +20 mV (Na^+-equilibrium potential).

The increase in Na^+-conductance is inactivated. This, with the outward movement of K^+ via transient K^+-channels results in a brief period of initial repolarization. The transmembrane potential returns from slightly positive to approximately 0 mV. This is Phase 1.

Following the initial repolarization, a constant Ca^{2+}-influx via slow (L-type, "long-opening") Ca^{2+}-channels, and an increase in K^+ conductance via delayed rectifiers main-

tains the membrane potential just below 0 mV. The electrical countercurrents are balanced. This is Phase 2, the plateau. The phase between the initiation of the upstroke and the end of the plateau is the absolute refractory period, during which the cell is unable to be depolarized regardless of the strength of the stimulus, and corresponds with phase between the beginning of the QRS complex and the beginning of the T wave on the electrocardiogram (ECG).

The next phase of the cardiac action potential is the rapid repolarization. Ca^{2+}-conductance via the L-channels is inactivated, but the K^+-channels remain open. Potassium is rapidly shifted out of the cell, and the transmembrane potential rapidly approaches the K^+-equilibrium. This is Phase 3. The phase between the initiation of the upstroke and the transition between Phase 2 and 3 is the relative refractory period, during which the cell may be able to be depolarized to allow for a non-propagated stimulus. This corresponds with the early upstroke of the T wave. During phase 3, the cell is able to be depolarized by supranormal stimuli (relative refractory period), resulting in an action potential. This corresponds with the dome of the T wave on the ECG. Membrane hyperpolarization at the end of this phase results in a hyperexcitable period, during which even weak stimuli can trigger an action potential. This brief phase corresponds with the downward slope of the T wave.

During Phase 4, Na^+ and Ca^{2+} channels are closed. There is a constant outflow of potassium ions through inward rectifier channels. This is the resting phase in the contractile cells, or spontaneous diastolic depolarization in the cardiac pacemaker cells.

Pacemaker Cells

Pacemaker cells are found primarily in the dominant and subsidiary rhythm generators (SA node, AV node, His-Purkinje system) of the heart. However, impulses may originate from other sites; for example, cells at the coronary sinus, atrioventricular valves, or cells at the crista terminalis. Abnormally, impulses may originate from around the pulmonary veins. These cells are different from contractile cardiomyocytes in that they share the characteristic to generate spontaneous cardiac action potentials. They exhibit automaticity, have an unstable membrane potential, and have no rapid depolarization phase.

Automaticity means that pacemaker cells are capable of initiating their own action potential without external stimulus. These cells undergo a spontaneous diastolic depolarization and action potential is triggered when threshold potential is reached.

Pacemaker cells undergo spontaneous diastolic depolarization during phase 4 (as opposed to the resting phase during phase 4 in contractile cells), and have no rapid depolarization phase. These cells have fewer inward K rectifier channels than contractile myocytes do, and their transmembrane potential is never lower than −60 mV. Therefore, the fast Na^+-channels that need −90 mV to get activated are permanently inactivated in these cells.

Multiple ion currents are responsible for the generation of spontaneous action potentials. The synergy of 3 different currents—(1) the decay of the K^+-efflux; (2) an inward depolarizing "funny" mixed Na^+-K^+ inward current, activated by membrane hyperpolarization, and playing a major role in the spontaneous depolarization of the sinoatrial node; and (3) an inward Ca^{2+}-current in the late phase of the spontaneous diastolic depolarization—determines the rate and shape of action potentials in cardiac pacemaker cells. Physiologically, the dominant pacemaker is the sinoatrial node. When its rate drops below the intrinsic rate of a latent, non-dominant pacemaker—for example, as a result of parasympathetic stimulation or SA nodal disease—the removal of the sinus overdrive leads to "escape-activation" of these non-dominant centers. Junctional rhythm may also occur when the AV junctional pacemaker rate exceeds and suppresses the sinoatrial rate.

Mechanisms of Cardiac Dysrhythmias

Cardiac arrhythmias are commonly defined as abnormalities of the normal sequence of impulse generation and propagation within the myocardium. While benign arrhythmias—for example, premature atrial contractions, isolated premature ventricular contractions, or atrial fibrillation in the absence of structural heart disease—are very common, malignant ventricular arrhythmias (monomorphic or polymorphic ventricular tachycardia [VT], ventricular fibrillation) accounted for an estimated 180,000–250,000 sudden cardiac deaths in the United States.

Underlying provoking factors are, for example, arterial hypoxemia, acidosis or alkalosis, electrolyte abnormalities, ischemia, increased sympathetic activity, atrial or ventricular dilation, or proarrhythmogenic drugs. In some cases, correction of these factors is sufficient to suppress cardiac ectopies. However, when this alone does not control cardiac arrhythmias, and/or hemodynamic compromise ensues, or the presence of a disturbance increases the risk of a life-threatening arrhythmia, administration of antiarrhythmic agents may be warranted.

The main mechanisms of cardiac dysrhythmias have been identified as:

Focal activity due to abnormal impulse generation This results from:

- Enhancement or reduction of normal automaticity (such as in sinus tachycardia and sinus bradycardia, accelerated junctional rhythm).
- Enhanced abnormal automaticity of the Purkinje-fibers, atrial or ventricular myocytes; ie, cells that do not normally display automaticity (for example, atrial tachycardia or accelerated idioventricular rhythm. Purkinje fibers are catecholamine-sensitive, and their activation can be augmented by increased sympathetic tone, for example during myocardial ischemia).
- Triggered activity. This occurs when early afterdepolarizations and delayed afterdepolarizations initiate spontaneous multiple depolarizations, such as in torsades de pointes, or ventricular arrhythmias in the setting of digitalis toxicity.

Abnormal conduction Delayed conduction (such as in atrioventricular blocks), or re-entrant mechanisms (for example, SA nodal re-entry, atrial flutter, AV nodal re-entry tachycardia, or ventricular tachycardia). Re-entrant tachycardias can be generated by 3 different mechanisms: reflection, circus movement re-entry, and phase 2 re-entry. Circus movement re-entry due to an anatomical or functional block is a major mechanism and the most commonly described. For a re-entrant circuit to occur, 2 roughly parallel conductive pathways must be connected with conductive tissue, capable of forming an electrical circuit. One of these pathways must have a refractory period substantially longer than that of the other pathway (pathway A). Finally, the pathway with the shorter refractory period (alternate pathway, pathway B) must conduct impulses more slowly than pathway A. Once an extra impulse (for example, premature contraction) encounters these 2 separate pathways of conduction when pathway A is unable to be depolarized due to being in the refractory period but pathway B is capable of depolarization, the impulse will be conducted via pathway B. The signal then travels to the distal end of pathway A to reconnect with it if it is no longer refractory, then it is conducted retrograde to the site where it reconnects with pathway B. Pathway B has a shorter refractory period and therefore it recovers faster: The impulse will travel into pathway B where it will reenter that portion of the circuit, completing the loop. Micro-re-entry occurs with ventricular tachycardia from conduction around scar tissue such as in myocardial infarction (MI). Macro-re-entry occurs via conduction through concealed accessory pathways, such as in Wolff-Parkinson-White syndrome.

Antiarrhythmic Agents: Classification and Mechanism of Action

Pharmacological management of arrhythmias is warranted when treatment of the underlying causes does not break the arrhythmia, the arrhythmia results in hemodynamic compromise, or it increases the risk of development of a life-threatening arrhythmia. The most widely used classification system of antiarrhythmic drugs was proposed by Vaughan Williams. This system classifies the antiarrhythmic agents based on their ability of abolishing an arrhythmia by blocking specific ion currents during the action potential.

Ion-specific channels exist in 3 different stages. During the upstroke phase (phase 0) of the action potential the channels are in the activated state. During the plateau phase of repolarization (phase 2), the inactivated state occurs: During the effective refractory period channels are unresponsive to new or continued stimulus. Ion channels are closed during the resting phase (phase 4).

The effects on the action potential and the effective refractory period of the cardiac action potential determine the clinical effect of antiarrhythmic drugs. Drugs blocking inward sodium ion flow will slow conduction and result in suppression of the maximum upstroke velocity of the cardiac action potential. Potassium channel blockers prolong repolarization by prolonging the duration QTc prolongation. L and T type calcium channels are present in the myocardium, and are targets of calcium channel blockers.

Classification

Class I

Class I antiarrhythmic drugs are fast Na-channel inhibitors. Fast sodium channels are blocked during phase 0 (upstroke) and phase 4 depolarization of the action potential with resultant decreases in the amplitude and rate of the action potential and conduction velocity.

Class IA for example, quinidine, procainamide, disopyramide. These drugs lengthen both the action potential and the effective refractory period reflecting sodium channel inhibition and lengthening of repolarization reflecting potassium channel blockade. These drugs are considered membrane stabilizers in the treatment of atrial, AV nodal, and ventricular arrhythmias. They may prolong the QRS and QT intervals.

- **Quinidine** – Quinidine has mild parasympatholytic and alpha-blocking effects and decreases systemic vascular resistance (SVR).
- **Procainamide** – Procainamide is used to suppress premature atrial and ventricular contractions and to prevent precipitation of atrial fibrillation or flutter. It increases refractoriness and can prevent accessory pathway re-entry tachycardias. High serum levels may cause direct myocardial depression and bradycardia requiring temporary pacing or administration of beta-agonists. Procainamide and its active metabolite N-acetylprocainamide may induce QT-prolongation and torsades de pointes. Long-term therapy may cause lupus-like symptoms.
- **Disopyramide** – Disopyramide has a vagolytic effect that is dose-dependent and reversible by pyridostigmine. It depresses myocardial contractility and increases SVR, and may thus precipitate or exacerbate congestive heart failure.

Class IB for example, lidocaine, tocainide, mexiletine. These are less powerful Na-channel blockers. They shorten action potential duration and refractory period in normal ventricular myocytes. Class II drugs have minimal effect on inotropy or SVR. In the ischemic tissue, lidocaine may block adenosine triphosphate-dependent channels, preventing ischemic-mediated shortening of ventricular depolarization. Lidocaine depresses the slope of phase 4 depolarization in Purkinje fibers and increases the fibrillation threshold in ventricular myocytes. Signs of toxicity are frequent with concentrations above 9 mcg/ml.

Class IC for example, flecainide, propafenone. Class IC drugs are potent sodium channel blockers, indicated for the treatment of ventricular arrhythmias. They markedly decrease the rate of phase 0 depolarization and speed of conduction. They have little effect on the duration of the action potential and the effective refractory period in ventricular muscular cells, but do shorten the duration of the action potentials in the Purkinje fibers. This inhomogeneity on the rate of cardiac repolarization plus the slowing of cardiac conduction may contribute to the prodysrhythmic effects of these drugs particularly in patients

with history of myocardial infarction, left ventricular dysfunction, or previous sustained ventricular tachycardia. Class IC drugs, especially flecainide, significantly depress inotropy and prolong the PR and QT intervals.

Class II

Class II drugs are beta-adrenergic receptor blockers. Beta-adrenergic receptor antagonists decrease the rate of spontaneous phase 4 depolarization, important in suppression of ventricular arrhythmias during ischemia and reperfusion. They are effective in the treatment of adrenergically mediated disease states, in which increased phase 4 depolarization, enhanced conduction velocity, and a shorter refractory period all contribute to increased automaticity. Beta-blockers decrease the rate of V_{max} of the action potential, prolongs its duration as well as the effective refractory period. Drug-induced slowing of the heart rate with resulting decreases in myocardial oxygen requirements is desirable in patients with coronary artery disease. Beta blockers slow the sinus rate, prolong AV-nodal conduction and enhance refractoriness. They prolong the PR interval on the ECG. Esmolol is used to convert atrial fibrillation with rapid ventricular response to normal sinus rhythm, or to maintain a slow ventricular rate. It also predictably reverses the fibrillation threshold lowering effects of catecholamines.

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Class III

Class III drugs are potassium channel blockers; for example, amiodarone, bretylium, sotalol. These drugs prolong cardiac repolarization, action potential duration, and the effective refractory period possibly by interference with sodium and calcium exchange. These effects are beneficial in preventing cardiac dysrhythmias by decreasing the proportion of the cardiac cycle during which myocardial cells are excitable and susceptible to a triggering event. Reentrant tachycardias may be suppressed if the action potential duration becomes longer than the cycle length of the tachycardia circuit.

- **Amiodarone** – In addition to class III effects, amiodarone exhibits class I Na^+-channel blocking, class II beta blocking, and class IV Ca^{2+}-channel blocking properties. It prolongs repolarization and cardiac action potential, it produces negative chronotropy in nodal tissues and as a Ca^{2+} and K^+-channel blocker, it slows SA-nodal conduction speed and prolongs refractory period. It is an α- and β-receptor antagonist with potent vasodilating and myocardial depressant potential. It may produce sinus bradycardia or heart block, necessitating administration of positive chronotropes or initiation of temporary pacing. Long-term side effects include pulmonary fibrosis, corneal microdeposits, liver cirrhosis, hyperthyroidism, or hypothyroidism.
- **Sotalol** – Sotalol is a mixture of isomers that possess similar class III effects, used for the treatment of atrial fibrillation or atrial flutter, as well as to treat ventricular arrhythmias. The L isomer of sotalol acts as a beta antagonist, whereas the D isomer may increase mortality in patients with ventricular dysfunction and recent myocardial infarction. Sotalol lacks intrinsic sympathomimetic activity or membrane-stabilizing properties. The lower incidence of dysrhythmia effects seen with amiodarone and racemic sotalol may be related to the beneficial class II effects.
- **Bretylium** is no longer available in the United States for clinical use.

Class IV

Calcium channel blockers: These agents act by inhibiting inward slow inward calcium currents that may contribute to the development of ventricular arrhythmias. These drugs are useful in the treatment of idiopathic ventricular tachycardias. Calcium channel blockers prolong neuromuscular blockade.

Prodysrhythmic Effects

Prodysrhythmia effects of antiarrhythmic agents describe bradydysrhythmias or tachydysrhythmias that represent new dysrhythmias associated with chronic antidysrhythmic drug treatment. Types of dysrhythmias include torsades de pointes, incessant VT, and wide complex ventricular rhythm.

Torsades de pointes (polymorphic VT) is the most common dysrhythmia and is triggered by early after-depolarizations in a setting of a delayed depolarization and increased duration of refractoriness manifesting as prolonged QT_c interval on the ECG. Class IA (especially quinidine) and class III drugs prolong QT_c by potassium channel blockade and provide the setting for torsades de pointes. Drug-induced torsades is often associated with bradycardia, because the QT_c interval is longer at slower heart rates. Exacerbating factors such as hypokalemia, hypomagnesemia, poor LV function, and concomitant administration of other QT-prolonging drugs are important predisposing factors in the development of torsades de pointes.

Incessant ventricular tachycardia may be precipitated by cardiac antidysrhythmic drugs that slow conduction of cardiac impulses (class IA and class IC) sufficiently to create a continuous ventricular reentry circuit. Incessant ventricular tachycardia is more likely to occur with high doses of class IC drugs and in patients with prior history of sustained ventricular tachycardia and poor LV function. Ventricular tachycardia due to this mechanism is generally slower because of the drug effect, but may be resistant to drugs or electrical therapy.

Wide complex ventricular rhythm is usually associated with class IC drugs in the setting of structural heart disease with excessive plasma concentrations or abrupt changes in the dose. Wide complex rhythm is thought to reflect a reentrant tachycardia and easily degenerates to ventricular fibrillation.

11.2.3 Antianginal Drugs: Coronary Vasodilators and Cardioinhibitory Drugs

Under normal physiological conditions oxygen delivery (DO_2, the amount of oxygen delivered to the cells) is adequate to meet cellular oxygen demand (VO_2, the amount of oxygen extracted from arterial blood) and maintain aerobic metabolism. The ratio of oxygen consumption to the oxygen available to tissues is the oxygen extraction ratio, which varies for different organs. During periods of increased workload and increased cellular demand, and/or decreased supply, aerobic metabolism can still be maintained independently of blood flow by increasing O_2 extraction. Critical O_2 delivery is the point at which the extraction ratio is maximized, and any further incongruence between demand and supply will lead to tissue hypoxia and subsequent activation of anaerobic metabolic pathways. When myocardial oxygen consumption exceeds the reserve in coronary blood supply to meet a given O_2 demand, ischemia is precipitated. The heart's high, 60–70% O_2 extraction ratio (compared to 25–30% for the rest of the body) can make it susceptible to even short periods of ischemia.

The major determinants of myocardial O_2 *supply* are coronary blood flow and arterial O_2 content. Coronary blood flow is further determined by the patency of the coronaries, coronary perfusion pressure, and coronary vascular resistance. The 3 major determinants of myocardial O_2 *demand* are heart rate, inotropic state, and wall tension (which is the function of intracavitary pressure, radius, and wall thickness, as well as preload and afterload). Antianginal pharmacotherapy is indicated when the supply/demand imbalance results in ischemia. In accordance with the 2014 American College of Cardiology/American Heart Association (ACC/AHA) Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes, standard medical therapy includes the use of beta blockers, nitroglycerin, calcium channel blockers, analgesics, and cholesterol management. This section will focus on role of nitroglycerin, beta-blockers and calcium channel blockers in the management of angina pectoris.

Coronary Vasodilators

Nitroglycerin

Nitroglycerin (NTG) is an endothelium-independent smooth muscle relaxant that acts predominantly on venous capacitance vessels and large epicardial coronary arteries, maximizing blood flow to the subendocardial areas. Peripheral venodilatory effects are prominent even at low doses and are not dose-dependent, whereas dilation of peripheral conductance and resistance vessels occur at higher doses, and further increases in dose result in more pronounced vasodilation. Nitroglycerin reduces myocardial O_2 demand and increases oxygen supply by reducing preload and decreasing ventricular dimension and wall tension, dilating normal and atherosclerotic coronary arteries, and enhancing collateral circulation. The degree to which coronaries are able to dilate is dependent on their baseline vascular tone. Nitroglycerin produces a dose-dependent systemic and pulmonary arterial vasodilatory effect, and predictably decreases cardiac filling pressures. Its use is indicated for initial treatment of nearly all types of myocardial ischemia, as well as for managing hypertension and heart failure. Elimination half-life of nitroglycerin is approximately 1.5 min.

Mechanism of Action

NTG enters the smooth muscle cells and generates nitric oxide through a glutathione-dependent pathway, which stimulates cyclic GMP production and causes peripheral vasodilation via a sequence of protein phosphorylation and dephosphorylation within the smooth muscle. Nitric oxide production via guanylate cyclase stimulation and cGMP production is a sulfhydryl (SH)-group dependent process. Depletion of SH-groups by prolonged exposure leads to dose- and duration-dependent tolerance, which may manifest within the first 24 hours of treatment. Restoring SH-supplies with reducing agents (for example, N-acetylcysteine) does not reliably reverse nitrate tolerance, therefore a drug-free interval of 12–24 hours is recommended to maintain drug efficacy. Rebound myocardial ischemia may occur during drug-free intervals.

Common Clinical Use

Nitroglycerin is available in intravenous (IV), sublingual, or topical formulations. A typical IV dose to treat acute ischemia is 50–10 mcg. For a continuous infusion, the dose range is 0.1–7 mcg/kg/min.

Adverse Effects

Nitroglycerin at low doses causes predominantly splanchnic venodilation that results in venous pooling, decreased cardiac filling, and decreased biventricular end-diastolic volume and pressure. Excessive decreases in diastolic blood pressure may decrease coronary blood flow and trigger reflex tachycardia and increased contractility mediated by the baroreceptor reflex. The combination of decreased coronary blood flow and increased myocardial O_2 demand may provoke angina pectoris. With administration of intravenous phenylephrine, adequate coronary perfusion pressure can be maintained.

In the lungs, nitroglycerin inhibits hypoxic pulmonary vasoconstriction and worsens hypoxia and gas exchange. It has been shown to have platelet-inhibitory effects, the clinical significance of which has not been elucidated.

Although an uncommon complication of nitroglycerin therapy, the nitrite metabolite of NTG is capable of oxidizing the ferrous (Fe^{2+}) ion in the hemoglobin into the ferric (Fe^{3+})

state, producing methemoglobin. Ferric (oxidated) iron is unable to carry O_2 effectively, and in sufficiently high concentrations (> 40%) it can impair tissue oxygenation. Treatment of methemoglobinemia is methylene blue, to facilitate the conversion of methemoglobin to hemoglobin. High doses of NTG is more likely to produce methemoglobinemia in patients with hepatic dysfunction.

The 2014 ACC/AHA guidelines recommend that nitrates should not be administered to patients with non-ST-elevation-acute coronary syndrome (ACS) who recently received a phosphodiesterase inhibitor (class III, level of evidence: B). Nitrates should not be administered to patients with signs of hypovolemia or hypotension, and it should be used with caution in patients with right ventricular infarction.

Cardioinhibitory Drugs

Beta-Adrenergic Blockers

As discussed in the previous section, beta-blockers are class II antiarrhythmics with a multitude of favorable properties utilized in the treatment of cardiac ischemia. Their negative inotropic, negative chronotropic, and antihypertensive properties allow for reduction in O_2 consumption and an increase in blood supply during diastole. Beta blockers slow spontaneous diastolic depolarization and shorten the duration of cardiac action potentials. Ventricular fibrillation threshold is increased. Beta blockers reduce myocardial infarct size. In the absence of contraindications (cardiogenic shock, decompensated heart failure, severe sinus bradycardia, second- or third-degree atrioventricular block, or active bronchospasm), beta blockers should be administered early in the treatment of myocardial ischemia. While early administration has not been shown to improve short-term survival, beta blockers decrease reinfarction and the frequency of ventricular dysrhythmias, and their use has been associated with mortality benefit after myocardial infarction. Perioperative beta blockers should be continued in patients already receiving beta blockers, according to class 1 indications for perioperative beta blockade from the 2014 ACC/AHA recommendations; patients at high perioperative risk for adverse cardiac events should be started on beta blockers preoperatively, and continued up to 30 days postoperatively. In these patients, it is reasonable to titrate beta blockers to heart rate and blood pressure.

Mechanism of Action

Beta blockers are competitive, reversible inhibitors of beta adrenergic receptors. Beta adrenergic receptors are G-protein coupled receptors. Stimulation by their agonists activates adenylate cyclase to produce cyclic AMP. Cyclic AMP in turn activates protein kinases pathways with subsequent phosphorylation of L-type calcium channels and troponin C, the net effect being enhanced inotropy, positive chronotropy and dromotropy. These responses are all blunted by receptor occupancy by beta antagonists.

- **Propranolol** – Propranolol is a non-selective β(beta)-1 and β(beta)-2 receptor blocker with no alpha-receptor activity. As the most soluble beta blocker, its use is associated with the highest frequency of central nervous system side effects. It is well absorbed when taken by mouth. For a comparable effect, higher oral than intravenous doses are required due to its very high (90%) hepatic first-pass metabolism. Its active metabolite does not add to the primary clinical effect due to its short half-life. Propranolol decreases cardiac output by decreasing the heart rate and reducing myocardial contractility, effects that are especially prominent in sympathetically driven disease states. Owing to its β(beta)-2 receptor antagonism, propranolol may increase systemic vascular and coronary vascular resistance. Increased airway resistance may be evoked by propranolol in asthmatic patients. Renal and hepatic blood flow is reduced with the administration of propranolol.
- **Metoprolol** – Metoprolol was the first β(beta)-1 selective receptor antagonist used in clinical practice to prevent increased chronotropy and inotropy in response to sympathetic stimulation. Its receptor selectivity is dose related. Metoprolol is lipid-soluble, it diffuses more readily into ischemic regions than hydrophilic drugs. Fifty percent of the drug administered is metabolized during first-pass hepatic metabolism. At the intravenous dose of 0.2 mg/kg, maximum beta receptor blockade is achieved.
- **Esmolol** – Esmolol is a short-acting cardioselective agent metabolized rapidly by red blood cell esterases. It is primarily a β-1 blocking agent, producing significant decreases in heart rate and contractility. It lacks the ability to block peripheral vascular β-2 receptors, therefore decreases in blood pressure and cardiac index is more pronounced due to unopposed peripheral vasodilation. Esmolol has been safely used in patients with reactive airway disease.
- **Sotalol** – Sotalol is a class III antiarrhythmic agent with both β-receptor and K^+-channel antagonistic effects. A relatively recent Cochrane database review found significant reductions in incidence of postoperative atrial fibrillation in the cardiac surgical population. Despite the conclusions of this review, the use of sotalol in the post-cardiac surgical population remains limited, owing to sotalol's undesired side effects, such as hypotension, bradycardia, QT-prolongation, and inducing torsade-type ventricular arrhythmias.

Calcium Channel Blockers

Calcium channel blockers (CCBs) comprise a diverse group of agents that selectively inhibit calcium influx into myocardial and vascular smooth muscle cells. Dihydropyridines (such as nifedipine, nicardipine, nimodipine, amlodipine, felodipine, isradipine) exert their effect on the peripheral arteriolar beds (nimodipine favors cerebral vessels), and produce marked peripheral vasodilation with little direct effect on heart rate, AV conduction, and inotropy. They may elicit reflex sympathetic activation via the baroreceptor reflex. Non-dihydropyridines (phenylalkylamines, for example, verapamil; and benzothiazepines, for example, diltiazem), on

the other hand, block AV nodal calcium channels, and have significant negative inotropic, chronotropic, and dromotropic effects. Their main anti-ischemic effects are due to their ability to reduce myocardial O_2 consumption by depressing contractility, decreasing heart rate and systemic afterload, and increasing O_2 supply by coronary and collateral vasodilation. Calcium channel blockers are preferred in vasospastic (variant) angina, as beta-blockers may provoke or aggravate ischemia in some patients. All calcium channel blockers are effective in the treatment and prevention of coronary vasospasm. They may reduce reinfarctions and long-term events in hypertensive patients with acute myocardial infarction.

Calcium Channels

Calcium channels display selectivity to calcium ions, and are present among others in myocardial, smooth muscle, skeletal muscle, and neural tissues, as well as in membranes of subcellular organelles, such as the mitochondria or the sarcoplasmic reticulum. Calcium channel blockers bind to voltage-gated transient (T), long (L) type channels in the myocardium and smooth muscle, or to neural (N) type channels, rendering them inactive. T-type calcium channels are activated at low voltages, play a major role in the phase 0 depolarization, and are not affected by calcium channel blockers. L-type channels are activated at higher voltages, playing a role in the phase 2 plateau of the cardiac action potential. These are the Ca^{2+}-channels that are able to be blocked by calcium antagonists.

Dihydropyridines: Smooth-Muscle-Selective Vasodilators

Dihydropyridines prevent calcium entry into the vascular smooth muscle cell by *extracellular modulation* of the L-type channels. The primary target of dihydropyridines is the peripheral arteriolar bed except for nimodipine, which favors cerebral vessels. Reflex tachycardia may be elicited with their use. Examples include nifedipine, nicardipine, nimodipine, amlodipine, and felodipine. The predominant action of these agents is decreasing systemic, coronary, and cerebrovascular vasomotor tone. Dihydropyridine calcium channel blockers, with the exception of the primarily antianginal nifedipine, will be discussed later.

- **Nifedipine** – Nifedipine was the first dihydropyridine calcium channel blocker in clinical use for its coronary and peripheral vasodilator properties. It has greater coronary and peripheral vasodilatory properties than verapamil with negligible effects on venous capacitance vessels. It has little or no effect on cardiac impulse generation and on SA and AV nodal conduction. Peripheral vasodilation and the resultant decrease of systemic blood pressure activate baroreceptors, leading to reflex sympathetic nervous system activity manifesting as tachycardia. In the absence of concomitant beta-receptor blockade, it may increase the risk of myocardial infarct or recurrent angina. Excessive peripheral vasodilation can be antagonized with phenylephrine. It may be combined with beta blockers without increasing the risk of AV-block. Nifedipine is used in angina pectoris due to coronary artery vasospasm. No IV preparation is available due to its extreme instability when exposed to light. Its abrupt discontinuation has been associated with coronary artery vasospasm.

Non-Dihydropyridines: Antiarrhythmics

Phenylalkilamines

Phenylalkilamines bind to the *intracellular portion* of the L-type calcium channel when it is in the open state, and occlude the channel.

- **Verapamil** – Verapamil is a synthetic derivative of papaverine. It is supplied as a racemic mixture, in which the D-isomer lacks Ca^{2+}-channel blocking properties and acts as a fast Na^+-channel blocker, accounting for local anesthetic effects, and the L-isomer is specific for slow Ca^{2+}-channels. The predominance of this action accounts for the classification of this drug as a calcium channel blocker. Verapamil decreases the heart rate by depressing sinoatrial and AV-nodal activity (hence its utility in the treatment of supraventricular arrhythmias), lowers systemic blood pressure due to myocardial depression and peripheral vasodilation, and produces moderate coronary artery dilation (preferred in essential hypertension and vasospastic angina). Its negative inotropy is more pronounced in patients who already have a depressed left ventricular function, therefore verapamil should be avoided in symptomatic heart failure, severe bradycardia, sinus node dysfunction, and AV nodal block. These effects of verapamil may be enhanced with concomitant β(beta)-blockade. In the presence of drug-induced heart block, isoproterenol may be useful to increase heart rate. Verapamil may also precipitate dysrhythmias in patients with Wolff-Parkinson-White (WPW) syndrome, and has proven effective in the treatment of hypertrophic cardiomyopathy with or without left ventricular outflow tract (LVOT) obstruction. Verapamil may be useful in the treatment of premature labor, as well as fetal and maternal tachydysrhythmias. It may decrease uterine blood flow, and should be administered with caution to parturients with impaired uteroplacental perfusion.

Benzothiazepines

Benzothiazepines block L-type channel via a mechanism that is not well understood. Diltiazem may act on the Na^+/K^+ pump, decreasing the amount of intracellular Na^+ available for exchange with extracellular calcium, and it may inhibit the calcium-calmodulin binding.

- **Diltiazem** – Diltiazem, like verapamil, blocks the calcium channels at the AV node. It is considered first-line treatment for supraventricular tachydysrhythmias. It may also be used for the control of chronic essential hypertension. Diltiazem has minimal cardiodepressant effects and is unlikely to interact with β-blockers to decrease contractility.

11.2.4 Inotropes and Vasopressors

Adrenergic Receptors

Alpha and beta adrenergic receptors are G-protein-coupled receptors present on various types of cells: pre-and post-synaptic sympathetic nerve terminals; as well as cardiac, skeletal, or smooth muscle cells; hepatocytes; pancreatic islets (beta cells); adipose tissue; platelets; and the renal juxtaglomerular apparatus. They bind endogenous and synthetic catecholamines. There are 2 discrete types of adrenergic receptors, each with several subtypes: alpha and beta.

Alpha receptors are predominant on the peripheral and pulmonary vasculature. They have 2 subtypes, α-1 and α-2. The α-1 subtype is G_q protein-coupled, expressed by smooth muscle, adipose tissue, the liver, sweat glands, and the kidneys. G_q protein-coupled receptors activate the phospholipase C (PLC) pathway: PLC cleaves phosphatidylinositol 4,5-bisphosphate (PIP_2) into diacyl-glycerol (DAG) and inositol triphosphate (IP_3). IP_3 in turn interacts with intracellular calcium stores and increases the intracellular calcium content. DAG activates protein kinase C, which further modulates ion channels. Stimulation of α-1 receptor results primarily in vascular smooth muscle contraction. Other effects include contraction of the pregnant uterus, contraction of urogenital smooth muscle (bladder neck, prostate), bronchoconstriction, mydriasis, glycogenolysis and gluconeogenesis, secretion from sweat glands, and renal sodium reabsorption.

Alpha-2 receptors are G_i-coupled receptors expressed by central presynaptic nerve terminals. G_i-proteins inhibit the production of cAMP from ATP, reduce Ca^{2+} permeability, and increase K^+ permeability. Presynaptic neuronal α_2 agonists cause inhibition of acetylcholine as well as norepinephrine release by negative feedback from norepinephrine present in the synaptic cleft. Stimulation of central presynaptic α_2 receptors inhibits sympathetic nervous system output and causes sedation. Peripheral α_2 receptor stimulation causes decreased insulin secretion from pancreatic beta cells, inhibition of lipolysis, platelet aggregation, and vascular smooth muscle contraction.

Beta-1 adrenergic receptors are found on the sinus node, AV-node, and the myocardium. These are G_s-protein coupled receptors and are expressed predominantly in the cardiac pacemaker cells, myocardium, salivary glands, as well as eccrine and apocrine sweat glands. Their stimulation activates adenylate cyclase, increasing intracellular cAMP-synthesis. cAMP as a second messenger activates intracellular signaling pathways that result in increased Ca^{2+} levels during systole. Calcium binds to troponin C, facilitates actin-myosin cross-bridge formation, and increases sarcomere contraction. This translates into faster heart rate, increased myocardial excitability, increased conductivity, and more forceful contractions.

Beta-2 receptors are located on the smooth muscle of the bronchial tree, some coronary vessels, skeletal muscle arteries, gastrointestinal tract, and the urinary bladder. Stimulation of a β_2 receptor may activate 2 G-proteins that regulate adenylate cyclase differently: the excitatory G_s and the inhibitory G_i proteins. Stimulation of the Gi protein results in decreased smooth muscle tone.

Adrenergic Receptor Agonists

Epinephrine

Epinephrine is an endogenous catecholamine produced by the adrenal medulla. It is a potent direct α_1-, α_2-, β_1-, and β_2-adrenergic agonist. In all dose ranges it has strong positive inotropic effects. Peripheral vascular resistance varies according to the dominant effect of the receptors activated: at low doses ($\beta > \alpha$) SVR is usually decreased. At moderate doses (β comparable to α), SVR may remain unchanged. At high doses ($\alpha > \beta$), SVR is increased. It increases myocardial oxygen consumption.

1. **Hemodynamic effects**
    1. Preload: increased due to α_1-effect on capacitance vessels
    2. Contractility: augmented due to β_1-effect on the myocardium; its lusitropic effects account for an enhanced rate of relaxation.
    3. Lusitropy: as a β_1-agonist, epinephrine enhances early diastolic filling by accelerating relaxation, augmenting filling, and reducing end-systolic ventricular size.
    4. Afterload: dose-dependent effect. Pulmonary hypertension may occur.
    5. Heart rate: tachycardia due to β_1-effect, increased excitability and conduction, increased risk of arrhythmias.
    6. Cardiac output: augmented.
2. **Common clinical use:** first-line agent in the treatment of asystole or cardiac arrest due to ventricular fibrillation; cardiogenic shock when administered with a vasodilator (for example, nicardipine or milrinone); low cardiac output after separation from cardiopulmonary bypass; drug of choice in anaphylaxis and anaphylactoid reactions; severe asthma due to its β_2 effects. It is not currently recommended as first-line pressor in the management of sepsis.
3. **Administration:** by central intravenous line via controlled infusion device. Peripheral extravasation may cause skin necrosis; via endotracheal tube (ETT); subcutaneously for mild allergic reactions or bronchospasm.
4. **Adverse effects:** hypertension, tachycardia, arrhythmias, decreased peripheral perfusion (kidney function, urine output, extremity perfusion should be monitored).
5. **Warnings/contraindications:** There are no contraindications to the use of epinephrine in a life-threatening medical emergency. Contraindications include: narrow angle glaucoma, labor, thyrotoxicosis. Epinephrine should be used with caution in patients with the following conditions: severe coronary artery disease, angina pectoris, irritable myocardium, diabetes, cerebrovascular insufficiency, thyroid disease, pregnancy. Rapid

administration, for example, in cardiac arrest, may cause devastating cerebrovascular hemorrhage. Clostridium gas gangrene has been reported after intramuscular injection for anaphylaxis, injection into the buttock should therefore be avoided. Hypovolemia should be corrected before administration. End-organ ischemia (myocardial, renal) may result with prolonged administration at high infusion rates. Epinephrine inhibits uterine contractions especially during the second stage of labor.

Norepinephrine

Norepinephrine (NE) is an endogenous catecholamine produced by the adrenal medulla and sympathetic neurons, which stimulates both alpha and beta adrenergic receptors, and acts as both a hormone and the primary postsynaptic sympathetic neurotransmitter. Its pharmacologic effects are predominant on peripheral α_1 receptors, resulting in vasoconstriction of both resistance *and* capacitance vessels. In most dose ranges, norepinephrine increases mean systemic and pulmonary arterial blood pressure. In low dose ranges, its less potent β_1 effects—translating into increased heart rate, positive inotropy, and a mild increase in cardiac output—become noticeable. Norepinephrine does not have significant β_2 effects.

1. **Hemodynamic effects:**
    1. Preload: NE recruits cardiac preload reserve and reduces preload dependency in patients with septic shock.
    2. Contractility: augmented.
    3. Lusitropy: as a β_1-agonist, norepinephrine enhances early diastolic filling by accelerating relaxation, augmenting filling and reducing end-systolic ventricular size.
    4. Afterload: increased SVR and PVR. Increased systolic, diastolic and mean arterial pressure.
    5. Heart rate (HR): varies, depending on blood pressure. Positive chronotropy is usually offset by reflexive increase in vagal tone in response to increased blood pressure. Heart rate may increase if hypotension persists.
    6. Cardiac output: increased or unchanged (depending on HR)
2. **Common clinical use:** peripheral vasoconstrictor. Agent of choice in septic shock and other states where normal sympathetic tone is lost. Short-term hemodynamic support in nonhypovolemic shock.
3. **Administration:** via central venous line, typical starting dose 0.03 mcg/kg/min via controlled infusion device.
4. **Adverse effects:** peripheral vasoconstriction reduces peripheral organ perfusion and risks ischemia. May precipitate arrhythmias or coronary vasospasm. May worsen pulmonary hypertension.
5. **Warnings and contraindications:** Contraindicated as a sole therapy in hypovolemic patients.

Dopamine

Dopamine is an endogenous catecholamine, a precursor to epinephrine and norepinephrine, found in the adrenal medulla and peripheral nerve terminals. It has effects on alpha, beta, and dopaminergic (DA) receptors. At the lowest doses (1–3 mcg/kg/min) its dopaminergic effects are dominant, resulting in the dilation of the cerebrovascular, renal, and mesenteric vascular beds. In low to moderate dose ranges its β_1-adrenergic effects are predominant, resulting in increased heart rate, increased contractility, and increased cardiac output. At high doses (greater than 10–20 mcg/kg/min) its α_1-agonist effects predominate: high-dose dopamine increases SVR, PVR, and decreases peripheral perfusion. It is an effective mixed inotrope and vasoconstrictor; however, it is not recommended as first-line therapy in the treatment of septic shock due to the side effects associated with its use. Dopamine has positive chronotropic effects in all dose ranges, and in higher dose ranges it may induce arrhythmias due to increased excitability and conduction. It does not have significant β_2 effects. Dopamine causes less increase in O_2 consumption than isoproterenol.

1. **Hemodynamic effects:** Direct agonist on α_1, β_1, β_2, and DA-receptors. Indirectly, it increases norepinephrine levels by its conversion into norepinephrine and by inducing norepinephrine release from storage sites. In low doses, it redistributes blood flow from skeletal muscle to the kidneys and mesentery.
    1. Preload: dopamine increases venous return.
    2. Contractility: augmented.
    3. Lusitropy: as a β_1-agonist, dopamine enhances early diastolic filling by accelerating relaxation, augmenting filling, and reducing end-systolic ventricular size.
    4. Afterload: increases SVR and PVR. Dopamine usually widens pulse pressure by increasing systolic, and to a much less extent, the diastolic pressure. At low doses, dopamine produces renal and mesenteric vasodilation. At high infusion rates, renal perfusion is decreased.
    5. Heart rate: increased,
    6. Cardiac output: augmented,
2. **Common clinical use:** treatment of hypotension due to low SVR or cardiac output. May be the first choice for temporizing hypotension until intravascular volume is restored. Current evidence discourages its use to treat kidney insufficiency or failure as it provides no mortality benefit or risk reduction.
3. **Administration:** IV only, preferably via central venous line via controlled infusion device, typical dose range 1–20 mcg/kg/min,
4. **Adverse effects:** Dopamine increases myocardial work without compensatory coronary vasodilation, and increases the size of myocardial ischemia; increases risk of arrhythmia.
5. **Warnings and contraindications:** In patients with prior history of occlusive peripheral vascular disease, dopamine may elicit peripheral circulatory insufficiency.

Monoamine oxidase (MAO) inhibitors may potentiate and prolong the effects of dopamine. Extravasation may result in skin necrosis. Contraindications to dopamine's use include hypersensitivity to dopamine, uncorrected tachyarrhythmias, ventricular fibrillation, uncorrected hypovolemic shock, and pheochromocytoma.

Dobutamine

Dobutamine is a synthetic derivative of dopamine that does not affect endogenous norepinephrine release. It is a racemic mixture of enantiomers of (−) dobutamine with vasoconstrictor (α_1-agonist), and (+) dopamine with vasodilator (α_1-antagonist) properties. It is a myocardial β_1-agonist with a predominant positive inotropic effect. Its β_2 and α_1 effects are limited, and it completely lacks α_2 effects. In the heart, it augments myocardial contractility and O_2 consumption, and increases cardiac output by increasing heart rate and stroke volume. Increased myocardial work is compensated by increased coronary blood flow. On all systemic vascular beds and pulmonary blood vessels it acts as a vasodilator and may cause hypotension. This is primarily mediated by its mild β_2 effects, which are partially unopposed by dobutamine's α_1 effects.

1. **Hemodynamic effects:**
    1. Preload: Dobutamine decreases venous resistance and mean systemic filling pressure. Left ventricular end diastolic pressure is decreased.
    2. Contractility: augmented.
    3. Lusitropy: dobutamine increases early peak diastolic filling rate in normal-weight patients, and this increase is linearly related to the increased heart rate. In obese patients, the correlation between heart rate and diastolic filling rate is lost as the rate of relaxation is significantly lower, suggesting that baseline relaxation reserve is impaired in obesity, and this impaired diastolic function is not resolved during stress.
    4. Afterload: decreased SVR and PVR. SVR may increase in the presence of β-adrenergic blockade.
    5. Heart rate: increased.
    6. Cardiac output: augmented.
2. **Common clinical use:** short-term inotropic support in low cardiac output states, especially in right ventricular failure, afterload reduction in left and/or right systolic heart failure (pulmonary congestion, cardiogenic shock; drug of choice in right heart failure), stress echocardiography. May be combined with dopamine to augment preload, contractility and systemic vascular resistance.
3. **Administration:** IV or IO, central venous administration is preferred via controlled infusion device. Typical dose range: 0.5–20 mcg/kg/min.
4. **Common side effects:** dose-dependent tachycardia and arrhythmias (less likely to induce tachycardia at therapeutic doses than dopamine or isoproterenol), angina pectoris, exaggerated hypertension (especially in patients with pre-existing hypertension), hypokalemia.
5. **Warnings/contraindications:** Contraindications to the use of dobutamine include hypersensitivity to dobutamine, dynamic left ventricular outflow tract obstruction such as in idiopathic hypertrophic subaortic stenosis/hypertrophic obstructive cardiomyopathy, pre-existing tachydysrhythmias or hypertension, acute coronary syndrome with ventricular irritability. Contraindicated as sole therapy in severely hypovolemic patients: Hypovolemia should be corrected before administration. May provoke atrial fibrillation with rapid ventricular response in patients with pre-existing atrial fibrillation.

Dopexamine

Dopexamine is a synthetic dobutamine-analogue with positive inotropy, positive chronotropy and peripheral vasodilator action, as well as minimal alpha-receptor activity. It is a potent agonist of DA1-receptors (and thus decreases renovascular resistance). It is indicated for treatment of low cardiac output states. It is widely used in Europe, but it is not approved by the Food and Drug Administration (FDA) in the United States.

Ephedrine

Ephedrine is an alkaloid-derivative with sympathomimetic effects. It has mild direct agonist on α_1-, β_1-, and β_2-receptors, and leads to indirect norepinephrine-release from the neurons. It is an easily titratable pressor and inotrope with a short duration of action that does not reduce placental blood flow, and is therefore safe to administer in pregnancy.

1. **Hemodynamic effects**
    1. Preload: increased due to β_1 effects on venous capacitance vessels.
    2. Contractility: increased.
    3. Lusitropy: likely enhances early diastolic filling by reducing end-systolic ventricular size.
    4. Afterload: increased.
    5. Heart rate: increased.
    6. Cardiac output: increased.
2. **Common clinical use:** correction of drug-induced hypotension and bradycardia under general anesthesia, or drug-induced sympathectomy with resultant relative hypovolemia and low SVR after placement of neuraxial block. May be used to temporize blood pressure in hypovolemia until intravascular volume is restored.
3. **Administration:** may be administered as an IV bolus via a peripheral vein. Typical dose: 5–10 mg titrated to target blood pressure. May be administered intramuscularly, subcutaneously, or by mouth.
4. **Adverse effects:** Its efficacy diminishes with the depletion of endogenous norepinephrine. The use of ephedrine increases the risk of malignant hypertension when used with cocaine or MAO-inhibitors. Tachyphylaxis may develop with repeated doses.
5. **Warnings/contraindication:** hypersensitivity to ephedrine. Overdose may manifest as convulsions, mydriasis, pulmonary edema, visual disturbances, pyrexia, hypertension, and tachycardia.

Phenylephrine

Phenylephrine is a synthetic noncathecolamine with nearly selective postsynaptic α_1 and minimal β effects. Due to its vasoconstrictor effects on resistance vessels, it is widely used for the treatment of intraoperative drug-induced hypotension. Its vasoconstrictor potency is less than that of epinephrine and norepinephrine. It is a direct α-agonist with short duration of action. It raises both systemic and pulmonary vascular resistance. Phenylephrine constricts coronary blood vessels and augments coronary blood flow. It constricts cerebral and renal vessels, but does not compromise blood flow to these organs. Phenylephrine may reduce renal, skeletal muscle, mesenteric, and skin blood supply. Myocardial O_2 requirement is usually unchanged unless hypertension is present. Vagally mediated reflex bradycardia commonly occurs as a response to increased vascular resistance and usually responds well to atropine; this response can be blocked by atropine. Its effects on cardiac output appears to be determined by preload-dependency.

1. **Hemodynamic effects:**
    1. Preload: Direct α_1-stimulation decreases venous capacitance and minimally increases venous return.
    2. Contractility: no direct effect.
    3. Lusitropy: unchanged.
    4. Afterload: increased SVR and PVR.
    5. Heart rate: unchanged or reflex bradycardia due to the aortic baroreceptor reflex. Phenylephrine is the adrenergic agonist least likely to elicit tachycardia.
    6. Cardiac output: unchanged in preload-independent patients, or decreased in preload-dependent patients.
2. **Common clinical use:** low SVR states, iatrogenic hypotension, nonhypovolemic shock, treatment of hypotension on patients with coronary artery disease, aortic stenosis, tetralogy of Fallot to counteract right-to-left shunting, or idiopathic hypertrophic subaortic stenosis. Although not harmful, phenylephrine is not the drug of choice in septic shock due to its decreased potency relative to norepinephrine.
3. **Administration:** IV, may be administered peripherally via the vein of the antecubital fossa via controlled infusion device; intramuscular (IM), subcutaneous (SC), intranasal.
4. **Adverse effects:** hypertension, reflex bradycardia, pulmonary edema, metabolic acidosis. An increased SVR may decrease stroke volume, subsequently decreasing the cardiac output.
5. **Warnings/contraindications:** Contraindications to the use of phenylephrine include hypersensitivity to phenylephrine or sulfites, severe coronary disease, severe hypertension, ventricular tachycardia, and close-angle glaucoma. Rarely it may provoke spasm of a coronary artery or a coronary bypass graft.

Isoproterenol

Isoproterenol is a pure direct β_1- and β_2-receptor agonist. It increases cardiac output by increasing heart rate, augmenting myocardial contractility as well as by afterload reduction. When inhaled, β_2-receptors mediate its bronchodilator effects.

1. **Hemodynamic effects:**
    1. Preload: increased.
    2. Contractility: augmented.
    3. Lusitropy: enhances early diastolic filling by reducing end-systolic ventricular size.
    4. Afterload: reduced SVR and PVR.
    5. Heart rate: increased.
    6. Cardiac output: increased due to increased heart rate and reduced afterload.
2. **Common clinical use:** bradycardia not responding to atropine in the absence of temporary pacemaker. Treatment of low cardiac output in cases when increased inotropy and chronotropy is needed; for example, in the denervated heart, in pediatric patients with fixed stoke volume, or ventricular aneurysm resection. Treatment of pulmonary hypertension. Status asthmaticus (continuous cardiac monitoring is required). β-blocker overdose. Heart block.
3. **Administration:** PO or IV: safe to administer via peripheral veins.
4. **Adverse effects:** tachycardia, arrhythmias, hypokalemia, dyspnea, pulmonary edema, angina pectoris.
5. **Warnings/contraindications:** Isoproterenol is contraindicated in digitalis intoxication, angina, preexisting ventricular arrhythmias. Not to be used for asystolic arrest. Isoproterenol may increase size of myocardial infarction, and may cause transient hyperglycemia.

Non-Adrenergic Vasoconstrictors: Vasopressin

Vasopressin

Vasopressin is a naturally occurring antidiuretic nonapeptide synthetized as a pro-hormone primarily in the supraoptic, and secondarily in the paraventricular nuclei of the posterior hypothalamus. After binding to carrier protein neurophysin, it is transported via the supraoptic hypophyseal tract to the posterior hypophysis, where it is stored and released into the circulation when plasma osmolality is higher than physiologic, or when profound hypovolemia is present. Normal plasma concentrations are less than 4 pg/ml. The half-life of endogenous vasopressin is 10–35 min, and it is metabolized via renal and hepatic pathways. Due to trypsin activity in the gastrointestinal tract it must be administered parenterally or intranasally. In concentrations higher than required for its antidiuretic effect, it acts as a non-adrenergic vasoconstrictor on peripheral vascular beds. It completely lacks beta-adrenergic effects; therefore, it produces less tachycardia compared to adrenergic agonists. In severe shock states, or in conditions where refractory vasoplegia is present, a deficiency in vasopressin levels may necessitate restoration of its physiological concentration by administration of low-dose exogenous vasopressin.

The effects of vasopressin are mediated by a family of G-protein coupled vasopressin receptors. V_{1a} and V_{1b} are G_q protein-linked, whereas V_2 is G_s protein-linked receptors.

V_{1a} is located primarily on the vascular smooth muscle of the systemic, coronary, splanchnic, and renal vessel bed, mediating pressor response by increasing peripheral vascular resistance. Intra-arterial infusion of vasopressin constricts all major celiac artery branches except the hepatic artery. A less well appreciated aspect is vasopressin's pulmonary vasodilatory effect by inducing constitutive endothelial nitric oxide synthase and increasing nitric oxide production. Vasopressin's vasodilatory effects are mediated by endothelial oxytocin receptors. V_{1a} is also expressed in diverse tissues such as hepatic, central neuronal, and myometrial tissues, as well as platelets. V_{1a} receptors are G_q-protein linked, activate phospholipase C, and ultimately increase intracellular calcium, leading to vasoconstriction. V_{1b} receptors activate adrenocorticotropic hormone (ACTH) release from the anterior pituitary gland.

V_2 receptors are located primarily in the distal tubules and collecting ducts of the kidneys, and play a role in the homeostatic regulation of plasma volume and preservation of serum osmolality. These receptors are Gs-protein-linked, and activate adenylate cyclase to ultimately increase intracellular cAMP levels. This in turn leads to mobilization of aquaporin 2 channels and their insertion into the luminal surface of the collection tubules, and the subsequent increase of water reabsorption. V_2 receptors are also expressed in endothelial cells, where they are involved in the release of von Willebrand factor (VWF) and factor VIII (F VIII). VWF protects F VIII from breakdown, and plays an important role in binding platelets to the site of bleeding.

1. **Hemodynamic effects:** adrenergic-independent direct peripheral vasoconstriction via V_{1a} receptors without affecting chronotropy or inotropy. Redistributes blood to the coronaries and the cerebral vasculature without β_1-induced increase in myocardial O_2 consumption.
    1. Preload: Vasopressin increases blood volume and venous return via constriction of capacitance vessels.
    2. Contractility: unchanged.
    3. Lusitropy: unchanged.
    4. Afterload: increased SVR; elevated systolic and diastolic pressures.
    5. Heart rate: unchanged.
    6. Cardiac output: unchanged or decreased due to increased SVR.
2. **Common clinical uses:** The 2015 AHA guidelines no longer recommend the use of vasopressin during advanced cardiac life support, and vasopressin has been removed from the adult cardiac arrest algorithm. Vasopressin is still recommended for the treatment of vasoplegia refractory to maximal catecholamine replacement such as in septic shock, vasoplegic syndrome after separation from cardiopulmonary bypass, residual ACE inhibitors/ARBs effect under general anesthesia.
3. **Administration:** In vasoplegic states: second-line agent, typical dose 0.02–0.04 units/minute via controlled infusion device.
4. **Side effects:** pallor, angina pectoris, bronchoconstriction, abdominal cramping, nausea, vomiting, uterine contractions, decreased platelet count, lactic acidosis.
5. **Warnings/contraindications:** Treatment is contraindicated in patients with hypersensitivity to vasopressin. In patients with coronary artery disease, peripheral vascular disease, heart failure, angina pectoris, migraine, and renal failure, vasopressin should be used with caution.

Phosphodiesterase-3 Enzyme Inhibitors

Milrinone

Milrinone is a noncatecholamine and nonglycoside inodilator with potent positive inotropic and vasodilator properties. It acts as a competitive inhibitor of phosphodiesterase-3 (PDE-3) in the cardiac and vascular smooth muscle cells, independently of β-adrenergic mechanisms. PDE-3 is an enzyme that hydrolyses intracellular cAMP into its inactive metabolite. Inhibition of the cAMP-breakdown allows for the cAMP levels to remain elevated. This in turn increases the Ca^{2+} influx into the myocardium, and increases Ca^{2+} efflux from the vascular smooth muscle, an effect translating into increased inotropy in the heart, and vasodilation of the peripheral arteries and veins. In the myocardium, milrinone augments contractility, facilitates diastolic relaxation, enhances automaticity, and shortens AV-nodal conduction time. Afterload reduction in the peripheral vessels usually has little effect on chronotropy. Overall, milrinone improves myocardial contractility, cardiac output, and ejection fraction. Myocardial O_2 consumption is unchanged or slightly increased.

1. **Hemodynamic effects:**
    1. Preload: decreased.
    2. Contractility: augmented.
    3. Lusitropy: augmented.
    4. Afterload: decreased SVR and PVR. Milrinone is primarily an afterload reducer.
    5. Heart rate: no direct effect; may induce supraventricular and ventricular arrhythmias or increase ventricular response rate in atrial fibrillation or flutter.
    6. Cardiac output: increased.
2. **Common clinical uses:** short-term treatment of low cardiac output syndrome, especially when the pulmonary capillary wedge pressure/left ventricular end diastolic pressure is elevated; may be considered as first-line therapy in decompensated congestive heart failure and evidence of pulmonary hypertension; depressed right ventricular function. Retains hemodynamic effects in the presence of beta-blockade.
3. **Administration:** by mouth, or through a central vein. When administered intravenously, milrinone should be administered with a loading dose (50 mcg/kg) over 10 min followed by slow continuous infusion by central intravenous line via controlled infusion device. Typical maintenance rate is 0.375–0.75 mcg/kg/minute. In renal impairment, the maintenance dose should be reduced.

4. **Adverse effects:** ventricular arrhythmias, supraventricular arrhythmia, hypotension, angina, rarely hypokalemia, bronchospasm, elevated liver enzymes, thrombocytopathy.
5. **Warnings/contraindications:** hypersensitivity to milrinone or inamrinone. Hemodynamics should be closely monitored. Liver function should be monitored during treatment with milrinone. Milrinone should be used with caution in patients with atrial fibrillation or flutter, due to positive dromotropy. It precipitates furosemide when administered in the same intravenous line.

Inamrinone

Inamrinone (formerly, amrinone; a selective competitive PDE-3 inhibitor) is another example of β-independent, noncatecholamine nonglycoside inotropes. It is a potent inodilator; its mechanism of action is similar to that of milrinone. It decreases preload and afterload, and enhances cardiac output. Generally, if any, there is little change in the myocardial O_2 consumption; the decreased ventricular wall tension and end-diastolic left ventricular pressure offsets the increased M_{VO2} resulting from increased cardiac output. This agent is losing popularity to milrinone due to milrinone's less pronounced effect on platelet function.

1. **Hemodynamic effects:**
   1. Preload: decreased. Inamrinone is primarily a preload reducer.
   2. Contractility: augmented.
   3. Lusitropy: augmented.
   4. Afterload: decreased. Mean arterial pressure (MAP) may or may not change, as the decrease in SVR and PVR may be offset by an augmented cardiac output.
   5. Heart rate: little or no change. At high doses, milrinone may potentiate atrial or ventricular arrhythmias.
   6. Cardiac output: increased.
2. **Common clinical uses:** severe decompensated congestive heart failure refractory to conventional therapy with diuretics, vasodilators, and inotropic agents. Effective in the presence of β(beta)-adrenergic blockade.
3. **Administration:** central IV infusion via controlled infusion device. Typical loading dose is 0.75–1.5 mg/kg, maintenance rate is 5–20 mcg/kg/minute. Incompatible with furosemide.
4. **Adverse effects:** arrhythmia (low risk), thrombocytopenia/thrombocytopathy, hypotension, hepatotoxicity with chronic administration.
5. **Warnings/contraindications:** hypersensitivity to inamrinone, milrinone or bisulfite preservatives. Inamrinone should be used with caution in patients with recent myocardial infarct, hypotension, severe aortic or pulmonic stenosis, or renal impairment. Inamrinone is not dialyzable.

Levosimendan

Levosimendan is a PDE-3 inhibitor that acts as an intracellular calcium-sensitizer to troponin C. It improves contractility in a calcium-dependent manner by binding to cardiac troponin C and stabilizing its calcium-induced conformational changes, and has vasodilatory effects by opening ATP-sensitive potassium (K_{ATP}) channels of the vascular smooth muscle. K_{ATP} channels close as intracellular ATP concentration increases, their selective blockade results in arteriolar vasoconstriction. Activation of K_{ATP} channels may also account for its anti-stunning effects without increasing intracellular calcium concentrations or energy consumption in the myocardium. The effects of levosimendan are greatest during systole when intracellular calcium levels are the highest, and diminish along with the decreasing intracellular calcium availability during diastole. Levosimendan acts independently of cAMP and has been used in beta-blocked patients. It does not increase myocardial oxygen consumption. It does not impair the baseline diastolic function and is tolerated without arrhythmogenicity. It is a systemic and coronary vasodilator used for treatment of acute decompensated congestive heart failure. The Levosimendan Infusion versus Dobutamine (LIDO) study demonstrated a significant survival benefit of levosimendan over dobutamine, and smaller studies described its benefits for pulmonary hypertension complicated by right ventricular failure. It is not FDA-approved for clinical use in the United States.

Papaverine

Papaverine is a nonspecific phosphodiesterase inhibitor, derived from opium; however, as a benzyl-isoquinolon, it is structurally and functionally unrelated to opioid alkaloids. It is used by surgeons to treat and prevent spasm of the internal mammary artery during cardiac surgery.

11.2.5 Antihypertensive Agents

Hypertension is a major risk factor for cardiovascular morbidity and mortality; essential hypertension accounting for the vast majority of adult cases. Based on recommendations of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7), the classification of blood pressure (BP) for adults has been as follows:

- Normal: Systolic lower than 120 mm Hg, diastolic lower than 80 mm Hg
- Prehypertension: Systolic 120–139 mm Hg, diastolic 80–89 mm Hg
- Stage 1: Systolic 140–159 mm Hg, diastolic 90–99 mm Hg
- Stage 2: Systolic 160 mm Hg or greater, diastolic 100 mm Hg or greater.

Antihypertensive pharmacotherapy is indicated when lifestyle modifications (weight loss; smoking cessation; limiting alcohol consumption; reducing dietary saturated fat and sodium intake; maintaining adequate dietary calcium, magnesium, and potassium intake; engaging in moderate intensity aerobic exercise for 30 min on most days) fail to achieve adequate blood pressure control. The updated eighth report of the JNC recommends treating to 150/90 mm Hg in patients over age 60 years; for everybody else, the goal BP is 140/90.

Diuretics, beta-blockers, angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and aldosterone antagonists are mainstays of pharmacologic management of essential hypertension. Specific antihypertensive classes target specific end-organ damage, hence the difference in drug combinations when coexisting risk factors are taken into consideration:

- Heart failure: diuretics, beta-blockers, ACE inhibitors/ARBs, aldosterone antagonists
- Post-myocardial infarction: beta-blockers, ACE inhibitors, aldosterone antagonists
- High coronary disease risk: diuretics, beta-blockers, ACE inhibitors, CCBs
- Diabetes: Diuretics, beta-blockers, ACE inhibitors/ARBs, CCBs
- Chronic kidney disease: ACE inhibitors/ARBs
- Recurrent stroke prevention: diuretics, ACE inhibitors

This section will focus on drugs used in the management of systemic hypertension, pulmonary hypertension, and heart failure.

Management of Systemic Hypertension

The primary determinants of blood pressure are cardiac output and peripheral vascular resistance. Cardiac output is maintained by heart rate and stroke volume. Stroke volume is determined by preload, contractility, and afterload, as well as the left ventricular and vascular compartmental size. Modulation of these factors by controlling input from vasoactive hormones, neurotransmitters, and local endothelium-derived factors will bring about a change in blood pressure: peripheral resistance is decreased by peripheral α-1 blockers, central α-2 agonists, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, diuretics, or direct vasodilators. Heart rate is modulated by beta-blockers, calcium channel blockers, or the novel agent ivabradine. Stroke volume is reduced by preload-reducer diuretics and venodilators, negative inotropy of calcium channel blockers, or afterload-reducing agents.

Peripheral α_1 Receptor Blockers

- **Labetalol** – Labetalol is a nonselective beta-blocker with selective α_1 receptor blocking properties. The potency of β-blockade is approximately 7-fold greater than α_1 blockade. Its partial β_2 agonism promotes peripheral vasodilation. Labetalol can be considered a peripheral vasodilator not triggering reflex tachycardia. In a dose-related fashion it decreases heart rate and peripheral vascular resistance, leaving the stroke volume and cardiac output unchanged. After oral administration labetalol is completely absorbed. Its significant first-pass metabolism produces inactive metabolites.
- **Phentolamine** – Phentolamine is a reversible nonselective competitive antagonist at the adrenergic α_1 and α_2 receptors, as well as at serotonin receptors. Its main action is arterial vasodilation with minimal venodilation. SVR and PVR is therefore decreased. Heart rate and contractility drastically increases due to both the baroreceptor reflex and phentolamine's direct effect on central presynaptic α_2 receptors, allowing for increased norepinephrine release and decreased reuptake. This results in unopposed β effects that may provoke arrhythmias and myocardial ischemia, and respond well to β-blockers. In patients pre-treated with phentolamine, administration of epinephrine may result in hypotension due to unopposed β_2 effects. Phentolamine is a gastrointestinal stimulant, may lower blood glucose, and causes histamine release. It is used for the diagnosis of pheochromocytoma (a drop in SBP >35 mm Hg and DBP >25 mm Hg is diagnostic for pheochromocytoma), management of hypertensive episodes associated with the resection of pheochromocytoma, as well as local treatment of skin necrosis associated with norepinephrine extravasation.
- **Phenoxybenzamine** – Phenoxybenzamine is a nonselective, noncompetitive adrenergic α_1- and α_2-antagonist at postganglionic synapses in smooth muscle and exocrine glands. Its main action is arterial vasodilation with minimal venodilation. It decreases SVR and PVR. Heart rate and contractility are increased due to both the baroreceptor reflex and phentolamine's direct effect on central presynaptic α_2 receptors, allowing for increased norepinephrine release and decreased reuptake. This results in unopposed β effects that may provoke arrhythmias and myocardial ischemia, and respond well to β-blockers. Phenoxybenzamine is available in PO form only. It is used for treatment of pheochromocytoma; it is started 10–14 days preoperatively to allow for expansion of blood volume. To avoid unopposed alpha-stimulation and life-threatening hypertensive episodes, β-blockers are not introduced until after adequate alpha-blockade. Due to its side effects—for example, orthostatic hypotension and tachycardia—especially after administering the initial dose, its dose should be increased slowly. Alpha- and beta-blockers should be continued until the morning of surgery.
- **Prazosin, Doxazosin, Terazosin, Tamsulosin** – Prazosin, doxazosin, terazosin and tamsulosin are selective α_1-antagonists. Their main cardiovascular action is decreasing SVR and PVR with only minimal increases in heart rate. Prazosin acts on arteries and veins. Prazosin and doxazosin are indicated for treatment of chronic hypertension. Terazosin blocks vascular α_{1B}, as well as α_{1A} receptors in the prostate and bladder neck. It is used for treatment of benign prostate hypertrophy (BPH) and hypertension. Tamsulosin is a selective α_{1A} receptor blocker used for symptomatic BPH and to help with passage of kidney stones. Orthostatic hypotension with syncope may occur with the use of peripheral α-blockers, especially after the first dose.

- **Tolazoline** – Tolazoline is a nonselective competitive α-adrenoceptor antagonist, structurally similar to phentolamine. It acts as a sympathomimetic and also stimulates muscarinergic ACh-receptors and causes histamine release. It decreases systemic and pulmonary vascular resistance. It markedly increases heart rate and may provoke arrhythmias due to its sympathomimetic effects and the reflex sympathetic activation associated with its use. Although it is used to treat persistent pulmonary hypertension in neonates, it is not a selective pulmonary vasodilator, and may worsen the SVR/PVR ratio when fixed pulmonary hypertension is present.

Central α_2 Receptor Agonists

Central α_2 receptor agonists reduce sympathetic outflow by stimulating bulbar α_2 activity and reducing peripheral norepinephrine release without eliciting reflex tachycardia and increased contractility. These agents potentiate the effects of anesthetics and may substantially reduce anesthetic and narcotic requirements. Central α_2 receptor agonists may exacerbate depression and are contraindicated for management of hypertension in patients treated with monoamine oxidase inhibitors.

- **Clonidine** – Clonidine is a centrally acting α-agonist with near selectivity on α_2-receptors (220:1 α_2 to α_1 effect). As a partial agonist-antagonist, it elicits submaximal response on central pre-and post-junctional α_2-receptors while blocking the effects of other agonists. It is a coronary vasodilator and acts as a sympatholytic—a property utilized to manage withdrawal symptoms in opioid and alcohol addicts. Clonidine effectively reduces SVR, PVR, and renal vascular resistance. Its half-life is 12 hours.
- Clonidine blocks pain signal transmission in the brain. It may potentiate opioid effects on the central nervous system and has local anesthetic properties. When administered epidurally, it produces dose-dependent analgesia not reversed by opioid antagonists—an effect utilized in the treatment of cancer pain. It doubles the duration of intermediate-duration local anesthetics when used as adjunct to peripheral nerve blocks. Due to risk of hypotension and bradycardia, epidural clonidine is not recommended in the perioperative, obstetric, and postpartum setting. It causes sedation in a dose-dependent manner. Due to lack of adequate data, it should not be administered above the C4 dermatome.
- Clonidine should not be discontinued abruptly, as rebound hypertension is frequently triggered. Its immediate-release oral formulations should be discontinued within 4 hours before surgery and resumed as soon as possible in the early postoperative period.
- **Methyldopa** – Methyldopa is a centrally acting antihypertensive. Its mechanism of action is not fully elucidated. Its antihypertensive effects are most likely due to its metabolism to α-methyl-norepinephrine, which stimulates central inhibitory α-receptors and lowers blood pressure by false neurotransmission and possibly by reducing plasma renin activity. It has no direct effect on cardiac and renal function. Reversible thrombocytopenia and leukopenia, hemolytic anemia, a positive Coombs test, and liver dysfunction including fatal liver necrosis has been reported with the use of methyldopa. Despite these adverse effect, methyldopa is still commonly used for the treatment of pregnancy-induced hypertension due to the lack of adverse effects of long-term treatment on the fetus.
- **Guanabenz** – Guanabenz is an oral antihypertensive active on central α_2-receptors. Its action is mediated by bulbar α_2 activation, leading to attenuated sympathetic outflow at the level of the brain stem. It effectively controls blood pressure without significant effects on renal function. It frequently causes sedation; therefore, additive sedative effects should be considered when used with other centrally acting depressants. Its abrupt discontinuation may rarely result in an increased production of endogenous catecholamines and subsequent rebound hypertension. In patients with coexisting liver and kidney disease, careful monitoring of blood pressure is recommended.
- **Guanfacine** – Guanfacine is a selective oral central postsynaptic α_{2A}–receptor agonist with a duration of action longer than that of clonidine. It reduces sympathetic outflow and with resultant decrease in heart rate and vasomotor tone. Guanfacine preferentially binds postsynaptic α_{2A}–receptors in the prefrontal cortex, and modulates behavioral responses. Its immediate release form is used for management of hypertension, whereas its extended release form is used for treatment of attention deficit/hyperactivity disorder as monotherapy or as adjunct to central nervous system stimulants. Its dose should be reduced with concomitant use with CYP3A4 inhibitors, and slowly increased with the use of CYP3A4 inducers.
- **Dexmedetomidine** – Dexmedetomidine is a selective central α_{2A} and peripheral α_{2B}–agonist with sedative and anesthetic properties. Centrally, it reduces sympathetic outflow and inhibits norepinephrine release at regular doses. At high doses, it activates peripheral α_{2B} receptors with resultant vasoconstriction, increased SVR, PVR, pulmonary artery occlusion pressure, and central venous pressure. Its use is indicated for procedural sedation for awake fiberoptic intubation, as well as sedation of intubated and mechanically ventilated patients in the intensive care unit. Its initial loading dose is 1 mcg/kg over 10 min, followed by a maintenance rate of 0.2–0.7 mcg/kg/hour, administered via a controlled infusion device, and titrated to effect. No dose adjustments are required in patients with severe renal impairment. In patients with severe hepatic impairment, dose reduction is recommended. It may cause episodes of hypotension, bradycardia, or sinus arrest. These adverse effects are enhanced in the presence of beta-blockers and antihypertensive agents, as well as in patients with advanced age, diabetes mellitus, pre-existing heart

block, bradycardia, hypovolemia, or depressed ventricular function. Limited information is available regarding its use in pregnancy. Dexmedetomidine is expected to cross the placenta.

Perioperative Management

Perioperative continuation of α_2 agonists are not recommended for prevention of major adverse cardiac events.

Angiotensin Converting Enzyme Inhibitors

When the circulating blood volume is low and renal perfusion is reduced (the afferent glomerular arteriolar pressure is decreased), the renal juxtaglomerular apparatus converts proenzyme prorenin into renin, which is then released into the circulation. Upon entering the circulation, renin cleaves a decapeptide from plasma protein angiotensinogen to produce angiotensin I, precursor to the potent vasoconstrictor angiotensin II. Angiotensin II (AT-II) is the primary vasoactive hormone of the renin-angiotensin system. It is generated from angiotensin I by the proteolytic action of angiotensin converting enzyme (ACE). It also stimulates aldosterone secretion by the adrenal cortex.

AT-II is therefore a potent vasoconstrictor of arteries and veins. It is responsible for increased aldosterone secretion and sympathetic nervous system stimulation. Angiotensin II normally binds to the AT1 receptor that ultimately leads to the increased release of calcium from sarcoplasmic reticulum to produce vasoconstriction. Besides its effects on vasomotor tone, AT II also mediates alveolar permeability and lung injury: excessive ACE inhibition is related to worse lung injury, an important consideration in the management of critically ill patients. Decreased generation of angiotensin II (for example, by inhibition of ACE) results in decreased vasoconstrictive effects, usually without eliciting reflex tachycardia or an increase in cardiac output. In addition, decreased concentrations of plasma aldosterone results in decreased sodium and water retention. ACE inhibitors block the AT-I to AT-II conversion, as well as the breakdown of bradykinin, an endogenous vasodilator substance, which contributes to the antihypertensive effects of these drugs. ACE inhibitors reduce activation of low density lipoprotein (LDL) receptors and decrease the concentrations of LDL cholesterol. If the concentration of LDL is already sufficiently low, ACE inhibitors may no longer be effective in reducing the rate of cardiovascular events.

ACE inhhibitors can be classified according to the structural element that interacts with the zinc ion of the enzyme, as well as the form in which the drug is administered (prodrug or active). Administration of ACE inhibitors (for example, benazepril, fosinopril, ramipril, or quinapril) as prodrugs increases the bioavailability prior to their hepatic metabolism to the active drug. Enalapril is the prodrug of the active ACE inhibitor enalaprilat, and its conversion may be altered in patients with hepatic dysfunction. Captopril, enalaprilat, and lisinopril are not prodrugs. The major difference among the clinically used ACE inhibitors is in duration of action.

In the absence of contraindications, ACE inhibitors and angiotensin receptor blockers are recommended in patients with systolic heart failure to reduce morbidity and mortality. They may be preferred in hypertensive patients with chronic kidney disease and/or diabetes mellitus. Unless contraindicated, ACE inhibitors are prescribed together with a beta blocker. Contraindications to the use of ACE inhibitors are prior life-threatening reactions (angioedema) and known or planned pregnancy. Caution should be used in the presence of low baseline blood pressure, elevated levels of serum potassium, increased serum creatinine, or bilateral renal artery stenosis.

Side Effects

Common side effects are cough, upper respiratory congestion, rhinorrhea, and allergic-like symptoms. It is speculated that these airway responses reflect potentiation of the effects of kinins due to drug-induced inhibition of peptidyl-dipeptidase activity and subsequent breakdown of bradykinin. If respiratory depression develops, prompt injection of epinephrine is advised. Angioedema is a potentially life-threatening complication of treatment with ACE inhibitors. Decreases in glomerular filtration rate may occur. For this reason, ACE inhibitors are used with caution in patients with preexisting renal dysfunction and are not recommended for patients with renal artery stenosis. Hyperkalemia is possible due to decreased production of aldosterone. The risk of hyperkalemia is greatest in patients with recognized risk factors (congestive heart failure with renal insufficiency). Measurement of plasma concentrations of potassium may be indicated in treated patients. ACE inhibitors are to be avoided in pregnancy due to their potential to induce oligohydramnios, other fetal developmental abnormalities, or fetal demise.

Perioperative Management

Although recent perioperative guidelines have suggested continuing ACE inhibitors/ARBs before non-cardiac surgery, adverse circulatory effects during anesthesia have been recognized in patients chronically treated with ACE inhibitors/ARBs, leading to the recommendation that these drugs be *discontinued* 24 hours before anesthesia and major, low-risk, urgent, or emergent surgery. Prolonged hypotension has been observed in patients undergoing general anesthesia for minor surgery in whom ACE inhibitor therapy was maintained until the morning of surgery. Surgical procedures with major fluid shifts have also been associated with hypotension in patients treated with ACE inhibitors.

Treatment with ACE inhibitors does not increase the incidence of hypotension after the induction of anesthesia in patients with infarction-induced myocardial dysfunction. Exaggerated hypotension attributed to continued ACE inhibitor therapy has been responsive to crystalloid fluid infusion and/or administration of sympathomimetics such as ephedrine or phenylephrine. If hypotension is refractory to treatment, treatment with vasopressin is usually effective. ACE inhibitors may increase insulin sensitivity and hypoglycemia, which is a concern when these drugs are administered to patients with diabetes mellitus.

- **Captopril** – Captopril is an oral vasodilator that inhibits the formation of angiotensin II in the lung. The subsequent decrease in plasma AT-II levels leads to decreased arterial and venous vasomotor tone, generally without eliciting tachyphylaxis or reflex hemodynamic changes.

  In common with all ACE inhibitors, captopril reduces preload and afterload on the heart. It promotes renal excretion of sodium and water, reducing the circulating blood volume. Treatment with captopril is associated with survival benefit after myocardial infarction, congestive heart failure, or hypertension. Captopril may delay the development of renal disease in patients with diabetes mellitus, and counteracts ventricular remodeling after myocardial infarction.
- Also in common with all ACE inhibitors, captopril may reversibly reduce kidney perfusion and decrease kidney function. Patients with bilateral renal artery stenosis are at risk for kidney failure. Due to suppressed aldosterone activity, hyperkalemia may occur. A common side effect is chronic nonproductive cough, secondary to the inhibition of the breakdown of bradykinin. Angioedema, a life-threatening condition potentially causing airway obstruction, is a rare adverse effect.
- **Enalapril and Enalaprilat** – Enalapril is an oral ACE inhibitor used for the treatment of hypertension and congestive heart failure. The therapeutic and side effects of enalapril are very similar to those of captopril. As an inactive prodrug, it first must undergo hepatic metabolism into its active form, enalaprilat.
- Enalaprilat is an intravenous ACE inhibitor, used primarily to treat severe hypertension. Its therapeutic and side effects are similar to those of captopril. It has a duration of action longer than nitrates, eliminating the need for continuous infusion. Enalaprilat decreases peripheral vascular resistance without eliciting reflex tachycardia, an increase in cardiac output and myocardial oxygen consumption.
- **Lisinopril and Ramipril** – Lisinopril and ramipril are oral ACE inhibitors—prodrugs used for the treatment of hypertension. They must first undergo hepatic metabolism into their active form. Their therapeutic and side effect profile is very similar to that of captopril. In renal insufficiency, dose adjustment is required.
- **Fosinopril** – Fosinopril is an oral ACE inhibitor used for the treatment of hypertension. It must be converted into an active metabolite in the liver and the gastrointestinal tract. It is eliminated by biliary excretion, therefore, unlike other ACE inhibitors, it does not need dose adjustment in patients with kidney insufficiency.
- **Perindopril, Trandolapril, Moexipril** – Perindopril, trandolapril, and moexipril are oral ACE inhibitors used for management of left ventricular dysfunction after myocardial infarct, as well as treatment of hypertension. These prodrugs must be hydrolyzed in the liver into their active metabolites. Their action and side effect profile is similar to that of captopril.

Angiotensin II Receptor Blockers

Angiotensin II levels may increase and maintain elevated blood pressure despite adequate treatment with ACE inhibitors, due to AT-II production via non-ACE-dependent pathways. Angiotensin II receptor blockers produce antihypertensive effects by blocking the vasoconstrictive actions of AT II without affecting ACE activity. Because these drugs do not inhibit ACE, they do not cause an increase in bradykinin, which contributes to some of the side effects, for example, dry cough and angioedema, of ACE inhibitors. Their effects and indications (hypertension, post-myocardial infarction and heart failure, prevention of renal insufficiency in diabetics) and are similar to angiotensin converting enzyme inhibitors.

ARBs are preload-and afterload-reducers, they downregulate sympathetic activity by blocking AT-II effect on peripheral norepinephrine release and reuptake, they act as diuretics and natriuretics by blocking aldosterone secretion, and counteract cardiac remodeling associated with hypertension, heart failure and myocardial infarction. ARBs may be preferred to ACE inhibitors in hypertensive patients with heart failure, ischemic heart disease, and/or post-myocardial infarction. Angiotensin receptor blockers are generally well tolerated with a low incidence of side effects and drug interactions. In common with ACE inhibitors, ARBs are contraindicated in pregnancy.

In the presence of bilateral renal artery stenosis, AT-II constricts the efferent glomerular arteriole more than the afferent arteriole, allowing for adequate glomerular capillary pressure and filtration. ACE inhibitors and ARBs eliminate this effect of AT-II. In the presence of at least 1 unaffected kidney, sufficient filtration can still be maintained even after AT-1 receptors are blocked; however, when a solitary kidney or bilateral renal artery stenosis is present, kidney function may worsen.

- **Losartan** – Losartan is an oral ARB indicated for the treatment of hypertension and lowering fatal and nonfatal cardiac and cerebrovascular events, especially when left ventricular hypertrophy is present. Both losartan and its first metabolite are active and effectively antagonize AT-II action on the AT-1 receptor. Volume and salt deficit should be corrected before treatment with losartan. In the presence of liver and kidney disease, or in patients whose kidney function depends on the activity of the renin-angiotensin-aldosterone system, dosage adjustment, withholding, or discontinuation may be required, and periodic monitoring of kidney function and potassium is necessary. It is contraindicated in pregnancy.
- **Valsartan** – Valsartan is an ARB used as monotherapy or in combination with amlodipine and/or hydrochlorothiazide for the initial management of hypertension and heart failure with reduced ejection fraction. It conveys morbidity and mortality benefit in clinically stable patients with symptomatic heart failure or left ventricular dysfunction after MI. Valsartan may be given as part of the standard post-MI regimen, along with aspirin, beta-blockers, statins, and thrombolytics. It is contraindicated in pregnancy.

- **Irbesartan** – Irbesartan is an oral ARB. Its indications, therapeutic and side effect profile is similar to that of losartan and valsartan.
- **Olmesartan, Candesartan, Telmisartan, Eprosartan** – Olmesartan and candesartan are taken as prodrugs, and are metabolized into their active form during their absorption from the gastrointestinal tract. Candesartan is the only ARB depending on its metabolism for clinical effect. Dose adjustment is required in the presence of kidney disease.
- Olmesartan, telmisartan, and eprosartan do not require dose adjustment in the presence of mild to moderate kidney disease.

Beta Receptor Blockers

Beta blockers have been shown to reduce mortality after myocardial infarction, congestive heart failure, hypertension, and chronic angina. The properties of these antiarrhythmic agents have been discussed previously. This section will briefly review the role of beta blockers in the treatment of hypertension and congestive heart failure.

Beta adrenoceptor antagonists blunt the effect of sympathetic stimulation on the cardiovascular system. The magnitude of this effect depends on the density of receptors at the effector sites, and the availability and relative concentration of both the agonist catecholamines, and the antagonist receptor blockers. Beta blockers inhibit myocardial and peripheral vascular β_1-receptors to reduce heart rate, contractility, and myocardial O_2 consumption. By decreasing heart rate, beta blockers increase diastolic filling time, and improve O_2 and substrate delivery to the left ventricle. By decreasing contractility, beta blockers reduce left ventricular ejection velocity and decrease shear forces on the aorta in the presence of dissection, and reduce dynamic ventricular outflow tract obstruction; for example, in hypertrophic obstructive cardiomyopathy or the tetralogy of Fallot. SVR may increase due to inhibition of β_2 vasodilation; beta blockers should therefore be used with caution in patients with peripheral vascular disease. Beta blockers are generally not preferred as a first-line agent for initial management of hypertension, but may be considered as add-on therapy in patients who do not respond adequately to treatment with other drug classes. They can precipitate congestive heart failure, especially when used with other myocardial depressants; for example, calcium channel blockers. Abrupt perioperative discontinuation of beta blocker therapy may produce rebound tachycardia and hypertension.

Traditionally, beta-receptor antagonists are classified on the basis of their relative selectivity for β_1- and β_2-receptors, the presence or absence of intrinsic agonistic (sympathomimetic) activity and their pharmacokinetic features.

Cardioselectivity

The first generation of beta blockers (propranolol) nonselectively blocked both β_1- and β_2-receptors. Second-generation cardioselective beta blockers have greater affinity for β_1- than for β_2-adrenoceptors, and are less likely to produce undesired side effects (bronchoconstriction, increased SVR). β_1-selectivity is dose-dependent; therefore, caution should be exercised when administering a beta-blocker to a patient with reactive airway disease.

Examples of cardioselective beta blockers: metoprolol, atenolol, bisoprolol, esmolol, betaxolol, and acebutolol.

Examples of nonselective beta blockers: labetalol, carvedilol, nadolol, timolol, sotalol, and propranolol. Timolol eye drops can produce systemic beta blockade.

- **Labetalol** – Labetalol is a long-acting nonselective beta-receptor blocker with selective alpha$_1$-receptor blocking properties. Its alpha$_1$ to beta receptor blocking ratio is 1:3 when administered by mouth, and 1:7 when administered intravenously. It produces dose-related vasodilation without eliciting reflex tachycardia. Labetalol decreases blood pressure and systemic vascular resistance. Heart rate may slightly increase; stroke volume and cardiac output remain unchanged. Due to its long duration of action, it is usually not preferred for intraoperative minute-to-minute control of hemodynamic variables.
- **Carvedilol** – Carvedilol is a nonselective beta-adrenergic blocking agent with selective activity on peripheral alpha$_1$ receptors. It is used for management of hypertension, either as monotherapy or in combination with other agents. Carvedilol has demonstrated survival benefit and is now also part of the standard treatment regimen for clinically stable patients who have survived the acute phase of MI and have a left ventricular ejection fraction of less than 40%. In hypertensive patients with left ventricular dysfunction (those who depend on beta-adrenergic stimulation in order to maintain cardiovascular compensation), the usual (lower) heart failure dosage applies (instead of that for hypertension). Contraindications to the use of carvedilol include high-degree atrioventricular block, bronchial asthma or other reactive airway disease, cardiogenic shock, decompensated congestive heart failure (CHF) requiring inotropes, severe liver dysfunction, and history of severe hypersensitivity reactions. Abrupt discontinuation of carvedilol may precipitate cardiac ischemia or malignant ventricular arrhythmias, as well as thyroid storm in patients with thyrotoxicosis.

Intrinsic Sympathomimetic Activity

Certain beta blockers may act as a competitive partial agonist-antagonist on peripheral β-receptors, and elicit a submaximal response at maximal occupancy. This phenomenon is referred to as intrinsic sympathomimetic activity, or ISA. These agents will prevent a beta-agonist from binding to its receptor, and will decrease blood pressure and systemic vascular resistance while resulting in less resting bradycardia and maintaining resting cardiac output than is observed with beta-blockers without ISA. Long-term treatment with agents with ISA result in a decrease of blood pressure due to

decreased vascular resistance, rather than decreased cardiac output. These agents may be useful in patients who are unable to tolerate excessive bradycardia resulting from treatment with beta blockers. Agents with ISA have not been shown to be beneficial after myocardial infarction and are not included in standard post-MI treatment regimens. They are less effective than other beta blockers in the treatment of angina and tachycardia.

Examples of beta blockers with ISA: pindolol and acebutolol.

Perioperative Management

Perioperative cardiac complications are not uncommon, with 2% of patients suffering major cardiac complications, and 8% showing evidence of significant myocardial injury. According to the 2014 ACC/AHA Perioperative Clinical Practice Guideline, continuation of long-standing beta blocker therapy is recommended. Beta blockers should not be started on the day of surgery in beta-blocker-naïve patients. In patients with intermediate or high perioperative risk, or in patients with at least 3 Revised Cardiac Risk Index (RCRI) risk factors, it may be reasonable to initiate beta blocker therapy at least 24 h prior to surgery. It may also be reasonable to initiate perioperative beta blocker therapy long enough in advance to assess safety and tolerability; however, it is uncertain whether starting beta blockers benefits those with long-term indications, but no other RCRI risk factors. In the perioperative setting, beta blockers have been confirmed to reduce the incidence of postoperative atrial fibrillation when started before or immediately after surgery. Initiation of beta blocker therapy prior to surgery is currently reserved for patients with significant coronary artery disease undergoing surgical coronary revascularization.

Calcium Channel Blockers: Dihydropyridines

Calcium channel blockers have a multifaceted profile of therapeutic effects. Calcium channel blockers are used primarily as anti-ischemic agents for treatment and prevention of stable angina pectoris. Common to all calcium channel blockers, but to a different extent in each class, they act as peripheral vasodilators without eliciting reflex tachycardia, they induce coronary vasodilation, they are negative inotropes, and have electrophysiologic depressant properties. The non-dihydropyridine diltiazem and verapamil are used for rate control in acute cardiac ischemia, when beta blockers are contraindicated. Most importantly, calcium channel blockers are first-line agents as potent coronary vasodilators in the treatment of Prinzmetal (variant, vasospastic) angina.

As discussed previously, dihydropyridines act on the peripheral arteriolar beds, and produce marked peripheral vasodilation with direct and indirect effect on heart rate, AV conduction, and inotropy. Examples are the rapid-acting antianginal nifedipine, the long-acting vasodilator nicardipine, the highly lipid-soluble nimodipine (favoring cerebral vessels), amlodipine, felodipine, or isradipine.

- **Nifedipine** – Nifedipine is primarily indicated in the management of Prinzmetal angina. Only its extended-release formulations are recommended for the treatment of hypertension, as well as the management of Raynaud's disease. Conventional (immediate-release) formulations are contraindicated in the management of acute myocardial infarction due to its negative inotropy and reflex sympathetic activation.
- **Nicardipine** – Nicardipine is a highly potent peripheral vasodilator that inhibits calcium influx into the myocardium and vascular smooth muscle. Nicardipine has no effects on the SA node and AV node. It produces clinically insignificant negative inotropy, and may be combined with a beta-blocker for the treatment of angina. This drug has the greatest vasodilating effects of all the CCBs, with vasodilation being particularly prominent in the coronary arteries. Because of all the antianginal drugs dihydropyridines produce the greatest peripheral vasodilation, either nifedipine or nicardipine may be useful in patients who have residual hypertension despite adequate beta-adrenergic blockade. Nicardipine produces dose-related decrease in both systolic and diastolic blood pressure. Nicardipine is frequently used as a tocolytic. When administered, it binds to the inside of the myometrial L-channels causing them to remain closed, and inhibiting uterine contractions. Pulmonary edema has been reported when nicardipine was used as tocolytic. Its use is contraindicated in patients with severe aortic stenosis: A decrease in diastolic pressure may worsen myocardial oxygen balance.
- **Nimodipine** – Nimodipine is a highly lipid-soluble analogue of nifedipine. This high degree of lipid solubility facilitates its penetration into the central nervous system, where it blocks the influx of extracellular calcium necessary for contraction of large cerebral arteries. This is especially valuable during the treatment and prevention of cerebral vasospasm after subarachnoid hemorrhage. Nimodipine has minimal negative inotropic effect on the myocardium.
- **Amlodipine** – Amlodipine is a dihydropyridine calcium antagonist only available in oral form, with minimal cardiodepressant effects. Its anti-ischemic effects are comparable to beta-blockers in patients with acute coronary syndrome. The combination of amlodipine and a beta blocker is more effective in the treatment of myocardial ischemia than either drug alone. Its actions are resembling those of nifedipine. It is used primarily for oral treatment of hypertension.
- **Felodipine** – Felodipine is primarily a peripheral vasodilator with no clinically significant negative inotropy. Its actions are resembling those of nifedipine. It is used for oral treatment of hypertension.
- **Isradipine** – Isradipine is a peripheral vasodilator with no clinically significant negative inotropy. Its actions are resembling those of nifedipine. It is used for oral treatment of hypertension.

Direct Vasodilators: Hydralazine, Nitroglycerine, Nitroprusside

- **Hydralazine** – Hydralazine is a direct systemic arteriolar vasodilator, with minimal venodilator (preload and postural) effects. Its mechanism of action is not fully understood. It appears to interfere with calcium movements within the cell that initiate and maintain the contractile state. Hydralazine decreases systemic blood pressure (systolic less than diastolic). Hydralazine may produce reflex sympathetic nervous system stimulation: It increases renin and AT-II activity, which leads to aldosterone stimulation and sodium reabsorption; tachycardia and increased myocardial contractility results in an increase in cardiac output, and may provoke angina. Patients with coronary artery disease should be monitored for myocardial ischemia. The use of hydralazine to treat pulmonary hypertension is not recommended since the associated systemic vasodilation may result in systemic hypotension. Hydralazine has a relatively slow onset of action with peak effect occurring by 20 min. With chronic PO use, a lupus-like reaction may occur.
- **Nitroglycerine** – Nitroglycerine is a direct coronary vasodilator with greater effects on the venous than on the arterial system. Its mechanism of action and effects are described in a previous section.
- **Nitroprusside** – Sodium nitroprusside (SNP) is a direct-acting, nonselective vasodilator. It is indicated for rapid correction of hypertensive emergencies. It produces vasodilation by directly increasing intracellular nitric oxide levels; its effects on arteries and veins are balanced. Nitroprusside lacks effect on nonvascular smooth muscle and the myocardium; however, reflex tachycardia and increased inotropy may occur, making it an undesirable drug of choice for the treatment of aortic dissection, where shear forces should be minimized. Its immediate onset of action and short duration allows for IV infusion and precise titration of dosage.

As nitroprusside interacts with oxyhemoglobin ($HbFe^{2+}$), it dissociates immediately and forms methemoglobin ($HbFe^{3+}$) while releasing nitric oxide (NO) and the highly toxic free cyanide ions. In contrast to the organic nitrates (for example, nitroglycerin), nitroprusside does not require the presence of sulfhydryl compounds to generate NO, instead it spontaneously produces them and therefore acts as a prodrug. Nitric oxide is the active mediator in the vasodilating effects of SNP: It activates the guanylate cyclase present in vascular smooth muscle and increases cGMP, which in turn decreases Ca^{2+} entry into the cell and intracellular Ca^{2+} concentration.

Nitroprusside's degradation products are rapidly cleared via non-enzymatic pathways. Each SNP molecule releases 5 cyanide ions. Cyanide ions undergo sulfurilation by the hepatic and kidney enzyme rhodanase (also known as thiosulfate sulfurtransferase, indicating that thiosulfate must be available for the trans-sulfuration to take place) to form thiocyanate, and are excreted in the urine. Availability of thiosulfate is the rate-limiting step in cyanide detoxification. Excess cyanide ions immediately react with methemoglobin to form cyanmethemoglobin. When sulfur donors and methemoglobin are exhausted, unscavenged free cyanide radicals may accumulate and bind to tissue cytochrome oxidase, to inhibit mitochondrial oxidative phosphorylation. This leads to tissue hypoxia despite adequate levels of available oxygen.

The most common adverse effect of SNP is hypotension and dysrhythmias. Tachyphylaxis may occur, requiring adjustments in dosage for the necessary effect. Thiocyanate toxicity is infrequent, and presents with nausea, abdominal pain, hyperreflexia, tinnitus, seizures, and changes in mental status. Thiocyanate clearance can be facilitated by dialysis. Rarely, cyanide toxicity ensues.

Signs and symptoms of cyanide toxicity are hypertension (secondary to tachyphylaxis), arrhythmias, ST segment changes, altered mental status, seizures, coma, elevated mixed venous pO2 (due to inhibition of cellular O_2 utilization), increasing base deficit, and metabolic acidosis. No cyanosis is seen; SpO_2 remains high.

Treatment includes immediate discontinuation of nitroprusside, mechanical ventilation with 100% oxygen, and correction of acidosis with bicarbonate. Mild toxicity (stable hemodynamics with discontinuation of SNP, base deficit less than 10) can be treated with thiosulfate (150 mg/kg IV bolus over 15 min). Severe toxicity (worsening hemodynamics even after discontinuation of SNP, base deficit greater than 10) is treated with 3% sodium nitrite (4–6 mg/kg over 5 min). Sodium nitrite converts oxyhemoglobin to methemoglobin, which competes with cytochrome oxidase for the cyanide ions. Hydroxocobalamin is an alternative to thiosulfate or sodium nitrite. It binds cyanide to form cyanocobalamin, which acts as a nontoxic reservoir and is excreted by the kidneys.

Ganglionic Blockade: Trimethaphan

Trimethaphan dilates peripheral arteries by blocking cholinergic transmission on nicotinergic autonomic ganglia by binding to the postsynaptic ACh-receptor. It is a short-acting competitive acetylcholine-antagonist with both sympatholytic and parasympatholytic effects. It causes vasodilation and tachycardia. Common side effects are mydriasis, urinary retention, and ileus. Its use is very limited; it has been used for inducing controlled hypotension during surgery, reduction of blood pressure during hypertensive emergencies (for example, in patients with a dissecting aortic aneurysm), or for the emergency treatment of pulmonary edema.

11.2.6 Considerations for Treatment of Pulmonary Hypertension

Pulmonary hypertension—sustained elevated pressure within the pulmonary artery—is a heterogenous and frequently

progressive disorder of the pulmonary vasculature that ultimately leads to increased pulmonary vascular resistance, right heart failure, and death, due to constrained pulmonary blood flow and vascular remodeling of the resistance arteries. Multiple pathways of pathogenesis have been implicated in the development of pulmonary arterial hypertension; excessive cell proliferation, reduced apoptosis, endothelial dysfunction, and an imbalance of the vasoconstrictor/vasodilator milieu appearing to be the predominant cause. Based on the etiology, the World Health Organization (WHO) classifies pulmonary hypertension into 5 groups:

1. Idiopathic pulmonary arterial hypertension, familial arterial hypertension, and pulmonary arterial hypertension associated with connective tissue disorders, portal hypertension, human immunodeficiency virus (HIV) infection, congenital left-to-right shunt, or venous or capillary involvement
2. Pulmonary arterial hypertension with left heart disease
3. Pulmonary arterial hypertension associated with hypoxia and/or lung disease
4. Pulmonary arterial hypertension caused by chronic thrombotic and/or embolic disease
5. Pulmonary arterial hypertension due to miscellaneous causes

Treatment is geared toward symptomatic relief, enhancement of functional capacity, improvement of quality of life, slowing disease progression, and prolongation of survival. Basic management strategies involve lifestyle modifications including physical activity appropriate to functional capacity, oxygen supplementation when chronic hypoxemia develops, diuresis for right ventricular preload reduction, avoidance of pregnancy, and oral anticoagulant therapy to decrease risk of venous thromboembolism. The optimal management of pulmonary hypertension is always individualized.

Calcium Channel Blockers

Based on the American College of Cardiology Foundation (ACCF)/AHA 2009 Expert Consensus Document on Pulmonary Hypertension, vasodilator testing (administration of a pulmonary vasodilator to assess pulmonary vascular reactivity) should be performed in patients with idiopathic pulmonary arterial hypertension, and chronic responders should be considered for long-term treatment with calcium channel blockers. Commonly used agents are long-acting nifedipine, diltiazem, or amlodipine. Verapamil should be avoided.

Endothelin-Receptor Antagonists

Endothelin-1 (ET-1) is a proinflammatory mediator—a direct vasoconstrictor that stimulates pulmonary vascular smooth muscle cell proliferation and induces fibrosis. Its effects are mediated through the ET_A receptors that mediate vasoconstriction and smooth muscle proliferation, and the ET_B receptors that induce production of nitric oxide and prostacyclin, and mediate ET-1 clearance. Clearance of ET-1 is diminished in pulmonary hypertension.

- **Bosentan** – Bosentan is an orally active dual ET_A and ET_B antagonist. It is approved for treatment of WHO group 1 pulmonary hypertension to slow clinical deterioration and enhance functional capacity in patients who are not candidates for treatment with calcium channel blockers.
- The use of bosentan increases the risk of severe hepatic injury, liver cirrhosis, and liver failure. Liver function should be monitored monthly while taking bosentan. Bosentan may cause serious birth defects. Pregnancy should be ruled out prior to initiation of treatment and monthly thereafter. It should be avoided in patients with elevated transaminases and is contraindicated in pregnancy. Angioedema, fluid retention, and possible dose-related decreases in hemoglobin and hematocrit has been reported.

Prostaglandin Analogues

Prostacyclin (prostaglandin I_2, PGI_2, PGX) and thromboxane A_2 are the main metabolites of arachinoid acid with opposing effects on the vascular smooth muscle. Thromboxane A_2 induces vasoconstriction and promotes platelet activation, whereas PGI_2 is a vasodilator with platelet inhibitor effects. In pulmonary arterial hypertension, their physiologic balance is shifted toward thromboxane A_2. This promotes smooth muscle cell proliferation, vasoconstriction, and thrombogenesis. The activity of prostacyclin synthase is decreased in pulmonary hypertension, leading to low levels of the vasodilator and antiproliferative PGI_2. Restoring the balance between vasodilating and vasoconstricting factors, including the administration of prostacyclin analogues, is a mainstay of the medical management of pulmonary hypertension.

- **Epoprostenol** – PGI_2-analogue epoprostenol is used for the long-term treatment of idiopathic pulmonary hypertension, and pulmonary hypertension associated with scleroderma spectrum diseases. It improves functional class, exercise tolerance, and hemodynamics. Its 2 main pharmacological actions are: (1) direct pulmonary and systemic vasodilation, and (2) platelet inhibition. It is an afterload reducer for both the left and the right ventricle. It produces dose-related decreases in pulmonary vascular resistance; it increases stroke volume and cardiac output.

  Epoprostenol is usually administered as a continuous infusion into a central vein. Dosing must be individualized; however, optimal dose range for long-term therapy is believed to be 25–40 ng/kg/minute, when used as monotherapy. Alternatively, it may be delivered as an inhaled aerosol, for example for the treatment of acute right ventricular failure in the intraoperative or early postoperative setting. Common side effects are headache, flushing, nausea, diarrhea, and musculoskeletal pain. Contraindications to its chronic use include

congestive heart failure due to severe left ventricular systolic dysfunction, pulmonary edema during initial treatment, or known hypersensitivity to epoprostenol or structurally related agents. Abrupt withdrawal or sudden dose adjustments should be avoided. Its use should be limited to centers experienced with its administration and with systematic follow-up with patients.

- **Iloprost** – Iloprost is a stable prostacyclin-analogue delivered as an inhaled aerosol to patients with idiopathic pulmonary hypertension, pulmonary hypertension associated with scleroderma spectrum diseases or appetite suppressants, or pulmonary hypertension related to chronic thromboembolic disease. In the acute setting, iloprost decreases pulmonary vascular resistance; with long-term use, in addition to its pulmonary vasodilator effects it suppresses pulmonary vascular smooth vessel proliferation.

  Iloprost is delivered as an inhaled aerosol. It is approved for functional class III and IV to relieve symptoms, enhance exercise tolerance, and diminish disease progression. Its adverse effects are similar to those of epoprostenol. Its use should be avoided in pre-existing hypotension. It may induce bronchospasm in patients with reactive airway disease. Caution should be used with its administration in the presence of increased risk of bleeding, anticoagulation, or other bleeding disorders. Abrupt withdrawal or sudden dose adjustments should be avoided. The use of iloprost should be limited to centers experienced with its administration and with systematic follow-up with patients.
- **Treprostinil** – Treprostinil is a stable prostacyclin-analogue that can be taken by mouth, administered into a central vein, or subcutaneously (preferred). Its main actions are pulmonary arterial vasodilation and inhibition of platelet aggregation. It is approved to decrease exercise-related symptoms and diminish clinical deterioration.

  Treprostinil may induce symptomatic hypotension. It may increase risk of bleeding. There appears to be an increased risk of Gram-negative bloodstream infections, especially in patients receiving intravenous treatment via a chronic indwelling catheter. Its side effects are similar to those of epoprostenol. Abrupt withdrawal or sudden dose adjustments should be avoided. Its use should be limited to centers experienced with its administration and with systematic follow-up with patients.

Phosphodiesterase-5 Inhibitors

Phosphodiesterase-5 (PDE-5) is the intracellular enzyme responsible for degrading cyclic nucleotide monophosphates. It limits signal transduction by cAMP and cGMP—second messengers implicated in pathogenetic pathways leading to pulmonary hypertension. cGMP is involved in mechanisms of pulmonary vasodilation; its rapid hydrolysis by PDE-5 significantly limits its effect on vasomotor tone.

- **Sildenafil** – Sildenafil is a PDE-5 inhibitor initially indicated for treatment of erectile dysfunction. It enhances the effect of nitric oxide in the corpus cavernosum and the pulmonary arterial smooth muscle. It is approved for treatment of WHO group 1 pulmonary hypertension to improve functional capacity and delay disease progression; its unlabeled indication is treatment of pulmonary hypertension after recent left ventricular assist device placement.

  Common side effects associated with the use of sildenafil are headache, flushing, dyspepsia, epistaxis, and disturbances of color discrimination. It may potentiate the effects of antihypertensive agents. The use of sildenafil for pulmonary hypertension should be avoided with strong CYP3A4 inhibitors. The use of sildenafil is contraindicated with concurrent use of organic nitrates and guanylate cyclase stimulant riociguat.
- **Tadalafil** – Tadalafil is a longer-acting PDE-5 inhibitor approved for treatment of erectile dysfunction, benign prostate hypertrophy, and WHO group 1 pulmonary hypertension in patients who are not candidates for treatment with calcium channel blockers. Its mechanism of action is similar to that of sildenafil. It is taken by mouth as a once-daily dose. It may be considered for combination therapy with a prostacyclin analogue or ET-1 receptor antagonist.

  Its side effects are similar to those of sildenafil. It may potentiate the effects of antihypertensive agents.

  Its use is not recommended in patients with recent myocardial infarction or stroke within 6 months; uncontrolled arrhythmias, hypotension, uncontrolled hypertension, heart failure, or unstable angina. It should be avoided when severe aortic stenosis or dynamic left ventricular outflow tract obstruction is present. Concomitant use of organic nitrates is contraindicated.

Nitric Oxide

Nitric oxide (NO) is a potent, endothelium-derived, cGMP-dependent direct vasodilator generated from the terminal guanidine nitrogen of L-arginine. It is produced by 3 isoforms of nitric oxide synthase (NOS) in response to hypoxia, pulsatile flow, and flow-induced sheer stress on the arterial wall. It exists in the gaseous form and is administered as an inhalational agent. Once inhaled, it diffuses to target cells and activates guanylate cyclase to increases cGMP production: an increased cGMP concentration subsequently leads to vasorelaxation. NO diffuses across the pulmonary capillary endothelium into the circulation. Once in the circulation, it avidly binds to the iron of heme-based proteins; it is rapidly inactivated by hemoglobin.

In pulmonary arterial hypertension decreased NOS3 activity is present, resulting in decreased NO-induced pulmonary vasodilation. The use of nitric oxide is favored in the treatment of pulmonary hypertension for its selective pulmonary vasodilator and antiproliferative effects. It vasodilates

the well-ventilated areas, and improves V/Q matching. It inhibits platelet activation, aggregation, and adhesion. It is synergistic with PGI2, allowing the endothelium to maintain its antithrombotic properties.

Nitric oxide is used to treat persistent pulmonary hypertension of the newborn. As with inhaled prostaglandin analogues, it does not appear to improve clinical outcomes in acute respiratory distress syndrome (ARDS).

11.2.7 Drug Therapy for Heart Failure

Heart failure is a constellation of clinical symptoms (primarily fatigue and dyspnea) secondary to impaired left ventricular systolic (reduced ejection fraction) or diastolic (preserved ejection fraction) function, and/or elevated intracardiac pressures. The 2013 AHA/ACC guidelines classify the syndrome by its evolution from asymptomatic preclinical stages to progression to advanced structural heart disease and symptomatology at rest, refractory to maximal medical management. These guidelines also complement the widely accepted functional classification of symptomatic heart failure by the New York Heart Association (NYHA I-IV).

Chronic heart failure is a condition characterized by vasoconstriction, volume overload, and neurohormonal activation. The goal of its pharmacological management is to reduce vascular tone, reduce sympathetic activation, and improve cardiac function. Conventional treatment options include angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, aldosterone antagonists, beta blockers, and the combination of isosorbide dinitrate and hydralazine and diuretics. Novel approaches are now the use of ivabradine and angiotensin receptor-neprilysin inhibitor/ARB combinations.

Nesiritide

Nesiritide is a recombinant human B-type natriuretic peptide with vasodilatory properties. It binds to vascular endothelial and smooth muscle A- and B-type natriuretic peptide receptors. It increases cGMP levels. cGMP serves as a second messenger to produce arterial and venous dilation. Much like endogenous natriuretic peptides, it suppresses the sympathetic nervous system, the renin-angiotensin-aldosterone system, and endothelin. Based on the results of initial trials and the observed reduction of pulmonary capillary wedge pressure and symptomatic relief, it was first approved for treatment of patients with acute decompensated heart failure; however, the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) demonstrated that nesiritide did not convey advantage over standard treatment of acute decompensated heart failure.

Ivabradine

Ivabradine is a novel sinoatrial modulator used for the treatment of chronic stable angina pectoris and heart failure with an ejection fraction lower than 35% inadequately controlled by beta blockers, in patients with native sinus rhythm. It reduces the heart rate by inhibiting cardiac pacemaker inward "funny" current in the sinoatrial node, which, unlike beta-blockers or calcium channel blockers, produces selective heart rate control without affecting ventricular repolarization or myocardial contractility. It may prove beneficial for the treatment of heart failure with reduced ejection fraction. It is contraindicated in sick sinus syndrome, as well as concomitant use of CYP3A4 inhibitors; for example, azole antifungals, macrolides, and protease inhibitor antiretrovirals. It is contraindicated with the concomitant use of verapamil or diltiazem.

Angiotensin Receptor-Neprilysin Inhibitors (ARNI)

Sacubitril/Valsartan

ARNI combinations have been shown to convey mortality benefit in patients with chronic heart failure, a condition in which neurohormonal activation, volume overload, and vasoconstriction play important roles. Natriuretic peptides are potent vasodilators with natriuretic properties. They reduce sympathetic tone and inhibit the renin-angiotensin-aldosterone (RAAS) axis. Neprilysin is an endopeptidase that degrades vasoactive and natriuretic peptides. Sacubitril is a neprilysin inhibitor, therefore it increases the concentration of natriuretic peptides. Its combination with a RAAS-inhibitor angiotensin receptor blocker conveys cardiovascular and renal protection. The PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial demonstrated significant reduction in cardiovascular and all-cause mortality, as well as heart failure-related hospital readmissions in patients with Class II-IV heart failure and reduced ejection fraction when treated with sacubitril/valsartan compared to enalapril alone. It should be avoided in pregnancy and it should not be administered concomitantly with ACE inhibitors.

The updated 2016 ACC/AHA/Heart Failure Society of America (HFSA) Guidelines for Management of Heart Failure include the addition of ivabradine and sacubitril/valsartan to the list of treatment options for patients with heart failure and reduced ejection fraction.

11.2.8 Digitalis

Digitalis is a cardiac glycoside that selectively and reversibly inhibits the integral membrane protein Na^+/K^+ ATPase ion transport system: the Na^+/K^+ ATPase maintains gradients for Na^+ and K^+ that determine myocardial excitability and action potential. Digoxin is the only commercially available digitalis preparation available in the United States. It binds on the external alpha subunit, increases intracellular Na^+ concentration, decreases Ca^{2+} efflux, and augments inotropy by releasing calcium from the sarcoplasmic reticulum into the cytoplasm,

making more calcium available to generate contraction. Digoxin makes resting potential less negative with a resultant increase in myocardial excitability. M_{VO2} is decreased due to its effects on wall tension, preload, and afterload.

Electrophysiologic Effects

1. Inhibits Na efflux during phase 0
2. Shortens duration of phase 2. This results in decreased duration of the action potential.
3. Decreases the slope of phase 3 depolarization. This results in digoxin's characteristic effect on the ST-segment of the EKG.
4. Increases the slope of phase 4 repolarization. This leads to increased automaticity and ectopic beats.
5. Shortens AV conduction time. Shortens the refractory period in the atria and the ventricles.

ECG Changes

1. Increases the PR interval due to delayed AV-conduction.
2. Characteristic scaphoid ST segment depression due to decreased slope of phase 3 depolarization.
3. Flat or inverse T-waves. The diminished amplitude or negative deflection does not correlate with serum levels.
4. Shortens QT interval. This leads to a more rapid ventricular repolarization. This is independent of parasympathetic activity.

Hemodynamic Effects

1. Preload: decreased
2. Contractility: augmented, ejection fraction increased
3. Lusitropy: increased
4. Afterload: decreased
5. Heart rate: Digoxin reduces ventricular response rate in atrial fibrillation or flutter. It sensitizes arterial baroreceptors in the carotid sinus, increases parasympathetic activity by activating the vagal nuclei and the ganglion nodosum with resultant decreases in SA node activity, prolonged effective refractory period and AV conduction time, resulting in slowed heart rate. Digoxin may trigger any type of arrhythmia.
6. Cardiac output: increased.

Common Clinical Uses Treatment of supraventricular tachyarrhythmias, ventricular rate control for atrial fibrillation with rapid ventricular response. It has been used for treatment of paroxysmal supraventricular tachycardia due to AV-nodal reentry or AV-reentry. Historically, it is used for the treatment of symptomatic heart failure associated with left ventricular dysfunction. Treatment may be initiated in patients who have not yet responded to the conventional treatment regimen with an ACE inhibitor or a beta-blocker. Digoxin does not provide overall mortality benefit, but alleviates symptoms and decreases heart failure related hospital admissions. Digoxin does not appear to have significant effect on disease progression in asymptomatic individuals.

Administration PO or IV. Assuming normal renal function, the loading dose for an adult is typically 0.25–0.5 mg increments IV or IM for a total of 1–1.25 mg. Maintenance dose is 0.125–0.250 mg/day, based on serum levels and clinical effect.

Adverse Effects dizziness, mental disturbances, diarrhea, nausea, vomiting, cardiac dysrhythmias, heart block, and visual disturbances.

Warning/Contraindication Administration of digoxin is not recommended for asymptomatic (NYHA class I) patients. Digoxin is contraindicated when dynamic LVOT obstruction is present and in pre-excitation arrhythmias. Caution should be used with concomitant use of beta-blockers, calcium channel blockers, or calcium. Digoxin has a very low therapeutic index with a nonlinear dose response. Dose should be reduced in hypokalemia, hypothyroidism, extensive myocardial or renal damage, and in geriatric patients.

Digitalis Toxicity

Due to its very narrow therapeutic range, increased latency of onset and long duration of action, careful dosage determination is essential to avoid digitalis toxicity. In addition to drug pharmacokinetics and pharmacodynamics, patient characteristics—for example, age, cardiac and renal functional status, other medical comorbidities and their pharmacotherapy—should be considered. Doses should be individualized. Digoxin toxicity has a relatively high mortality rate.

Therapeutic digoxin levels fall between 0.5–2.5 ng/ml. Levels of lower than 0.5 ng/ml are non-toxic. Levels higher than 3 ng/ml are definitely toxic. Infants and children appear to be more tolerant of higher digoxin levels without manifesting signs and symptoms of toxicity.

Signs of toxicity include extracardiac (primarily central nervous system and gastrointestinal) and cardiac effects. Extracardiac manifestations are similar in both acute and chronic intoxication.

In pediatric patients, drowsiness, nausea, and vomiting are common signs of early toxicity, and may present before or after the manifestation of cardiotoxicity. In neonates and infants, sinus bradycardia is a premonitory sign of digitalis cardiotoxicity.

In adults, early gastrointestinal effects include nausea, vomiting, and anorexia. These may present before or after the manifestation of cardiotoxicity. Central nervous system effects include headache, drowsiness, generalized weakness, visual disturbances (color vision is commonly affected), disorientation, confusion, delusions, hallucinations, delirium, or amnesia. Cardiovascular toxicity may develop in the absence or presence of other signs and symptoms of toxicity, and includes new arrhythmias, especially those that exhibit features of increased automaticity and AV-block, premature atrial and ventricular beats, and malignant ventricular arrhythmias.

Acute toxicity is usually associated with hyperkalemia, whereas chronic toxicity is associated with hypokalemia or normokalemia.

Factors that predispose to toxicity are electrolyte derangements such as hypokalemia, hypomagnesemia, or hypercalcemia, diuretic use, alkalosis or acidosis, impaired kidney function, hyperventilation, hypocapnia, arterial hypoxemia, treatment with quinidine, and decreased muscle mass. Hypokalemia increases myocardial binding of glycosides; binding of cardiac glycosides to the Na^+/K^+ ATPase enzyme complex is inhibited by elevated potassium levels.

Treatment of Digitalis Toxicity immediate discontinuation of digoxin, correction of predisposing factors, treatment of cardiac dysrhythmias (phenytoin, amiodarone, beta-blockers), and temporary pacing. Supplemental K decreases the binding of digitalis to myocardial tissue. Digoxin Fab is a special digoxin-binding antidote that prevents and reverses toxic effects and enhances elimination; as there is no comparable alternative treatment, it should be promptly administered to patients with digitalis toxicity.

11.2.9 Questions and Answers

Questions (Choose the Most Appropriate Answer)

1. You are taking care of a patient undergoing mitral annular valvuloplasty for severe mitral regurgitation. Shortly after separation from cardiopulmonary bypass, ST-segment elevations are noted in lead V5 with reciprocal ST-segment depression in lead II. The hypokinetic region of the left ventricle most likely reflects compromised flow through which coronary artery?
   A. Left anterior descending artery
   B. Left circumflex artery
   C. Left main stem
   D. Right coronary artery
2. Common ECG findings of hypercalcemia are:
   A. Slightly prolonged PR interval, shallow or biphasic T-waves, prominent U-waves, ST-segment depression
   B. Wide or flat P wave, prolonged PR interval, wide QRS, prolonged QT, peaked T-waves, ventricular fibrillation
   C. Prolonged QT_c (lengthened ST segment), third-degree AV-block, torsades de pointes, ventricular tachycardia
   D. Short PR or QT interval (shortened ST segment), flattened T-wave, Osborn-waves
3. For a chronic beta blocker user patient with recent history of percutaneous myocardial revascularization with a bare metal stent 10 days prior to his non-emergent noncardiac surgery, the recommended course of action is:
   A. Continue beta blockers and proceed to surgery in 10 days.
   B. Wait at least 30 days after bare metal stent placement before undergoing non-emergent noncardiac surgery, continue beta blockers in the perioperative period.
   C. Wait at least 365 days after bare metal stent placement, hold beta blockers preoperatively.
   D. Start clonidine for perioperative cardiac risk reduction.
4. Through what mechanisms does propofol affect blood pressure?
   A. Propofol decreases systemic vascular resistance and directly depresses the myocardium in the absence of significant cardiovascular disease.
   B. At standard induction doses, propofol maintains baseline mean arterial pressure by augmenting inotropy in response to vasodilation.
   C. At high doses, propofol maintains baseline cardiac output by proportionally increasing the heart rate for a given decrease in SVR and mean arterial pressure.
   D. Propofol does not affect systemic vascular resistance or cardiac output.
5. Through what mechanisms does ketamine change blood pressure?
   A. Ketamine enhances cardiac output by directly stimulating the sympathetic nervous system; it causes tachycardia and acts as a vasoconstrictor by increasing peripheral arteriolar resistance.
   B. Ketamine augments myocardial contractility in patients with depleted sympathetic reserves.
   C. In patients with adequate myocardial and catecholamine reserve, ketamine decreases baseline mean arterial pressure as a result of vasodilation and myocardial depression.
   D. Ketamine does not have significant cardiovascular effects at standard induction doses.
6. Which statement about the hemodynamic effects of etomidate is correct?
   A. Etomidate causes significant cardiorespiratory depression in the presence of cardiac and pulmonary disease.
   B. Etomidate causes significant cardiorespiratory depression in the absence of cardiac and pulmonary disease.
   C. Etomidate may cause a small increase in heart rate and cardiac output, and may decrease systemic vascular resistance and mean arterial pressure regardless of pre-existing cardiopulmonary reserves.
   D. Etomidate does not have any cardiovascular effects.
7. An 82-year-old patient presents for laparoscopic cholecystectomy. His medical history is significant for severe aortic stenosis with an estimated orifice area of 1 cm^2. The goals of induction are:
   A. Ensure full preload to maintain adequate left ventricular end diastolic pressure and forward stroke volume, maintain normal sinus rhythm, avoid extremes of heart rate, maintain adequate coronary perfusion by avoiding any significant drop in cardiac output or systemic vascular resistance.

B. Decrease afterload to promote forward flow.
C. Allow the heart rate to increase above 90 beats per minute to raise aortic diastolic pressure.
D. Minimize IV hydration to avoid volume overload.

8. The preferred agent to treat drug-induced hypotension in the patient from question 7 is
A. Ephedrine
B. Phenylephrine
C. Epinephrine
D. Norepinephrine

9. In patients with an intact circulation, rapid infusion of intravenous amiodarone leads to
A. Rapid restoration of native sinus rhythm and hemodynamic stability
B. Shortened refractory period
C. Hypotension and bradycardia
D. Increased speed of conduction in the sinoatrial node

10. Which of the following statements about the cardiovascular effects of norepinephrine is correct?
A. The primary effect of norepinephrine is direct β(beta)$_2$-agonism.
B. Norepinephrine increases cardiac output to a greater extent than phenylephrine.
C. Norepinephrine augments renal and mesenteric blood flow.
D. The arrhythmogenicity of norepinephrine is significantly greater than that of epinephrine, dobutamine, dopamine or isoproterenol.

Answers

1. **B**. Left circumflex artery. ST elevation in the septal (V1, V2) and anterior (V3, V4) leads reflect compromised flow across the left anterior descending artery. ST-changes in the high (I-aVL) and low (V5, V6) lateral leads reflect compromised flow through the left circumflex artery. The inferior wall (leads II, III, and aVF) is supplied by the right coronary artery in 80–90% of the cases, and by the left circumflex artery in the remaining 10%. A recognized immediate surgical complication of mitral valve surgery is left circumflex coronary injury, due to the proximity of the left circumflex artery to the mitral valve annulus: Any suture placed during mitral annuloplasty, or changes in coronary caliper as a result of a posterior leaflet plication may result in compromised blood supply to the lateral wall of the left ventricle. ST-segment elevations in leads V1-V6, I, and aVL indicate an extensive anterior myocardial infarct, and would most likely result from compromised flow through the left main coronary artery.
2. **D**. Electrolyte abnormalities may cause ECG changes due to altered ion fluxed across the membrane resulting in altered transmembrane potentials. The cardiac effects of hypercalcemia (usually at levels greater than 15 mg/dL) are shortened PR or QT interval with or without widening of the QRS complex, flattened T-wave, or the Osborne-waves, typically seen in hypothermia. Treatment is hydration with normal saline to decrease plasma calcium levels by dilution, administration of non-thiazide diuretics, and avoidance of thiazides. Non-depolarizer muscle relaxant doses should be decreased in patients with hypercalcemia and muscle weakness. The cardiac effects of hyperkalemia are peaked T-waves at mildly elevated potassium levels (6–7 mEq/L), and wide or flat P wave, prolonged PR interval, wide QRS, prolonged QT, ventricular fibrillation, and asystole at higher serum potassium levels (10–12 mEq/L). Treatment is: (1) temporary membrane stabilization with IV calcium (commonly administered dose: 500 mg $CaCl_2$ or 1 g Ca-gluconate), (2) inducing intracellular K + −shift by administering intravenous insulin and glucose (commonly administered dose: 25 to 50 g intravenous dextrose along with 5 to 10 units of insulin), and (3) promoting excretion (diuretics, hemodialysis, resins). Slightly prolonged PR interval, shallow or biphasic T-waves, prominent U-waves, and ST-segment depression reflects hypokalemia; whereas prolonged QT_c, third degree AV-block, torsades de pointes or ventricular tachycardia may reflect hypocalcemia.
3. **B**. According to the most recent ACC/AHA guidelines, there is Class I recommendation for continuing beta blocker therapy in patients using beta blockers chronically. It may be reasonable to start beta blockers in patients with 3 or more RCRI risk factors; however, beta blockers should not be started on the day of surgery. Alpha-2 agonists are not recommended for risk reduction of major adverse cardiac events. It is a Class I recommendation to wait at least 14 days after percutaneous myocardial revascularization with balloon coronary angioplasty, 30 days after bare metal stent placement, and 365 days after drug eluting stent placement.
4. **A**. Propofol is a GABAergic agent. It causes central nervous system inhibition by decreasing the rate of dissociation of GABA from its receptor, and prolonging the GABA-mediated chloride influx into the cell, causing membrane hyperpolarization. Its induction dose for a normovolemic adult patient with normal cardiac function is 2–2.5 mg/kg. Propofol decreases mean arterial pressure by producing direct myocardial depression and decreasing SVR. It alters the baroreceptor reflex and causes a disproportionally small compensatory increase in heart rate relative to the decrease in blood pressure. It decreases cerebral metabolic rate of oxygen consumption, cerebral blood flow, and ICP; however, at high doses, it may significantly decrease cerebral perfusion pressure. Propofol may trigger histamine release, and allergic reactions are therefore possible. It is not associated with increased incidence of postoperative nausea and vomiting.

5. **A**. Ketamine is a phencyclidine derivative interacting with numerous receptors: primarily, it acts as a glutamate-antagonist at both NMDA and non-NMDA receptors; additionally, it is an opioid receptor agonist (opioid-sparing effects) and an M2 muscarinergic acetylcholine receptor antagonist (bronchodilation). It interacts with nicotinergic and monoaminergic receptors, as well as with voltage-dependent Na^+- and L-type Ca^{2+} channels. Its actions on the NMDA-receptors account for its psychomimetic, analgesic, and amnestic effects. The incidence of emergence delirium may be reduced by concomitant administration of a benzodiazepine and by minimizing external stimulation during emergence. Ketamine produces centrally mediated sympathetic activation: It increases plasma epinephrine levels, heart rate, and mean arterial pressure. It is the only anesthetic that increases peripheral arteriolar tone. In catecholamine-depleted patients, or in those with limited inotropic reserve, its intrinsic cardiodepressant properties predominate, and may cause hypotension. Absolute contraindications to the use of ketamine are hypersensitivity to ketamine or chemically related agents, significantly elevated blood pressure, stroke, intracranial hemorrhage, active delirium or psychosis, porphyria, pregnancy, and preeclampsia.
6. **C**. Etomidate is a lipid-soluble nonbarbiturate hypnotic and anesthetic without analgesic effects. It is a carboxylated imidazole, structurally unrelated to other intravenous anesthetics. It is frequently used for rapid intravenous induction of anesthesia at standard doses of 0.2–0.3 mg/kg. Its short duration of action is subsequent to its rapid redistribution to peripheral compartments. Etomidate causes minimal cardiorespiratory depression even in the presence of cardiac and pulmonary disease. It may increase heart rate and cardiac output by 3% to 4%, and may produce a 10–15% decrease in systemic vascular resistance and mean arterial pressure. It decreases cerebral blood flow, $CMRO_2$, and ICP. Even a single induction dose of etomidate suppresses cortisol production by inhibiting the activity of 11-β(beta)-hydroxylase. Etomidate causes pain on injection and it is associated with increased incidence of postoperative nausea and vomiting. There are no absolute contraindications to the use of etomidate as an induction agent.
7. **A**. Aortic stenosis, congenital or acquired, is the most common valvular disease in the United States. Most common etiologies are senile degeneration and congenital bicuspid aortic valve. Asymptomatic patients even with severe aortic stenosis carry a small risk of sudden cardiac death, whereas the occurrence of symptoms are ominous signs of poor outcome. The classic triad of symptomatic aortic stenosis are angina pectoris (life expectancy is about 5 years, unless the aortic valve is replaced), syncope (average life expectancy: 3–4 years), and congestive heart failure (average life expectancy: 1–2 years). Treatment is surgical.

   As the severity of the stenosis progresses, a pressure gradient develops between the left ventricle and the aorta, causing the left ventricular wall tension to increase (fixed increase in LV afterload). This leads to a compensatory increase in wall thickness. According to the law of Laplace, the wall tension within a sphere filled to any given pressure depends on the thickness of the sphere: Pressure = (2 * wall thickness * wall tension)/radius. Consequently, at a constant pressure, wall tension can be decreased by increasing the thickness of the sphere's wall: left ventricular wall tension = (LV pressure * radius)/2* LV wall thickness. Wall stress is a major determinant of myocardial O_2 demand. Concentric left ventricular hypertrophy with an increasing wall thickness but unchanged chamber size therefore reduces wall stress and O_2 demand. Chamber size, contractility, and stroke volume are usually preserved until late in the disease process.

   The increasing LV wall thickness will eventually lead to impaired left ventricular relaxation and decreased compliance, and eventually a fixed stroke volume. To maintain an adequate stroke volume, preload augmentation is necessary.

   A thick, noncompliant heart has an increased basal myocardial O2 consumption. In the hypertrophied left ventricle, capillary density does not adapt to the increased wall thickness, and any decrease in coronary perfusion pressure will compromise myocardial O2 supply. Maintenance of adequate afterload to ensure adequate systemic diastolic and coronary perfusion pressure is essential in preventing hypotension and the resultant risk of subendocardial ischemia.

   Extremes of heart rate are poorly tolerated in patients with hemodynamically significant aortic stenosis. Maintenance of normal rate and sinus rhythm is essential, as a noncompliant left ventricle is unable to augment stroke volume to maintain cardiac output during bradycardic episodes to restore cardiac output, and excessive tachycardia will reduce coronary perfusion during diastole. Atrial contraction contributes up to 30% to 40% of the left ventricular filling, maintenance of sinus rhythm is essential, and any supraventricular arrhythmias should be aggressively treated.
8. **B**. Patients with concentric LVH and a hemodynamically significant aortic stenosis are unable to augment cardiac output in response to any sudden decrease in systemic vascular resistance. Administration of an α_1- adrenergic agent—for example, phenylephrine—improves coronary perfusion pressure without adding to the already existing fixed afterload, and increasing myocardial work. Concomitant venoconstriction increases venous return and

augments preload. Reflex bradycardia may improve myocardial O_2 consumption. It is essential not to delay treatment of hypotension, as the thick myocardium is at risk for ischemia, further worsening cardiac output and coronary perfusion, leading to sudden death. Agents with the potential to increase heart rate or myocardial O2 consumption are not first choices for treatment of hypotension in this patient with severe aortic stenosis.

9. **C**. Amiodarone is a class III antiarrhythmic agent used for the treatment of atrial and ventricular arrhythmias. It is used during cardiac arrest to aid defibrillation of recurrent or refractory ventricular fibrillation. Amiodarone has Na^+, K^+, Ca^{2+} – channel, as well as alpha- and beta-adrenergic receptor blocker properties. Its rate-dependent (rapid) administration may cause profound hypotension and bradycardia. Treatment is volume expansion, administration of vasoconstrictors and positive chronotropes, or temporary pacing.
10. **B**. Norepinephrine is an endogenous catecholamine with peripheral post-synaptic α_1- and β effects. Its peripheral α effects predominate over its myocardial β_1 effects. The effects of norepinephrine mediated by β_2-receptors are not clinically significant. Norepinephrine is a potent vasoconstrictor (MAP and SVR are increased) with mild positive inotropy. It does increase myocardial O2 requirements. Its β-induced positive chronotropy is counteracted by the reflex bradycardia resulting from the α-mediated increase in afterload. Norepinephrine does not significantly increase cardiac output; an effect different from that of phenylephrine (phenylephrine may decrease cardiac output). Norepinephrine is less likely to induce tachyarrhythmias than epinephrine, dobutamine, dopamine, or isoproterenol.

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