Cardiac Pharmacology

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Abstract

The incidence of cardiovascular disease is rapidly increasing around the world. The pharmaceutical industry has played an important role in advancing new medications to treat cardiovascular disease, and certainly there are significant benefits as more and better medications become available to treat patients. However, the rapid growth in the field of cardiac pharmacology means that medical professionals are challenged to stay on top of these advances in order to provide their patients with the right drug at the right time. A large percentage of cardiovascular patients suffer from a range of comorbidities, which makes this need even more critical.

Policy Statement

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Continuing Education Credit Designation

This educational activity is credited for 5 hours. Nurses may only claim credit commensurate with the credit awarded for completion of this course activity.

Pharmacology content is 5 hours.

Statement of Learning Need

Identifying the cardiac pharmacological resources to prevent and treat cardiac conditions affecting blood pressure, contractility and perfusion of blood through the vascular system requires continuous learning for health providers, nurses and ancillary staff involved in the care of patients with a cardiac diagnosis. As new medications and treatment guidelines develop so must the skill of the cardiac care team.

Course Purpose

To provide nursing professionals with knowledge of pharmacological treatment of heart conditions, such as the use of antiarrhythmic, antihypertensive, pressors, vasoconstrictors and vasodilators, and thrombolytic medications.

Target Audience

Advanced Practice Registered Nurses and Registered Nurses

(Interdisciplinary Health Team Members, including Vocational Nurses and Medical Assistants may obtain a *Certificate of Completion*)

Course Author & Planning Team Conflict of Interest Disclosures

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Susan DePasquale, MSN, FPMHNP-BC – all have no disclosures

Acknowledgement of Commercial Support

There is no commercial support for this course.

Please take time to complete a self-assessment of knowledge, on page 4, sample questions *before* reading the article.

Opportunity to complete a self-assessment of knowledge learned will be provided at the end of the course.

1. **Angina is a condition where a patient experiences**

    a. chest discomfort.
    b. insufficient blood and oxygen to the heart muscle.
    c. pain only upon exertion.
    d. Answers a., and b.

2. **Vasoactive drugs, including pressors and inotropic medications are often given to patients experiencing**

    a. hypertension.
    b. cardiogenic shock to resolve some hypotension.
    c. chest pain.
    d. kidney failure.

3. **Thrombolytic drugs are typically administered**

    a. subcutaneously.
    b. intramuscularly.
    c. intravenously.
    d. sublingually.

4. **One particular type of beta-blocker, _____ showed significant results in decreased overall patient mortality when used among those with heart failure.**

    a. inderal
    b. carvedilol
    c. lidocaine
    d. nitroglycerin

5. **True or False: Indapamide, a thiazide diuretic, has been shown to have some calcium channel blocking effects in the arteries.**

    a. True
    b. False

Introduction

Cardiovascular disease involves numerous medical conditions that affect the heart and the circulatory system. There are several circumstances that are classified as cardiovascular disease, and they each affect the heart and the blood vessels in different ways. Some conditions affect the diameter or elasticity of the blood vessels, while other cardiovascular conditions impact the heart's actual ability to pump blood in a normal manner. Regardless of the exact mechanism that causes the particular circumstance, all cardiovascular conditions can ultimately affect how the rest of the body receives oxygen and nutrients through the blood.

In response to the large number of conditions that impact the heart and circulation, there are a variety of medications available for treatment. Whether these drugs manage only the symptoms of the disease, prevent it from worsening, or actually treat or cure the condition, they provide options for treatment that were once not available. The pharmacological industry continues to develop new medications and more advanced options. The healthcare professional who administers cardiovascular drugs must stay on top of the latest treatment parameters, dosage guidelines, and appropriate directives for use of these drugs to not only provide accurate treatment, but also to maintain patient safety with dose administration.

Antianginal Drugs

Each year, approximately 9.8 million Americans experience some form of angina.[29] Angina is a condition in which a patient experiences chest discomfort that develops when the heart muscle does not receive enough blood and oxygen because the amount of blood flow needed is not being met by the blood supply at hand. Antianginal drugs are designed to control the symptoms of angina. When the heart and surrounding tissue lack

appropriate blood flow, they are said to develop ischemia. When ischemia continues for too long, the affected tissue may become necrotic, *i.e.*, the tissue actually dies as a result of inadequate blood flow. Affected individuals suffer from the painful and sometimes debilitating symptoms associated with ischemia. Fortunately for many people who suffer from angina, the symptoms do not progress to tissue necrosis.[29]

When the heart becomes ischemic, the affected individual experiences chest pain, tightness, and a feeling of pressure in the chest. These symptoms may be described as mild to crushing and severe. The pain in the chest may radiate to the jaw, the shoulder, or the arm. Other symptoms may also develop in addition to the chest pain, including breathing difficulties and shortness of breath, lightheadedness or dizziness, and pallor; the patient may be visibly sweating and may complain of nausea or the patient may vomit. It should be noted that symptoms of angina may be similar to other conditions, such as indigestion, choking, or back pain.

Angina may be classified as stable or unstable. Angina is classified based on how the symptoms develop, the causative factors of the angina, and how well it is managed. Stable angina occurs when the coronary vessels become occluded, often because of a condition such as atherosclerosis. Blood flow is reduced to sections of the heart muscle, thereby causing ischemia. A patient with stable angina may experience pain and other symptoms during times when the heart needs greater amounts of oxygenated blood, such as during times of significant stress or during exercise. Stable angina can often be relieved with rest and with prescription antianginal drugs.

Alternatively, unstable angina describes a condition in which a person experiences angina, but it may be due to other factors, such as coronary

vasospasm or a clot that has partially blocked one of the coronary arteries. Unstable angina causes pain that is often more severe than stable angina. Unlike stable angina, unstable angina can occur without warning and may even happen when the patient is at rest. It is therefore not relieved by rest or by medications designed to improve blood flow and control the pain, such as nitroglycerin. A patient who is experiencing unstable angina requires emergency treatment to prevent the condition from progressing to myocardial infarction.

Angina may be classified according to its severity, as well, which can help to differentiate the most appropriate forms of treatment. One of the most common classification systems used is the Canadian Cardiovascular Society grading scale, which is described as:[30]

- *Class I:*
  In Class I, angina occurs only during strenuous physical activity. Routine activities, such as walking, do not induce episodes of angina.

- *Class II*:
  In Class II, angina occurs during strenuous physical activity and the affected patient shows slight limitations in abilities. Rapidly climbing stairs or climbing more than one flight of stairs, as well as exposure to significant stress or cold temperatures may all induce angina.

- *Class III*:
  In Class III, angina occurs with normal levels of activity; the affected patient may experience angina with routine actions, such as walking 1-2 blocks or climbing a flight of stairs at a normal pace.

- *Class IV*:
  In Class IV, angina is present at rest and the affected patient is unable to carry out any physical activities without experiencing symptoms.

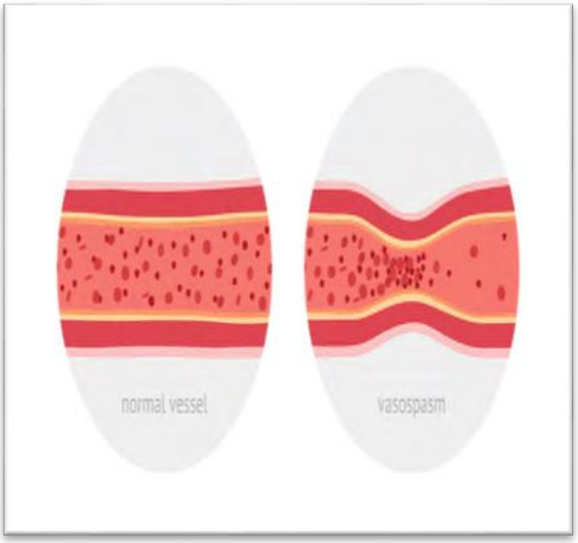
Because angina results from a lack of blood supply, antianginal agents are designed to improve blood flow to prevent ischemia. Other drugs may also be administered that are designed to correct or prevent the conditions that caused the disrupted blood flow. For example, when coronary vasospasm develops, the affected patient may experience angina because the vessels have constricted during spasms and blood flow is inadequate. Drugs that control vasospasm are designed to inhibit this process so that blood flow is restored and is sufficient to supply enough blood and oxygen to the heart muscle.

The type and extent of angina experienced also depends on the patient's heart rate and cardiac contractility. An individual with an increased heart rate, whether due to external factors such as an increase in activity through exercise, or due to internal factors such as stress and anxiety, will typically pump more blood at a faster rate into the circulatory system. This process increases oxygen demand; furthermore, increases in both preload (the amount of blood returning to the heart from systemic circulation) and afterload (the amount of resistance the heart must pump against when ejecting oxygenated blood into circulation) also affect myocardial oxygen demand. As a result, when there is an increase in demand, there must also be an increase in blood flow to meet that demand.

The coronary arteries, being the main vessels that supply blood to the heart, must be able to keep up with the increased oxygen demand as a result of an

increase in heart rate or other factors that increase oxygen demand. When the coronary arteries cannot supply enough blood and oxygen to the heart, the result is ischemia and concomitant angina. This condition can develop as a result of several reasons, including decreased overall oxygenation in the blood to begin with because of poor oxygen saturations; decreased blood flow through the coronary arteries due to a reduction in vessel diameter, such as what occurs with coronary artery stenosis, or decreased blood flow through the coronary arteries due to blockage or arterial obstruction. Often, antianginal drugs are administered to manage the two latter conditions.

Coronary Vasospasm



When angina develops, a cause of the blood flow becoming restricted to the heart muscle may be due to vasospasm of the coronary artery. The condition occurs when one of the coronary arteries suddenly constricts and narrows; the walls of the artery squeeze together and block blood flow through the vessel. Vasospasm of the coronary artery most often occurs in vessels that are not "hardened" by atherosclerosis and instead have more movement of the vessels. However, coronary artery spasm can occur in persons who have atherosclerosis of the coronary vessels.

Coronary artery vasospasm plays a significant role in the development of angina and eventual myocardial infarction if the condition is not well controlled. Described as smooth muscle constriction of the coronary artery,

coronary vasospasm leads to angina because the vessel physically blocks blood flow that would normally provide oxygen to the heart muscle.[2] The resulting ischemia causes pain from poor oxygenation, which may be relieved when blood flow is restored. Typically, in order to restore blood flow, the vasospasm must be relieved. Some drugs prevent vasospasm from occurring in the first place, while others are designed to manage the condition once it develops and prevent further complications associated with myocardial ischemia.

In 1959, Dr. Myron Prinzmetal and colleagues described a form of angina that differed from classic forms of stable angina that developed as a result of exertion. Eventually, termed "Prinzmetal's angina" or "variant angina," this specific type differed from the classic form in several ways. Firstly, it did not develop as a result of exertion or exercise. Secondly, it demonstrated ST segment elevation on electrocardiogram, rather than ST segment depression as seen with other types of angina. Additionally, its symptoms often returned at approximately the same time of day and it was prone to waking affected patients from their sleep; and, the associated episodes of angina were more likely to progress to periods of cardiac arrhythmia and potential myocardial infarction.[2,3]

Prinzmetal eventually coined the term "variant angina" to describe the condition and determined that it developed due to spasm of the coronary artery, which blocked blood flow and resulted in cardiac ischemia. Variant angina is more likely to occur during the early morning hours, which is why affected patients are often awakened from sleep when it develops. In addition to the previously described characteristics, variant angina is also less commonly associated with atherosclerotic conditions, and it may be

more likely to develop after exposure to cold temperatures, tobacco use, or after periods of hyperventilation.[2,3]

There is a range of vasoconstriction that may occur with this type of angina. For some patients, there is only mild vasoconstriction in which blood flow is reduced, such that increased exertion, which requires more blood flow, may lead to symptoms of angina. Alternatively, some patients experience such significant vasoconstriction that the coronary artery is almost completely blocked and they experience angina symptoms even at rest.

The treatment of choice to control coronary vasospasm is with nitrate therapy, particularly administration of nitroglycerin. Deficiency of nitric oxide (NO), a substance produced by the body that has vasodilator effects, has been considered a potential cause of coronary artery vasospasm. Acetylcholine is a neurotransmitter that eventually contributes to vasodilation through its release of NO. Unfortunately, some patients who suffer from coronary artery vasospasm experience the opposite result and suffer from vasoconstriction with the release of acetylcholine.[1,2] Alternatively, these same patients also seem to have a greater response to the vasodilator effects of nitrate medications.

Lanza, *et al*., in an article in the journal *Circulation,* discussed the actual mechanisms of coronary artery spasm and why they occur and concluded that two mechanisms take place at the time when one of the coronary arteries is experiencing vasospasm. Some type of abnormality associated with the coronary artery makes it more prone to severe vasoconstriction in one or more areas of the vessel and some type of stimulus must be present that sets off the vasospasm.

The endothelial layer of the blood vessel plays a large role in controlling vasodilation or vasoconstriction; when there is damage to the endothelial layer, it may respond abnormally to external stimulants, such as acetylcholine, which would normally produce vasodilation. Furthermore, hyperactive vascular smooth muscle cells found in the coronary arteries have also been shown to contribute to vasospasm development and may be considered the main abnormality associated with its development.[5] This hyperactivity may develop as the result of various conditions, including vessel inflammation, oxidative stress, or genetic abnormalities.

Nitroglycerin is a nitrate medication that causes relaxation of the smooth muscles of the blood vessels, leading to vasodilation and improved blood flow. The vasodilator effects on the arteries reduce systemic vascular resistance as well as mean arterial pressure, placing less stress on the cardiac muscles. Nitroglycerin is most commonly given once symptoms of angina have developed; it quickly relieves the pain and pressure associated with the condition and it may reduce the frequency with which recurring episodes of angina occur. Although it is more commonly administered after symptoms have developed, nitroglycerin is also effective when administered prophylactically before those activities that may precipitate angina.

Nitroglycerin is effective in that it is easy for many patients to access. Once prescribed, nitroglycerin can be administered in various forms and it may be carried with the patient so that if angina symptoms develop, the individual can receive quick relief through nitroglycerin administration. The drug is available in many forms that can be rapidly administered outside of the healthcare facility, including oral or sublingual tablets, transdermal patches, or topical ointment.

Nitroglycerin may be administered as a short-acting agent or as a long-acting agent. The type and dose administered depends on the patient's condition. Short-acting nitroglycerin (Nitrostat®, Nitro-bid®) is administered intravenously if a patient is intolerant to sublingual nitroglycerin; it is given at a rate of approximately 5 mcg/min, but it may be increased by 5 to 10 mcg/min every 3 to 5 minutes, depending on the patient's response and resolution of symptoms.[29]

Long-acting nitroglycerin is typically administered as isosorbide dinitrate (Isordil®), which is available orally as an immediate-release tablet or as a sublingual (SL) preparation. The dosage ranges from 2.5 to 5 mg when given SL, and from 5 to 20 mg when administered as immediate release.[29] Isosorbide dinitrate resolves coronary vasospasm by causing dilation of the coronary arteries. It is also effective by decreasing stress on the left ventricle of the heart and reducing the pressure against which the heart must pump blood, since it is also a smooth muscle relaxant. Use of either short-acting or long-acting nitroglycerin should successfully manage angina symptoms and restore blood flow to the heart by relieving coronary vasospasm. However, if this is not possible and anginal pain is refractory to nitroglycerin, further emergency treatment is necessary.

Calcium channel blockers are drugs that are more commonly administered to prevent the onset of vasospasm that would lead to angina. The consistent use of these drugs has been shown to reduce recurrence of vasospasm that leads to angina.[4] As with nitroglycerin, calcium channel blockers also work as vasodilators to relax the smooth muscles of the blood vessels and to promote blood flow. The drugs bind to certain calcium channels that are located on the vascular smooth muscle and some of the cardiac muscle cells; the channels control the amount of calcium into the muscle cells, which

ultimately stimulates smooth muscle contraction. Some calcium channel blockers also decrease heart contractility and overall heart rate, which places less stress on the heart muscle.

The effects of calcium channel blockers are twofold. Firstly, by controlling calcium exposure to the heart muscle cells, they can prevent many instances of vasospasm associated with the smooth muscles of the coronary arteries. Secondly, they improve blood flow to the heart muscle through their effects of vasodilation, thereby reversing the cause of angina and preventing its symptoms from developing. A common type of calcium channel blocker that is used for the management of angina due to coronary vasospasm is amlodipine (Norvasc®), which is typically administered as an oral tablet that the patient takes each day whether they are experiencing angina symptoms or not. Amlodipine is often administered at doses between 5 and 10 mg per day.[29]

Dilitiazem (Cardizem®) is another form of calcium channel blocker that may be administered orally or intravenously. As an oral preparation, the patient typically takes the dose 3 to 4 times per day with dosages up to 360 mg per day, divided between the total doses.[29] Dilitiazem is administered in this method to prevent the onset of angina, rather than stopping its symptoms once it has started.

As with other antianginal drugs, it is important to note the success of the drug's effects on the patient's angina symptoms. If a patient continues to take calcium channel blockers but is unable to control symptoms of angina, then further treatment is necessary to discover the cause of the condition and to prevent significant complications, including myocardial infarction.

Inhibit Clot Formation

In some cases, angina can develop because a clot has entered one of the coronary vessels and has occluded some of the blood supply to the heart muscle. The resulting pain and discomfort associated with angina occurs because the clot within the blood vessel is physically preventing blood flow to certain areas of the heart muscle, while ultimately causing angina symptoms. As with other causes of the condition, angina that develops because of occlusion due to a blood clot is the result of an imbalance between the supply of oxygen and the heart muscle's demand.

The blood clot that develops within the coronary artery, known as a thrombus, may partially occlude the vessel. When this occurs, the thrombus is called a *non-occlusive clot*. If the thrombus completely occludes the blood vessel, it is referred to as an *occlusive clot*. The thrombus formation and dissolution may be transient or it may be constant.[6] Without resolution of a lasting thrombus, the affected patient is at high risk of permanent damage from myocardial ischemia and infarction.

Angina that develops because of a blood clot in the coronary artery is a type of unstable angina. The resulting symptoms develop not necessarily because of exertion and increased myocardial demand, but because of reduced overall blood flow due to the clot formation. The blood clot that forms within the coronary arteries is most often a result of atherosclerotic lesions that have formed in the area and subsequent plaque rupture from these lesions.

In some cases, though, decreased secretion of NO, which is normally a vasodilator, combined with dysfunction of the endothelial layer of the blood vessel, leads to clot formation because the body is unable to inhibit platelet aggregation in the dysfunctional area.[6] When a thrombus does develop within the coronary vessels, the most appropriate medications are those that are designed to dissolve the clots, prevent further platelet aggregation, and restore normal blood flow.

Aspirin is one of the more common oral agents that may be administered during cases of unstable angina. Aspirin (Bayer®, Ecotrin®) prevents the buildup of platelets within the blood vessels; if a diseased area of the coronary artery is present, such as with atherosclerotic lesions or damage to the endothelium, aspirin can prevent platelet aggregation at the site and subsequent clot formation. Aspirin is one of the oldest forms of medication used as a pain reliever and anti-inflammatory agent. It originally stems from willow bark, which contains salicin, a chemical similar to aspirin (acetylsalicylic acid). It was later developed during the 19th century as salicylic acid and primarily for symptoms associated with malaria.

Today, more people worldwide use aspirin than any other drug.[31] The use of aspirin is promoted to help control pain and as a fever reducer, an anti-inflammatory drug, as well as for control of "aches and pains" associated with a wide number of medical conditions. Aspirin is used as a preventive measure against blood clots that can develop due to atherosclerotic heart disease.

Aspirin's main mechanism of action is inhibiting the enzyme cyclooxygenase (COX), which is normally responsible for promoting prostaglandins. These prostaglandins play various roles at the sites of illnesses or injuries within

the body, such as controlling inflammation and blood flow, as well as forming blood clots. One type of COX enzyme works within platelets to produce thromboxane A2, a lipid eicosanoid that promotes platelet aggregation. Aspirin's antiplatelet effects work by blocking COX-1, which blocks production of thromboxane A2 and subsequent platelet aggregation.[32]

The administration of aspirin is a proven method to control complications of coronary artery disease. For symptoms of unstable angina, aspirin may be given as an oral tablet at a dose of 160 to 325 mg.[29] Chewable forms of aspirin are rapidly absorbed and may be given as soon as a patient presents with symptoms. If the individual cannot tolerate oral aspirin, rectal suppository administration is the next choice. A patient with coronary artery disease who is at high risk of clot formation may also take aspirin as a maintenance dose on a daily basis to prevent further complications. The typical dose is 81 mg daily as one chewable tablet, although the maintenance dose could be increased up to 325 mg per day.

Clopidogrel (Plavix®) has various indications, but it can be used for the management of unstable angina that develops as a result of clot formation in the coronary vessels. Clopidogrel is a type of drug known as an adenosine diphosphate (ADP) receptor inhibitor, which is a specific type of antiplatelet drug. Platelets contain ADP receptors on their surfaces, which are also known as $P2Y_{12}$ receptors; these sites interact with ADP to promote platelet function as part of the blood clotting process. When an ADP receptor inhibitor blocks the effects of ADP, platelet function is markedly reduced, and the effects last for the lifetime of the affected platelets, which is typically between 7 and 10 days.[36]

Clopidogrel may be a beneficial drug to administer for those patients who cannot tolerate aspirin. However, studies have shown that it is also beneficial when taken with aspirin, and is more valuable as a second therapy when compared to aspirin alone in the prevention of stroke.[35] Clopidogrel may be administered in cases of unstable angina to patients with acute coronary syndrome by giving an initial loading dose of 300 mg, followed by daily doses of 75 mg.[29] Because its effects are mostly prophylactic, clopidogrel is intended for routine administration and not necessarily for cases when a patient presents with acute chest pain due to unstable angina.

A review by Wijeyeratne, *et al*., in the *British Journal of Clinical Pharmacology*, stated that although clopidogrel is commonly used as a protective mechanism against thrombotic events, its onset of action in inhibiting platelet function is somewhat slower after the initial loading dose.[36] However, clopidogrel remains a standard form of prevention of coronary complications associated with clot formation. The American College of Cardiology and American Heart Association Task Force on Practice Guidelines recommends use of clopidogrel for patients suffering from acute coronary syndrome and for prevention of further events affecting the coronary arteries.[33] Because it inhibits platelet function, patients who take clopidogrel should be cautioned to monitor for signs of bleeding, and it should be discontinued for several days prior to an invasive procedure that could cause bleeding for the patient.

Antiarrhythmic Drugs

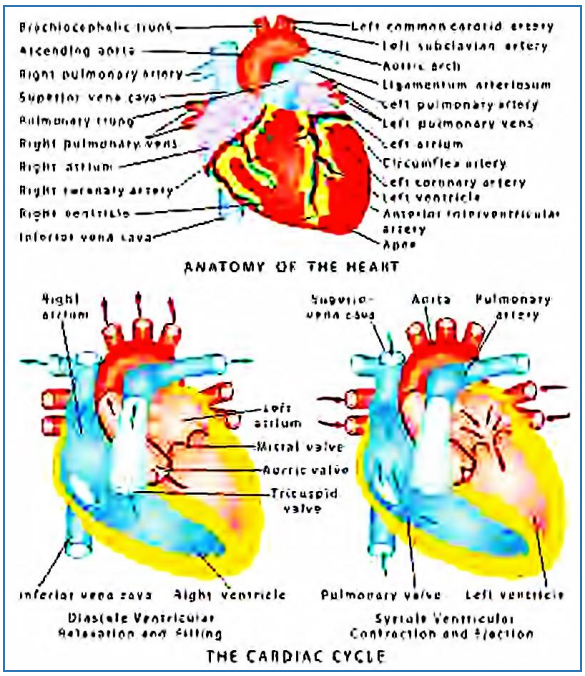
Some patients suffer from cardiac arrhythmias, which can affect the heart's ability to contract normally. In general, arrhythmias occur as conduction abnormalities in the electrical system of the heart. Normally, the heart's electrical conduction system maintains a regular heart rate and rhythm so

that the heart beats in such a way that it can effectively and efficiently pump blood. The heart's conduction system consists of specialized cells that send messages between various portions of the cardiac muscle, which stimulate it to contract. Normally, the conduction impulses begin in the sinoatrial (SA) node, which is located in the right atrium at the junction of the right atrium and the superior vena cava.

The SA node, called the "pacemaker" of the heart, transmits an electrical impulse through depolarization of cells and the atria initially contract. The impulse then moves through fibers in both the right and left atria to the atrioventricular (AV) node, at the junction between the right atrium and the right ventricle, which is a position known as the triangle of Koch.[7] The AV node is the main connection through which electrical impulses pass between the atria and the ventricles.

The AV node plays a critical role in transmitting electrical impulses from the atria to the ventricles; it regulates how fast or how slowly the impulses are transferred. Once the impulse reaches the AV node, there is a small delay in which the atria finish contracting and the ventricles start filling with blood. After passing the AV node, the impulse continues along the ventricles by way of the bundle of His and the right and left bundle branches. Finally, it reaches the Purkinje fibers at the base of the ventricles, and the impulse rapidly travels through an extensive network so that cardiac cells are depolarized within the ventricular tissue. The ventricles are stimulated to contract as the impulse travels through the fibers at a rate of less than 0.23 seconds.[8] The Purkinje fibers coordinate the contraction in a synchronized manner so that the heartbeat is regular and synchronized on the right and left sides of the heart.

There are many different types of abnormalities that can occur along various points of the cardiac conduction pathway. Consequently, there are also various types of cardiac arrhythmias. The regulation of cardiac impulses is actually controlled through the autonomic nervous system, most often at the point of the AV node. However, cardiac arrhythmias are typically manifested as various dysfunctions of heart rate and rhythm. They may consist of premature or extra heartbeats, tachyarrhythmias that originate in the AV node, including atrial fibrillation, atrial flutter, or paroxysmal supraventricular tachycardia, as ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation, or bradyarrhythmias.



To best manage an arrhythmia, the healthcare provider must be certain of the exact type of abnormality present. Because there are so many different types of cardiac arrhythmias, an electrocardiogram is essential to pinpoint the specific abnormality to best understand how to treat it.

When selecting the most appropriate type of medication to administer to control the arrhythmia, the Vaughan-Williams classification system is most often used.[11] The system breaks down the different types of antiarrhythmic agents available and places them into four different categories:

- *Class I*: Sodium channel blockers
- *Class II*: Beta-receptor blockers
- *Class III*: Potassium channel blockers
- *Class IV*: Calcium channel blockers

There are also some drugs that do not fit into any of these categories, but are still used to treat arrhythmias. Furthermore, some drugs are in overlapping categories and may display activity that could fit into more than one class.

All antiarrhythmic drugs alter the movement of certain ions across cell membranes, which affect the action potential of cardiac conduction. The differences typically lie in which ions are affected. For instance, sodium channel blockers (Class I) are used to block the movement of sodium ions into the cell during the initial phase of action potential; alternatively, potassium channel blockers prolong repolarization by preventing the movement of potassium ions during later stages of action potential.

It should be noted that some drugs can cause further cardiac complications when they are used to treat arrhythmia conditions. While certain drugs may be administered to effectively manage abnormalities in electrical rhythms, they could also be too effective and lead to consequences from an opposite outcome. For example, procainamide, a sodium channel blocker used to decrease conduction velocity, may also increase the risk of *torsades de pointes,* a potentially lethal arrhythmia that causes ventricular tachycardia. Use of certain types of beta blockers, while administered to control conduction velocity, could lead to significant hypotension and its resultant negative effects. Healthcare providers who administer antiarrhythmic

medications should do so with caution, understanding the affected patient's background and sensitivity to the effects of these drugs.

Conduction Velocity

Conduction velocity describes the speed at which electrical impulses travel through the cardiac conduction system. As stated, the regulation of cardiac conduction impulses is through the autonomic nervous system. The sympathetic nervous system portion of the autonomic system can increase the rate of depolarization within the cardiac conduction pathways, which describes increased conduction velocity. Sympathetic activation of the AV node increases the rate of depolarization and increases conduction velocity, which can then decrease the time between atrial and ventricular contractions.[8] This is noted as a decrease in the P-R interval as seen on the electrocardiogram.

Part of the mechanism of how the sympathetic nerves are able to affect AV node cells and potentially increase conduction velocity is due to the release of norepinephrine, which binds to beta-adrenergic receptors. Common drugs used for the management of increased conduction velocity within the heart are the beta-blockers, which can convert activity into a normal pace of conduction. Cardiac dysrhythmias associated with increased conduction velocity may include supraventricular tachycardia, atrial fibrillation, or atrial flutter. Examples of beta blockers that specifically target cardiac beta-adrenergic receptors are atenolol, esmolol, and metoprolol.[11]

Atenolol (Tenormin®) is a cardioreceptive adrenoreceptor blocker that inhibits the effects of the sympathetic nervous system on the cardiac conduction system. It is technically used as an off-label medication for the management of supraventricular arrhythmias and it is administered

prophylactically. The patient must take atenolol on a daily basis to prevent certain cardiac arrhythmias; the usual dose is 50 mg PO daily, but it may be increased to 100 mg.[37]

Esmolol (Brevibloc®), while primarily used for management of hypertension, can also be used to control conduction velocity problems that lead to cardiac arrhythmias, namely, supraventricular tachycardia, atrial fibrillation, atrial flutter, or *torsades de pointes.*[38] Esmolol is administered intravenously and may often need to be given emergently, or in cases where a patient is symptomatic due to the associated cardiac arrhythmia. It requires a loading dose, which starts at about 500 mcg/kg given over 1 minute. Any following doses of 50 mcg/kg/min may be given x 4 minutes.[38] The dose may be increased if there is no response or change in cardiac rhythm.

Metoprolol (Lopressor®) also works by blocking beta-adrenergic receptors to modify the cardiac conduction velocity and control the heart rate and rhythm. Metoprolol may also be used for management of angina, as treatment of hypertension, and to prevent myocardial infarction. Similar to atenolol, metoprolol is used off label for management of cardiac arrhythmias, including treatment of acute tachyarrhythmias. It is administered intravenously and a typical dose is 5 mg IV, given over 1 to 2 minutes. The total dose administered should not exceed 15 mg.[37]

Calcium channel blockers may also be used to control conduction velocity through the AV node. Drugs such as diltiazem and verapamil may be likely choices as calcium channel blockers to reduce elevated conduction velocity from the AV node, since the cells in the AV node, as well as the SA node, depend on calcium as part of depolarization. Alternatively, when increased conduction velocity arises outside of the AV node and occurs within non-

nodal tissue, other drugs, such as sodium channel blockers (Class I), may be used instead. Sodium channel blockers reduce conduction velocity by inhibiting the rate of membrane depolarization. Examples of these drugs that may be administered with depolarization outside of nodal tissue include quinidine and flecainide.

Quinidine sulfate (Quinidex®) is classified as a Class IA sodium channel blocker because of its moderate effects on sodium channels. It reduces cardiac conductivity and prolongs repolarization, which can then normalize the heart rate and rhythm. Quinidine is most commonly used for tachyarrhythmias, including atrial fibrillation, atrial flutter, and supraventricular tachycardia. It is commonly used as a preventive measure when the patient takes it as an oral tablet. The average dose varies slightly, depending on the particular arrhythmia, for instance, a patient with atrial fibrillation may benefit from a dose of 300 to 400 mg PO every 6 hours, while someone with paroxysmal supraventricular tachycardia (PSVT) would need 600 mg, administered more often, until the condition resolves.[37] When administered for PSVT, the patient can still take the dose orally.

Flecainide (Tambocor®) is a Class IC sodium channel blocker; it can significantly reduce cardiac conductivity when administered. Unlike some of the other drugs listed here, flecainide's main use is for management of cardiac arrhythmias and little else. It is indicated for tachyarrhythmias such as atrial fibrillation and PSVT, as well as sustained ventricular tachycardia. A typical dose is approximately 50 mg per day and is given orally. When given for sustained ventricular tachycardia, it should be administered within the hospital.[37]

When decreased conduction velocity develops, the rate of depolarization slows and the affected individual suffers from an arrhythmia associated with bradycardia. Drugs that are given to increase conduction velocity and to therefore increase a slowed heart rate are known as cardiostimulatory drugs. These drugs typically not only increase conduction velocity, but they also improve cardiac contractility, which leads to increased cardiac output and arterial pressure. They may also increase the heart rate, increase electrical conduction, and promote vasodilation, depending on their effects.[39]

One example of a disorder of the cardiac conduction system associated with little to no conduction through the AV node is heart block, which can actually be further classified into first, second, or third degree heart block, depending on severity. When heart block develops, the electrical conduction system slows and the signals move more slowly between the SA and AV nodes. With complete heart block, also known as third-degree block, no electrical signals reach the AV node from the SA node. There is complete dissociation and no relationship between the contractions of the atria and the ventricles when this occurs.[41]

When heart block occurs, the conduction velocity is so slowed that bradycardia and poor perfusion develops. The patient is typically symptomatic and may complain of weakness, dizziness, chest pain, or dyspnea; additionally, confusion may develop or the patient may have syncope. Upon examination, the individual will often have significant bradycardia and signs of poor peripheral perfusion as a result. Poor cardiac output can eventually lead to signs and symptoms of heart failure, and the affected patient may demonstrate pulmonary rales upon auscultation, jugular venous distention, and hypotension.

Drugs used to increase conduction velocity then have the opposite effect of those administered to slow the rate of conduction velocity, such as those used for tachyarrhythmias. As described, the SA and AV nodes are innervated by the sympathetic nervous system, which is responsible for releasing the neurotransmitter norepinephrine, which further binds to specific receptors known as adrenergic receptors. This means that norepinephrine could also be called an adrenergic agonist. The beta-1 adrenoceptor, when activated by norepinephrine or the hormone epinephrine, causes an increase in heart rate, conduction velocity, and cardiac contractility.[40]

Unfortunately, heart block and slowed conduction velocity can develop as a result of using other types of medications that are designed to treat other cardiac conditions, such as beta blockers, calcium channel blockers, or digoxin. Recognition of these medications and their management is essential to controlling the effects of heart block.

Drugs that are used in these situations are often sympathomimetic agents or catecholamines, either of which can stimulate the electrical conduction system of the heart. Atropine is one of the more common agents administered to offset the effects of bradycardia associated with heart block and to restore a normal cardiac rhythm. Atropine is known as an antimuscarinic agent, in that it attaches to the acetylcholine muscarinic receptors in the heart and prevents it from binding to the neurotransmitter. Blocking this receptor then increases the speed of conduction by increasing firing from the SA node and conduction of the impulse through the AV node. The typical dose of atropine is 0.5 mg, with an option to repeat the dose every 3 to 5 minutes and a maximum dose of 3 mg.[42] Atropine is given

intravenously, and preferably with another form of medical treatment for the cardiac arrhythmia, such as transcutaneous pacing.

It should be noted that atropine is not necessarily indicated for treatment of some classifications of second-degree heart block (Mobitz II) or third-degree heart block. With more significant episodes of heart block, there is greater dissociation between the atria and the ventricles. Because atropine increases firing from the SA node, the impulse will not necessarily affect ventricular contractions when the atria and ventricles are functioning independently of each other.[42]

If atropine is not effective or transcutaneous pacing is not available, isoproterenol (Isuprel®) may be used as another option. It is indicated for use in cases of AV block with symptomatic bradycardia, but is typically only administered as a temporary measure and not as a complete treatment. Isoproterenol is a nonselective beta-agonist and it is always administered as an intravenous dose. The typical dose for cases of heart block is an initial dose of 5 mcg/min, followed by doses ranging from 2 to 20 mcg/min.[41]

Catecholamines are naturally occurring substances that are derived from the amino acid tyrosine. Epinephrine is a catecholamine that binds to adrenergic receptors to increase heart rate and conduction velocity. As a sympathomimetic drug, epinephrine was one of the first medications developed and used in the clinical setting for management of bradycardia, however, in cases of symptomatic bradycardia, epinephrine is administered after atropine where atropine has been ineffective.[42]

Epinephrine may be administered through various routes, depending on the condition being treated. For management of symptomatic bradycardia

associated with heart block, epinephrine is typically administered intravenously at a rate of 2 to 10 mcg/min, depending on the patient's response. It may also be administered through an endotracheal tube, or through intramuscular, subcutaneous, or intracardiac methods, although at different concentrations and dosages than when administered intravenously.[43] In emergency situations, epinephrine is also used as treatment for some types of life-threatening cardiac arrhythmias, including cases of ventricular fibrillation, pulseless ventricular tachycardia, or even asystole.

Cardiac Cell Excitability

Excitability refers to the cardiac cells' abilities to continue with depolarization along the pathway in which the electrical impulse is traveling. When a cardiac cell depolarizes, it then initiates depolarization in the surrounding cells as well. This occurs as response to the transfer of sodium ions across the cardiac cell membranes. In this manner, surrounding cells respond to the initial depolarization event and the process spreads from cell to cell, which is how the impulse is conducted along the electrical pathway.

The electrical activity of the heart occurs with the transfer of certain ions, specifically sodium, potassium, calcium, and chloride ions across the cell membranes. The transmembrane potential describes the slight difference in voltage between the intracellular and extracellular compartments. A cardiac cell is considered to be excitable when it has the ability to be depolarized and to stimulate action potential. The excitability of the cell membrane is further dependent on the exchange of ions and a change in the transmembrane potential.[44]

Alterations in the excitability of cardiac cells lead to cardiac arrhythmias when the cells depolarize at an inappropriate rate or time. If the cardiac cells are too excitable and depolarize beyond the normal channels of the electrical impulse, the heart may beat abnormally, resulting in tachyarrythmias that can be dangerous for the patient. *Re-entry* is another mechanism of cardiac arrhythmia associated with altered cardiac cell excitability, which is further described below.

Each cardiac impulse passes through the normal pathway in the manner of a continuous loop, with each cell depolarizing and then repolarizing after the impulse is complete. This repolarization is what sets the cells up for the next impulse to pass through the heart and the cycle continues. Re-entry describes a situation in which the electrical signal does not complete a normal circuit but instead develops its own different circuit where it loops back on itself. Re-entry can occur in one area of the heart, such as only within the ventricles, or it may affect most of the electrical conduction pathway of the entire heart. Ventricular tachycardia is an example of an arrhythmia that may develop as a result of re-entry that impacts the ventricles.

Because cardiac excitability is affected by the passage of ions through the cell membrane, drugs that alter this transfer are typically those administered for treatment of arrhythmias associated with alterations in cardiac excitability. Potassium channel blockers also affect the transfer of ions across cell membranes. Potassium channel blockers slow the movement of potassium ions during a certain phase of the action potential, which slows repolarization of cells. Because of the effects of altered levels of potassium on cardiac tissue, potassium channel blockers should be used with caution to avoid inducing potentially life-threatening arrhythmias.

Sodium channel blockers, as discussed, impact the flow of sodium into the cardiac cells to stabilize cell membranes. When the sodium channels are dampened, the cells are less excitable, and the cells will be less likely to create their own abnormal pathways for electrical impulses to pass. Quinidine, as previously mentioned, is one of the more common sodium channel blockers used to control cardiac excitability. As a Class IA agent, quinidine decreases excitability of the cardiac cells and it prevents re-entry arrhythmias.[45]

Disopyramide (Norpace®) is also a Class IA sodium channel blocker and it has effects similar to those of quinidine. It is typically administered as an oral agent in regular or immediate-release tablets. The standard dose is between 400 and 800 mg PO per day, with divided doses. With immediate-release formulations, the dose is given every 6 hours, and with extended release forms, the dose is given every 12 hours.[46] The drug is often administered as a daily medication and is prophylactic in nature to prevent the development of arrhythmias and to maintain a normal heart rhythm if the patient has suffered a previous arrhythmia. However, it is also available in intravenous form and should be initiated in the hospital environment when used for the first time.

Disopyramide is often initially administered when a patient is having a potentially life-threatening cardiac arrhythmia, such as ventricular tachycardia. The drug can be initiated for treatment of the arrhythmia while the patient is in the hospital, and the patient can continue to receive the oral form of the drug as an ongoing preventive measure.

Abnormal Automaticity

Abnormal automaticity describes a situation in which other cardiac cells beyond those of the SA node send spontaneous electrical impulses. Consequently, the heart begins to beat abnormally and typically experiences premature contractions. Normally, only the cells of the SA node are responsible for firing electrical impulses, these cells are then said to have normal automaticity. This automaticity is the cell's ability to generate depolarization, which is the initial step of sending a cardiac electrical impulse.

Before depolarization begins at the start of the electrical impulse, ions transfer across the cell membrane so that a difference develops between the voltage inside the cell and the voltage outside of the cell. This is known as the transmembrane potential, which was described in the previous section. Spontaneous depolarization occurs once the transmembrane potential reaches a specific point.[9] Sodium ions then enter the cell and depolarization begins, triggering the beginning of systole.

The transmembrane potential must reach its critical threshold at a specific time in order for the process of creating the impulse to go smoothly. The transmembrane potential reaches its threshold at a faster rate in the SA node than anywhere else in the heart, which is why the SA node cells are those that stimulate the initial cardiac electrical impulses. Note that almost all cardiac cells have the potential to generate electrical impulses, but those in the SA node do so more rapidly under normal conditions.

When other cells beyond those of the SA node are damaged or otherwise receive messages to begin depolarization and their transmembrane potentials reach thresholds more quickly than the cells of the SA node,

ectopy occurs. An ectopic beat is described as any heartbeat that originates from another area outside of the sinus node. When ectopic beats occur continuously, the affected individual is experiencing an arrhythmia.[9]

An article by Antzelevitch in *Cardiac Electrophysiology Clinics* described the nearby cardiac cells as subsidiary or latent pacemakers because they take over the actions of the SA node to initiate impulses when the SA node is otherwise unable to do so.[10] Because the SA node produces the fastest rate of sending electrical impulses, when another area of cells takes over automaticity and tries to send electrical impulses, the depolarization does not occur as quickly as when the impulses are fired by the SA node. This results in arrhythmias that are slower than the normal pace of the heart, including bradycardia.

Abnormal automaticity may also involve a tachycardic state where the heart beats at a pace that is too fast. When the SA node is unable to function properly as a pacemaker and the surrounding cells must take over automaticity, some areas may accelerate their pace to keep up and may actually exceed the original pace set by the SA node. For example, when an AV junctional rhythm occurs, the cells of the AV node have often increased their rates of depolarization to exceed the rate of the SA node. Arrhythmias may therefore develop when the normal system of automaticity is enhanced or when it is suppressed. Some of the more common causes that lead to abnormal automaticity include electrolyte imbalances and cardiac ischemia.

Sodium channel blockers may be used to suppress abnormal automaticity when it develops outside of the SA node. Class I drugs, including those in the subcategory of Class IA may be used to block sodium channels to not only reduce conductivity, but to also prolong repolarization. Class IA drugs

such as quinidine or procainamide may suppress automaticity when it develops in the Purkinje fibers or the bundle of His, rather than in the SA node.[12] Sodium channel blockers decrease the slope of phase 4 of the conduction cycle, which is when the cell is ready for the next round of depolarization.

Quinidine is used to restore normal sinus rhythm and may be administered to suppress ventricular tachycardia. As previously discussed, quinidine is a Class IA sodium channel blocker. It is classified as such because it has a moderate effect on sodium channels to prolong repolarization and action potential. The dose administered depends on the type of arrhythmia present. Quinidine may be used to treat different forms of arrhythmias, including atrial fibrillation or supraventricular tachycardia. It is often administered as an oral dose in a range between 200 and 600 mg PO.[29]

Procainamide can also be administered for supraventricular tachycardia, as well as for atrial fibrillation or flutter. Procainamide (Pronestyl®) can convert atrial fibrillation or atrial flutter back to normal sinus rhythm; it is also beneficial for treatment of PSVT when other measures have not been successful. The drug is available as an IV injection. An oral form of this medication is not available in the U.S. It is typically administered as a loading dose followed by maintenance doses of the drug; the amount and the rate of infusion also depend on the urgency of the situation. For patients with moderate cardiac impairment, a loading dose of 15 to 18 mg/kg administered as a slow infusion over 30 minutes, followed by a maintenance dose of 1 to 4 mg/kg by continuous infusion is a standard form of administration.[47] When the patient has a life-threatening arrhythmia, a loading dose is given at a much faster rate.

Procainamide has the potential to cause some cardiac arrhythmias in addition to its use in controlling others. It should be used with caution, particularly among patients who have had previous myocardial infarction or among patients with potassium imbalances.

Lidocaine, a Class IB sodium channel blocker, is another drug that may be used to suppress automaticity when it arises from the ventricular cells instead of the SA node. It is most often used to treat tachyarrhythmias, such as ventricular tachycardia or cardiac arrest as a result of ventricular fibrillation. Lidocaine has been shown to slow depolarization and to decrease automaticity without affecting cell excitability.[45] The drug is not effective against cardiac arrhythmias when given orally, and is administered intravenously.

Advanced cardiac life support (ACLS) guidelines state that lidocaine doses and rates of administration vary slightly depending on the patient's cardiac rhythm. A dose of 1 to 1.5 mg/kg IV may be given to a patient who is in cardiac arrest as a result of ventricular fibrillation or ventricular tachycardia. If the arrhythmia does not initially respond to the dose, it may be repeated at 0.5 to 0.75mg/kg IV push to a maximum of 3 mg/kg. A patient with stable arrhythmia, such as significant premature ventricular contractions or ventricular tachycardia that has not caused cardiac arrest can receive 0.5 to 0.75 mg/kg up to a total of 1.5 mg/kg.[48]

Antihypertensive

Elevated blood pressure levels, particularly when they occur over a prolonged period, can cause significant damage to the intravascular lining of the blood vessels. In contrast, maintaining normal blood pressure levels decreases the risk of and prevents intravascular and cardiac damage to the

heart and blood vessels, such as thickening of the arterial walls, reduced blood flow due to decreased lumen diameter, and left ventricular hypertrophy.

Hypertension is technically described as persistently elevated blood pressure. Because of the changes that it can cause within the cardiovascular system, hypertension is associated with a greater risk of complications such as stroke, ischemic heart disease, vision loss, kidney damage, and heart failure. The danger associated with hypertension is that many people who suffer from the condition are unaware of it until they develop symptoms of its associated complications.

The American Heart Association has defined normal blood pressure readings and levels of hypertensive readings as follows:[13]

- *Normal blood pressure*:
  Less than 120/80 mmHg
- *Prehypertension*:
  120-139 mmHg (systolic) and 80-89 mmHg (diastolic)
- *Stage 1 hypertension*:
  140-159 mmHg (systolic) and 90-99 mmHg (diastolic)
- *Stage 2 hypertension*:
  160 mmHg or greater (systolic) and 100 mmHg or greater (diastolic)
- *Hypertensive crisis*:
  180 mmHg or greater (systolic) and 110 mmHg or greater (diastolic)

Unfortunately, hypertension is prevalent in society, affecting 1 out of 3 Americans over age 18.[14] Although there have been proposed definitions of

normal blood pressure that have been developed to prevent cardiovascular damage associated with high pressure, organ damage and injury to peripheral tissues has been noted even in some patients with blood pressure readings as low as 115/75 mmHg, which would be considered normal.[15] Therefore, one specific number given to define "high blood pressure" is ineffective in terms of describing and preventing complications among some people. Instead, a range of normal values must be given to patients that would prevent cardiac complications and that is based on individual factors, including age and weight, as well as the presence of chronic medical conditions, such as diabetes or metabolic disorder.

Hypertension is generally divided into two main types: primary hypertension and secondary hypertension. Primary hypertension develops under circumstances where there is no obvious cause of the condition, although the affected patient may have risk factors. Secondary hypertension describes high blood pressure that has developed as a result of a medical condition or some other reason that provides a specific cause for the hypertension. Primary hypertension is more commonly seen among those who have certain factors in common, and it is thought to have a genetic component. Risk factors associated with primary hypertension include advancing age, elevated dietary sodium intake, obesity, sedentary lifestyle, excess alcohol intake, and increased stress or anxiety.[15]

Despite the listed risk factors associated with hypertension, an exact cause has not been isolated to describe why a particular individual develops high blood pressure. However, several mechanisms play a role in the development of the condition, such as increased vasomotor tone due to an elevated sympathetic drive, alterations in the renin-angiotensin-aldosterone system, and increased blood volume. These mechanisms have been

identified in multiple cases and they may describe some of the pathophysiological processes of hypertension. Management of these conditions through pharmacologic interventions may successfully control the underlying circumstances that contribute to high blood pressure and may also satisfactorily control primary hypertension.

When secondary hypertension develops, it is typically as a result of an underlying condition that, with treatment, can ultimately control high blood pressure levels as well. For example, when hypertension develops as a result of an endocrine disorder, such as Cushing's disease, the main treatment involves surgery, radiation, or cortisol replacement and not necessarily antihypertensive medications. It should be noted, however, that treatment of the underlying condition does not necessarily bring elevated blood pressure readings back down to within normal limits in all cases. For some patients who struggle with chronic disease, the body has compensated for and adjusted to elevated blood pressure levels that then remain elevated, even with treatment of the chronic condition. In these cases, the hormonal or cardiovascular systems involved have adjusted to higher blood pressure levels and have modified what is considered "normal" blood pressure for the body, even if it is higher than recommended levels for the rest of the population.

The patient with secondary hypertension may benefit from antihypertensives for a period of time until the underlying condition causing the blood pressure problems has been resolved. However, this is often a temporary measure to prevent complications from hypertension and from the chronic illness and is often not meant to be a permanent solution. Instead, blood pressure levels may come under control with treatment of the disease. When the disease is ongoing and causes hypertension, such as in some cases of chronic kidney

disease, antihypertensive medications are part of ongoing treatment to prevent further kidney damage. As with other diseases of the cardiovascular system, management of secondary hypertension is best done with consideration of the patient's unique health history and physical factors in mind.

Blood Volume

Increased amounts of blood in the intravascular space equals a larger amount of fluid flowing through the blood vessels, which can further induce high blood pressure. Therefore, using some drugs that reduce blood volume may be helpful in controlling hypertension. The actual amount of blood volume in the intravascular system may vary and is dependent on several factors, including the amount of fluid and salt a person consumes, how much fluid is excreted by the kidneys, and how much fluid is lost through insensible loss, such as through breathing and through the skin.

The kidneys normally maintain normal blood volume in the body; excessive blood volume leads to an increase in fluid excretion through the urine by the work of the kidneys. When blood enters the kidneys, it is originally filtered in the glomerulus and the result contains several elements, including sodium and water. The fluid then moves through the proximal tubule, the loop of Henle, and the distal and collecting tubules. During this process, some of the sodium and water are transported across the walls of the tubules and back into circulation via a network of capillaries within the renal system.

There are various points in which more sodium and water are absorbed within the renal system, which is often part of the body's response to maintaining normal blood volume levels. More sodium and water may be absorbed in different areas, such as in the loop of Henle or in the collecting

ducts. This is regulated by angiotensin II and aldosterone. Anti-diuretic hormone also decreases water loss through urinary excretion when it stimulates more water to move from the tubules into the circulatory system.[20] This prevents excess urine production and retains more water within the body, but it can also contribute to increased blood volume.

The body may attempt to compensate for some increased blood volume by excreting more sodium and water through the urine. An increase in blood volume leads to increased renal perfusion and an increase in the glomerular filtration rate; in turn, this affects the amounts of sodium and water that enter the renal tubules and a greater rate of excretion of sodium and water from the body through the urine. Additionally, activation of the renin-angiotensin-aldosterone system also contributes to decreased fluid loss through the urine and an increase in the amount of blood flow in the intravascular space.

Elevated blood volume contributes to high blood pressure and increased stress on the heart because it ultimately increases ventricular preload, stroke volume, and cardiac output. Because levels of blood volume are typically controlled by hormones within the renal system, drugs that are administered to control blood volume are therefore designed to control some of these hormones that aim at regulating sodium and fluid reabsorption.

Diuretics are some of the more commonly prescribed drugs that can reduce blood volume in the cardiovascular system. Diuretic medications affect sodium and water reabsorption in the kidneys to promote fluid excretion in the urine and prevent excess fluid from building up within the body. Recommendations by the Eighth Joint National Committee of the American Medical Association for the general population, including those with diabetes,

are that initial antihypertensive treatment should include a thiazide diuretic, as well as the inclusion of other drugs such as angiotensin-converting enzyme inhibitors or calcium channel blockers.[49] Thiazide-like diuretics, as suggested, can remove excess fluid from the body through the urine, decrease fluid buildup, and can reduce overall blood volume.

Thiazide diuretics promote excretion of sodium, chloride, potassium, and bicarbonate and prevent reabsorption of sodium and chloride to increase output. Hydrochlorothiazide (Microzide®) is an example of one of these drugs. A typical dose is available as an oral tablet that the affected patient takes on a daily basis; the dose ranges from 12.5 to 50 mg PO.[50] A benefit of this drug is that it may be combined with other antihypertensive agents, including angiotensin-converting enzyme inhibitors.

Angiotensin-converting enzyme (ACE) inhibitors, while known for their effects on vasodilation, may also reduce blood volume as a mechanism of controlling high blood pressure. They prevent the creation of angiotensin II by blocking angiotensin-converting enzyme. Angiotensin II, along with aldosterone, is responsible for sodium and fluid retention that can lead to increased blood volume and potentially high blood pressure. The use of ACE inhibitors, which block creation of angiotensin II then prevent excess sodium and fluid reabsorption, can be very useful in controlling blood volume levels and high blood pressure. Examples of ACE inhibitors that are often prescribed for this purpose are captopril (Capoten®), enalapril (Vasotec®), and lisinopril (Prinivil®).[21]

Captopril is given as an oral agent to control blood pressure levels on a daily, ongoing basis. Captopril can be administered with other drugs, including thiazide diuretics. The typical dose is 12.5 to 25 mg PO daily, and

this can be repeated as needed. When starting captopril, the initial dose is actually given 2 to 3 times daily until normal blood pressure levels are achieved. If normal blood pressure levels cannot be attained within a couple of weeks of use, the dose can be increased to 50 mg; although, depending on the patient's level of hypertension, captopril doses could be prescribed as high as 150 mg.[50]

Enalapril is a drug that can also be used with other medications to treat hypertension, including diuretic medications, without the risk of hypotension. The initial dose is 5 mg daily, although doses can reach up to a total of 40 mg/day, given in divided doses. Enalapril may also be administered intravenously when needed; and, the typical dose is approximately 1.25 mg IV that is given over 5 minutes.[50] The drug is also useful for the treatment of other conditions in addition to hypertension, including heart failure.

Lisinopril is given as an initial dose of 10 mg PO to be taken on a daily basis; this dose can be continued if it is therapeutic or the dose can be increased up to 40 mg/day as needed, particularly if the patient is not taking a concomitant diuretic.[50] Lisinopril may be used alone or in combination with other drugs. It is also used for the management of myocardial infarction. It should not be taken with a diuretic medication, as the combination of the two agents may lead to hypotension. Diuretic use should be discontinued prior to starting lisinopril therapy because of its potency.

Systemic Vascular Resistance

A patient may develop hypertension when the blood vessels have lost some of their elasticity and they are more resistant to blood flow. Systemic vascular resistance (SVR) describes the amount of resistance to blood flow from the peripheral blood vessels; it does not necessarily include resistance

formed from the pulmonary blood vessel network. The amount of SVR that can develop is dependent on several factors that contribute to increased amounts of resistance from the vascular network, either because of factors inherently associated with the blood vessel structures or because of external forces that affect blood flow through the cardiovascular system. Increased vascular resistance may develop due to intrinsic factors such as increased blood viscosity, turbulent blood flow, or size of the vessel diameter.[24]

The sympathetic nervous system is one of the main components that controls blood pressure, as it impacts vasomotor tone. An increase in sympathetic output from the medulla in the brain can lead to an increase in intravascular resistance and increased vasomotor tone. This is often able to explain how certain factors, such as increased stress and anxiety, may contribute toward high blood pressure when these elements contribute to an increase in the sympathetic nervous system output.

Vasoconstriction may also develop as a result of activation of the renin-angiotensin-aldosterone system, in which the blood vessels constrict with the release of angiotensin II and aldosterone leads to sodium and water retention. The system is responsible for regulating blood pressure. When blood pressure levels drop too low, the kidneys release the enzyme renin; and, renin travels to the liver to convert angiotensinogen, an inactive protein, to its active form, angiotensin I. Angiotensin I then travels to the lungs where it is converted to angiotensin II through the angiotensin-converting enzyme. As noted, angiotensin II has the potential to increase blood pressure. Normally, the body wants to secrete more angiotensin II if the blood pressure drops too low.

Angiotensin II also stimulates the adrenal glands to produce aldosterone, which stimulates the reabsorption of sodium in the kidneys. This would then increase blood volume because sodium and water are being reabsorbed and are not being excreted through the urine. ACE inhibitors, when administered to control hypertension, prevent the angiotensin converting enzyme from creating angiotensin II, which then prevents an increase in blood pressure and an increase in blood volume because it prevents further aldosterone secretion. Therefore, ACE inhibitors can be given to promote vasodilation and reduce systemic vascular resistance. Some drugs already described that are ACE inhibitors and that affect blood pressure levels include captopril and lisinopril. Other examples include ramipril (Altace®) and fosinopril.

As described in the previous section, thiazide diuretics are a type of diuretic medication that are responsible for stimulating the body to release excess fluid through the urinary tract, thereby lowering plasma levels and levels of extracellular fluid to control blood pressure levels. Thiazide diuretics are frequently prescribed in conjunction with some other types of cardiac medications for the management of hypertension. Although thiazide diuretics primarily work by promoting fluid loss, which decreases overall blood volume levels, they may also have some effects on vascular resistance.

Various animal studies have shown vasodilatory effects with use of different types of thiazide diuretics. A review by Duarte, *et al.*, in the journal *Expert Review of Cardiovascular Therapy* looked at a number of studies that tested the effects of thiazide diuretics and their mechanisms of action to manage hypertension, considering that these drugs may have more than a diuretic effect as part of their success. The review showed that indapamide, a thiazide diuretic, has been shown to have some calcium channel blocking effects in the arteries. Additionally, hydrochlorothiazide and chlorthalidone

have been shown to have weak vasodilating effects because of their affinity for albumin in the plasma, and hydrochlorothiazide and chlorthalidone both are able to inhibit vasoconstriction induced by production of angiotensin II and release of norepinephrine.[18] Despite these outcomes, most of the studies evaluated in the review were of tests performed on animals and not necessarily on humans. However, there remains evidence that thiazide diuretics can impact vascular resistance through some of their mechanisms to control blood pressure levels in addition to their activity to increase urine production.

Indapamide inhibits sodium reabsorption in the kidneys and enhances sodium and water excretion through the urine. It is a potent drug that should only be taken once daily. A typical dose is administered orally at approximately 1.25 mg, although this amount may be increased up to 5 mg daily.[50] Indapamide should be taken in the morning, as it increases urinary output and would prevent the patient from nighttime awakenings to urinate. Because indapamide controls blood volume levels so well, it has the potential to cause hypotension among some patients, although for those who initially suffer from hypertension, its effects are more likely to lead to normalization of blood pressure levels. Its potent blood volume lowering effects are thought to explain why indapamide is also able to affect the cardiovascular system through decreasing vascular resistance.

Cardiac Output

Blood pressure levels may not only become elevated because of increased vascular resistance, but also because of increased cardiac output. The level of cardiac output is affected by heart rate and stroke volume. This cardiac output describes the rate and amount of blood that is ejected from the ventricles with each heartbeat.

As discussed, an individual's blood pressure can be affected by various factors, including cardiac output, blood viscosity, and resistance of peripheral vessels. As the heart works harder and has increased cardiac output, it pumps more blood at a faster rate, which in turn affects blood pressure levels and causes them to increase. Decreasing or inhibiting factors that cause an increase in cardiac output can also help to manage the blood pressure as a result. Because cardiac output is mainly impacted by two factors, heart rate and stroke volume, medications that reduce cardiac output often target these two features to decrease the work of the heart.

Stimulation of beta-receptors in the cardiac tissue causes an increase in heart rate and the heart beats more forcefully. To counteract this effect and to therefore decrease cardiac output and high blood pressure, beta-blockers are employed to block the beta-receptors. Some beta-blockers are classified as selective, in that they target specific beta-receptors in the heart, such as beta-1 receptors or beta-2 receptors. Because beta-1 receptors are predominantly found in the heart, while beta-2 receptors are located in other organs, medications used for decreasing cardiac output should be focused on beta-1 antagonist activity.

Beta-blockers are drugs that reduce cardiac output by acting as antagonists to the effects of the sympathetic nervous system and circulating catecholamines, such as epinephrine and norepinephrine. These drugs work by blocking beta-1 receptors in the heart; in the SA node, this effect reduces the heart rate, while blocking beta-1 receptors in other parts of the myocardium decreases cardiac contractility. Reduction in both of these factors can then decrease overall cardiac output and reduce arterial blood pressure.

Nebivolol (Bystolic®) is considered a cardioselective beta-blocker in that it has selectivity for beta-1 receptors. It is prescribed as indicated for the treatment of high blood pressure and works by decreasing the heart rate and the overall workload on the heart. Nebivolol is taken as an oral medication on a daily basis to provide continuous control of blood pressure. An initial dose is 5 mg PO daily, which can be titrated up at 2-week intervals to a maximum of 40 mg per day.[51]

Most beta-blockers can be combined with other drugs to treat high blood pressure, such as with diuretic medications. There are various brands of cardioselective beta-blockers that can decrease cardiac output to control blood pressure and they all tend to reduce blood pressure to about the same extent. Typically, there is not one particular kind of beta-blocker that has been shown to be much more powerful when compared to others. Although they may be combined with other drugs to increase their blood pressure-lowering effects, they should be used with caution with some calcium channel blockers because of the potential for severe bradycardia.

Cardioinhibitory Drugs

Cardioinhibitory drugs are those medications that suppress cardiac function by decreasing heart rate and cardiac contractility. They may also be implemented to decrease blood pressure levels, particularly when hypertension leads to complications of increased cardiac output. Cardioinhibitory drugs work by inducing negative chronotropic effects, described as those effects that change the heart rate, as well as negative inotropic effects, which actually decrease the force of the heart's contractions. These types of drugs are most often prescribed when it is necessary to decrease demands on the heart, such as in cases of heart

failure, following myocardial infarction, among patients with hypertension, or in those with coronary heart disease who experience angina.

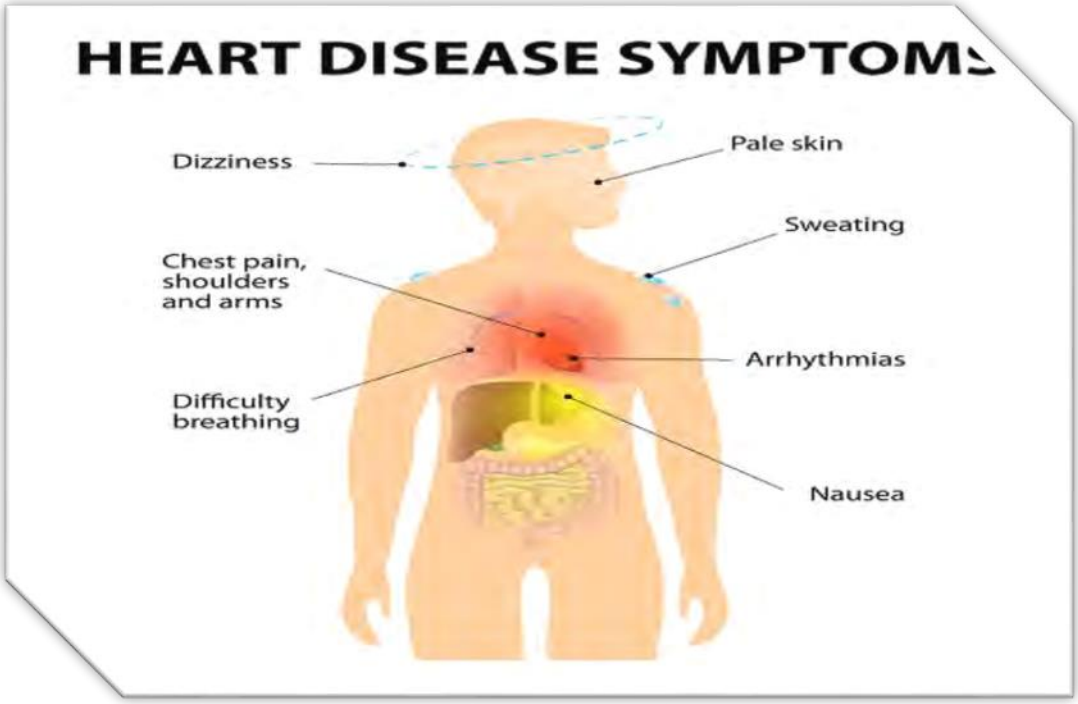
Cardioinhibitory drugs may also be prescribed in some cases of cardiac electrical conduction abnormalities. They may be used to treat cardiac arrhythmias caused by abnormal automaticity because they are able to alter the pacemaker activity of the heart. Because of their mechanisms of action, they are able to control conduction abnormalities that otherwise cause cardiac arrhythmias by regulating cardiac output and normalizing electrical conduction. Cardioinhibitory drugs are typically classified as beta-blockers, calcium channel blockers, or centrally acting sympatholytics.

Cardiac Rate and Contractility

Cardioinhibitory drugs decrease the work of the heart by decreasing heart rate and cardiac contractility, which decreases oxygen demand of the heart. This is beneficial in situations in which the affected individual is suffering from cardiac ischemia and possible angina as a result of poor oxygenation of the cardiac muscle. When oxygen demands are lessened because of decreased cardiac output, the affected patient may be less likely to suffer from symptoms of angina or the complications of cardiac ischemia.

As described with some other cardiac conditions listed, beta blockers are one type of drug that decrease cardiac output to decrease the overall workload of the heart. Beta-blockers work through blocking beta-adrenergic receptors, which normally respond to such neurotransmitters as epinephrine and norepinephrine that increase the heart rate and cause vasoconstriction. Beta-blockers prevent this activity so that the heart rate is decreased and the blood vessels do not constrict. Ultimately, these drugs then prevent excess stress on the heart so that in cases where an affected patient is

struggling to maintain normal cardiac output, such as in the case of heart failure, cardiac output is decreased and the patient is less likely to suffer from disease complications.



Some patients with heart failure benefit from administration of cardioinhibitory drugs because these drugs reduce the workload of the heart. Although heart failure actually describes a condition in which there is decreased cardiac function as a result of a disease process, cardioinhibitory drugs have still been successfully prescribed as part of treatment in some of these situations because they reduce some of the negative cardiac changes that occur due to heart failure. Beta-blockers are the cardioinhibitory drugs prescribed specifically for cases of heart failure.

Many experts believe that all beta-blockers work in a similar manner and that they produce many of the same effects. For instance, when beta-

blockers are used to decrease blood pressure in cases of hypertension, they are often noted to decrease blood pressure levels to about the same extent and that one particular type of beta-blocker works no more strongly than others.

Among patients with heart failure, one type of beta-blocker used as a cardioinhibitory drug may work in much the same manner as the rest; however, a review in the *American Journal of Cardiology* showed that one particular type of beta-blocker, carvedilol, showed significant results in decreased overall patient mortality when used among those with heart failure. The review compared the effects of carvedilol to other similar beta-blockers that might be prescribed as cardioinhibitory drugs, such as atenolol, bisoprolol, metoprolol, and nebivolol. The results showed that among studies of patients with systolic heart failure who used carvedilol, there was a decrease in all-cause mortality rates when compared to other beta-blockers.[52] Although further research is most likely needed to fully confirm these facts, it may be that carvedilol becomes a foremost choice for managing cardiac output for patients with heart failure.

Carvedilol (Coreg®) is a non-selective beta-blocker, which means that it may block both beta-1 and alpha-1 receptors. It is prescribed not only for the management of heart failure, but also for treatment of hypertension and for those recovering from myocardial infarction because it reduces strain on the heart. Carvedilol is taken as an oral preparation, typically on a daily basis. A standard dose of an immediate-release tablet is 3.125 mg PO daily for approximately 2 weeks, with an increase in the dose every 2 weeks, as tolerated to a maximum of 25 mg daily.[53] The drug is also available in extended release form.

Arterial Pressure

The sympathetic nervous system plays a significant role in regulating arterial blood pressure. Sympatholytic drugs are those that affect the sympathetic nervous system to control cardiac output, cardiac contractility, and arterial pressure. Increased arterial pressure may lead to hypertension; and, cardioinhibitory drugs that are sympatholytic control blood pressure levels, often when increased cardiac output or increased systemic vascular resistance causes hypertension. These drugs can reduce arterial pressure by reducing cardiac stroke volume and/or heart rate.[15]

Sympatholytic drugs work through one of three mechanisms. They may block the effects of norepinephrine in the heart, and impulses in the sympathetic ganglia in the spinal cord that communicates with the medulla in the brain; or, they may block sympathetic activity in the brain. The latter type of drugs is known as centrally located sympatholytic drugs.[54] These drugs work by activating alpha-2 adrenoceptors in the smooth muscles and in the nerves, which decreases cardiac contractility and decreases the heart rate. Blood vessel tone is also decreased, which causes vasodilation and a subsequent decrease in arterial pressure.

Centrally acting sympatholytic drugs are often used as cardioinhibitory drugs for the management of hypertension because they can decrease arterial pressure. They may be used with other drugs for blood pressure treatment, but caution is advised to prevent hypotension from their effects. They are safe to use in patients who have kidney disease, as they do not cause damage to the renal system. Examples of these types of drugs include clonidine and alpha-methyldopa.

Clonidine (Catapres®) is classified as a centrally acting anti-hypertensive medication because it inhibits signals from the brain to the circulatory system that would normally cause them to constrict. It is available as an oral tablet and is taken by the patient on a daily basis to control blood pressure levels. The typical dose is 0.1 mg PO daily, which may be increased up to 0.6 mg as needed, although dose increases should be made slowly over the course of several weeks. Clonidine is also available as a transdermal patch which may also be titrated according to the patient's requirements for blood pressure control.

Methyldopa (Aldomet®) is an antihypertensive agent that is used to decrease arterial pressure to decrease some of the work of the heart. Methyldopa is classified as a centrally acting alpha-adrenergic agonist; it stimulates both alpha-1 and alpha-2 receptors to lower blood pressure levels. The drug has similar effects on blood pressure as clonidine. It is mainly used for the treatment of hypertension and hypertensive crisis; and, it may also be used for pregnant patients to manage high blood pressure associated with preeclampsia. Methyldopa is administered daily as an oral agent at doses that range from 250 to 1000 mg/day in divided doses. When given intravenously, it is given in doses from 250 to 1000 mg, infused over 30 to 60 minutes every 6 to 8 hours as needed.[55]

Diuretic Drugs

Diuretic drugs are those medications that remove excess fluid from the body by stimulating the kidneys to increase excretion of water and certain ions. They may be prescribed to control some symptoms of heart disease by increasing fluid loss, most often through urine output. Diuretics are most commonly prescribed for cardiac conditions such as heart failure and

hypertension that develops as a result of increased intravascular fluid volumes.

Heart failure develops when the heart is unable to pump blood effectively enough to meet the body's needs for oxygenation and nutrients through the circulatory system. The heart cannot pump enough blood to keep up with oxygen demands of the body, often because part of the heart has been damaged in some way, such as through coronary heart disease, hypertension, or cardiomyopathy; damage to the heart valves, such as with inflammation or infection, or due to congenital anomalies that weaken the heart.

When the ventricles do not fill properly when they are supposed to, this leads to heart failure. Often, the ventricles become stiff and are weakened, which makes them ineffective to pump what blood does enter the ventricular chambers. The condition can affect primarily the left ventricle, the right ventricle, or both sides, although left-sided heart failure is more common. If the ventricles are unable to pump blood effectively, blood and excess fluid backs up in the cardiovascular system, causing congestion in other areas, including in the liver, the lungs, the abdomen, or the lower extremities. Because of this fluid back up, the condition was formerly called "congestive heart failure;" however, congestion is not present in all cases, so the condition is now more commonly referred to as simply "*heart failure*."

Heart Failure

The signs and symptoms of heart failure are typically associated with increased fluid volume that develops because of poor cardiac output and the heart's inability to keep up with fluid volumes in the circulatory system. The affected patient may experience shortness of breath, particularly when

activity and lung sounds may sound wet upon auscultation. Fatigue, weakness, anorexia, increased urination, tachycardia or cardiac arrhythmia, and difficulty concentrating are all potential manifestations of heart failure. Patients may also experience excess fluid in the tissues, causing swelling and edema, weight gain associated with fluid retention, and abdominal ascites.

Diuretic medications are often prescribed as part of therapy for management of excess fluid associated with heart failure. These drugs are often administered in conjunction with other types of drugs that support cardiac function, such as ACE inhibitors or beta-blockers.

Hypertension

Diuretics may also be administered for treatment of hypertension, particularly when the condition is caused by excess fluid volume. By decreasing some of the fluid in the intravascular space, these drugs may also decrease the level of blood pressure. As described, excess fluid in the circulatory system can increase blood pressure because there is more fluid in the blood vessels overall. The increased fluid requires the heart to pump more blood with each heartbeat and increased volumes of intravascular fluid place more pressure on the interior walls of the blood vessels.

Diuretics used for management of hypertension may be combined with some other drugs designed to manage hypertension. However, they primarily work by increasing excretion of excess fluid through urine output, which reduces the amount of fluid in the intravascular system and diminishes blood pressure levels.

Urine Output

Diuretics prevent fluid from accumulating in the body and thereby prevent some of the complications of heart failure, such as peripheral edema, breathing difficulties because of fluid and congestion in the lung tissue, fluid retention and weight gain, or ascites. They work because they stimulate production of urine, so that the body will get rid of excess fluid by excreting it through urine output. Many patients may refer to diuretics as "water pills" because of their effects on urine output.

Diuretic medications are typically classified according to their mechanisms of action. There are some differences in how they work, although their outcomes are quite similar. There are three major types of diuretic drugs:

- *Loop Diuretics*
- Loop diuretics are typically quite effective in their actions to control fluid levels. They are most commonly used in the treatment of heart failure. Loop diuretics work specifically by affecting the transport of sodium and water across cells in the loop of Henle in the kidney and prevent sodium and chloride reabsorption. Loop diuretics are able to induce up to 20 % of sodium excretion through the urine because of their effects.[16]
-
- Loop diuretics also promote calcium excretion and they may cause difficulties with fluid and electrolyte imbalance. They are one of the most commonly prescribed drugs in the U.S., and were among the top 10 percent of the 200 most prescribed generic medications in the year 2008.[17]

- *Thiazide Diuretics*

  Thiazide diuretics are one of the more commonly used drugs for management of cardiovascular disease, particularly for the treatment of hypertension. They work through increasing urinary excretion of salt and of water in part of the loop of Henle and the early distal tubule. They also contribute to urinary excretion of several other electrolytes as well, including bicarbonate, potassium, and magnesium, so they may be more likely to cause electrolyte imbalances.

- *Potassium-sparing Diuretics*

  These drugs work in the cortical collecting tubule of the kidney to prevent sodium reabsorption and to prevent excess secretion of potassium in the urine. They block sodium channels so that sodium is unable to access the sodium pump and pass into cell membranes. Potassium-sparing diuretics typically must be combined with other drugs in order to work most effectively; they do not have very strong diuretic capabilities when used alone. Because they prevent loss of potassium, they should not be used with potassium supplements or with other substances that also prevent potassium loss in order to avoid development of hyperkalemia.

When used for control of heart failure to increase urinary excretion of fluid, loop diuretics are the most common types of drugs prescribed. Because they promote fluid excretion, use of these drugs can control some of the difficult symptoms associated with heart failure. For example, when an individual with heart failure suffers from breathing difficulties because of pulmonary edema, loop diuretics are often able to control some of the fluid buildup by promoting salt and water excretion to decrease fluid accumulation in the lungs. They do this by decreasing left ventricular preload, increasing the

ability of the veins to increase their blood-carrying capacity without significantly raising blood pressure, and decreasing wedge pressure.[17] Examples of loop diuretics often prescribed for management of heart failure symptoms include furosemide (Lasix®), bumetanide (Bumex®), and torsemide (Demadex®).

Furosemide stimulates diuresis in the affected patient by inhibiting sodium and chloride reabsorption from the ascending loop of Henle and the distal renal tubule. Its dose is individualized to each patient's needs, depending on heart failure symptoms and response to the drug, but typical doses range between 20 and 80 mg per day. Furosemide is delivered as an oral agent that the patient takes on a daily basis. Its dose may be increased as needed if the current amount is ineffective in controlling heart failure symptoms. The drug is approved for the control of edema associated with heart failure as well as liver cirrhosis and nephrotic syndrome.[53]

Bumetanide works in a manner similar to furosemide in that it inhibits sodium and chloride reabsorption in the kidney; this drug tends to have powerful effects and can result in significant diuresis. For control of edema, bumetanide may be administered as an oral tablet, or as an intramuscular or intravenous dose. Doses range between 0.5 and 2 mg, which may be repeated depending on patient response. Because it can cause such significant diuresis, increases in dosage should be made in small amounts at a time to prevent excess fluid loss.

Torsemide is approximately twice as potent as furosemide in its ability to induce diuresis. As with other loop diuretics, it induces urinary excretion of sodium, chloride and water; however, it does not necessarily affect acid-base balance. As an oral or intravenous dose, torsemide may be

administered at 10 to 20 mg. Its dose can then be doubled as needed to achieve the desired effects but the patient should not receive more than 200 mg. If the patient has not achieved diuresis within 6 hours of onset of the drug, then torsemide should be discontinued and another intervention applied.[53]

To facilitate urinary excretion, loop diuretics increase movement of fluid and electrolytes from the kidney tubules. The decrease in plasma volume then stimulates production of aldosterone, a steroid hormone that impacts blood pressure by regulating salt and fluid levels in the bloodstream. Sodium is reabsorbed in the distal tubules, while potassium and hydrogen ions are excreted.

Unfortunately, people with heart failure may be less likely to respond to the effects of loop diuretics as their conditions advance in severity.[17] The response is often to administer greater doses to be able to continue to control fluid volume levels. While this can be effective, it is not always optimal because affected patients may then be more likely to suffer from electrolyte imbalances and other complications associated with increased loop diuretic use. They may also deplete levels of other electrolytes in the bloodstream, including magnesium and potassium, when administered with other types of diuretics.

A study by Chiong and Cheung in the journal *Clinical Cardiology* considered the use of loop diuretics as the primary source of fluid reduction in patients with heart failure to regard possible adverse outcomes as a result of overuse and too frequent prescriptions of loop diuretics, such as furosemide. The study concluded that loop diuretics are useful in heart failure treatment, and

that they should be used in moderation with modest dose adjustments and regular clinical evaluations to assess patient outcomes.[17]

Thiazide diuretics may be prescribed for the management of arterial hypertension when elevated blood pressure levels are due to increased fluid volume. Many diuretics have been replaced by other antihypertensive drugs, including beta blockers and ACE inhibitors, however thiazide diuretics have been shown to successfully remove excess fluid to be able to control hypertension in some patients, particularly when they are prescribed with other cardiac medications. Common examples of thiazide diuretics include hydrochlorothiazide (HCTZ), chlorthalidone (Thalitone®), indapamide (Lozol®), and metolazone (Mykrox®).

Hydrochlorothiazide may be known by its brand name, Microzide; its main mechanism of action is to prevent reabsorption of sodium and chloride in the distal tubules, compared with action in the loop of Henle as is seen with loop diuretics. Oral doses administered for management of hypertension range from 12.5 to 50 mg PO, while doses given for the control of edema associated with heart failure are somewhat larger, ranging from 25 to 100 mg PO per day.[53]

Chlorthalidone also works in the distal tubules in a manner similar to hydrochlorothiazide. In addition to causing excretion of sodium and chloride ions into the urine, chlorthalidone may also augment the excretion of potassium and hydrogen ions. Patients who use this drug should be monitored for changes in electrolyte levels, particularly alterations in potassium. A typical dose of chlorthalidone, when given for hypertension, is 12.5 to 25 mg per day, while a dose given for the management of edema due to heart failure is 50 to 100 mg per day.[53]

Indapamide has been previously discussed and it works in a manner similar to chlorothalidone and hydrochlorothiazide. It may be prescribed for management of edema due to heart failure, in which a typical dose is 2.5 mg PO each day. When given for hypertension, the dose is slightly smaller at 1.25 mg PO.[53]

Metolazone is prescribed for the management of edema associated with heart failure, hypertension, or kidney disease. It may be used with some other drugs but is not recommended for use with loop diuretics, such as furosemide or torsemide. It should also not be combined with some other drugs used to treat heart conditions, including some sodium channel blockers such as flecainide. For management of edema, a typical dose is 5 to 20 mg PO daily, while a dose given for hypertension is approximately 2.5 to 5 mg PO daily.[56]

The sodium/chloride co-transporter is a component of the kidney that reabsorbs sodium and chloride ions in the distal convoluted tubule in the nephron of the kidney through molecule transport and movement. The co-transporter is responsible for approximately 7 percent of total sodium reabsorption within the distal convoluted tubule.[18] Thiazide diuretics primarily work by inhibiting the mechanisms of the sodium/chloride co-transporter, resulting in an increase in fluid loss within the urine. The effects of these drugs also lead to decreased plasma volume in the intravascular space, decreased fluid volume in the interstitial spaces, decreased venous return, decreased cardiac output, and ultimately, decreased blood pressure.

Studies have also shown that chronic use of thiazide diuretics eventually results in a return of plasma and extracellular fluid levels to normal within several weeks of starting the drug, however, blood pressure levels remain

lowered and hypertension does not return with continued drug use. Furthermore, when the drug is discontinued, blood pressure levels will return to their pre-dose states, but they tend to do so quite slowly instead of rapidly bouncing back.[18] This suggests that thiazide diuretic use, while it controls hypertension, does not necessarily do so solely through fluid volume excretion.

Some patients are more likely to suffer from electrolyte imbalances when they use diuretic medications because they excrete high levels of fluid and electrolytes out of the body through the urine. When this happens, electrolyte abnormalities can actually become dangerous for some people, particularly with potassium abnormalities that can develop as a result of loss of too much of the electrolyte. When there are changes in the amount of potassium in the extracellular fluid because of increased urinary excretion, the cells' membrane potential, or the small amount of voltage maintained across the cell membrane, is adversely affected. Changes in this membrane potential can then lead to alterations in the cardiac electrical conduction system that result in cardiac arrhythmias, some of which may be life threatening.

Hypokalemia may also develop with diuretic use when sodium reabsorption is blocked. The amount of sodium reabsorption is connected to potassium excretion in the cortical collecting duct in the kidney; therefore, when more sodium reabsorption occurs, excessive potassium excretion may follow. Potassium-sparing diuretics are often administered to prevent this from occurring. They may be given individually or they may be administered concomitantly with other types of diuretics, including loop or thiazide diuretics. Examples of some types of potassium-sparing diuretics include

amiloride (Midamor®), eplerenone (Inspra®), and spironolactone (Aldactone®).

Amiloride has a different chemical composition compared to other diuretics, although it is classified as a potassium-sparing agent. It may be administered at doses of 5 to 10 mg PO daily for hypertension and for fluid retention due to heart failure.[53] This drug should be used with caution in some patients because it may cause potassium retention and hyperkalemia.

Eplerenone is an aldosterone blocker, so it prevents the release of the hormone, which then blocks reabsorption of sodium and water. As an oral dose, eplerenone may be given for management of hypertension or heart failure symptoms. For heart failure, the initial dose is 25 mg PO daily, which may be increased up to 50 mg daily. For hypertension, the starting dose is 50 mg once per day, but it can be increased to 50 mg twice per day as needed.[57]

Spironolactone is one of the more common potassium-sparing diuretics used among patients with heart failure. Spironolactone competes with aldosterone for receptor sites within the kidney, thus preventing some of the effects of aldosterone and resulting in increased fluid excretion while preventing excess potassium losses. Its dosage range is between 25 and 200 mg PO each day for management of edema; it is also prescribed for controlling hypertension and for treatment of primary hyperaldosteronism.[53] Potassium-sparing diuretics work in the cortical collecting duct of the kidney; this segment of the collecting duct system is normally regulated by aldosterone.

Some potassium-sparing diuretics are known as aldosterone receptor antagonists because they block the effects of aldosterone to maintain a balance of salt and fluid excretion.[19] As previously defined, amiloride works by blocking the epithelial sodium channel in the distal tubule, which is normally important for transport of sodium ions and control of the regulation of sodium excretion into the urine. When amiloride blocks this system, it causes sodium reabsorption within certain portions of the kidneys that does not simultaneously lead to a loss of potassium. Most potassium-sparing diuretics are relatively weak as diuretics as compared to some of the other medications available. However, they are often beneficial when combined with other diuretic medications to promote fluid volume and to control hypertension or some symptoms of heart failure. Routine monitoring of electrolyte levels and renal function is essential when prescribing any diuretic medication to prevent potentially dangerous electrolyte imbalances and to avoid kidney damage.

Vasopressor Drugs

Vasopressors are types of vasoactive drugs that decrease the diameter of the blood vessels. They are most often used in conditions in which the patient is experiencing a drop in blood pressure and is suffering from the negative effects of hypotension. This hemodynamic instability can develop due to a number of conditions, often during illness or injury that would lead to shock, including hemorrhagic, septic, or cardiogenic shock.

Hemorrhage following a traumatic injury or after a surgical procedure can lead to rapid and destructive blood loss. The bleeding may occur externally or internally but, in either condition, it results in a decrease in the total amount of blood circulating through the cardiovascular system. An individual who is experiencing hemorrhage may have few symptoms at first. If the

bleeding is internal, there may be discomfort but, in many situations, there is no sign of bleeding at all. With enough blood loss, the patient will eventually begin to show signs of intravascular fluid loss, demonstrated as low blood pressure, weakness, shortness of breath, and dizziness.

A drop in blood pressure due to blood loss can be dangerous since the organs are not receiving enough critical oxygen and nutrients from the blood. When the body cannot provide enough blood to adequately perfuse the organs, the patient is entering a state of hemorrhagic shock.

Vasopressor medications may be indicated for use in the management of hypovolemic shock that has developed due to hemorrhage. Because hemorrhagic shock can quickly lead to irreversible complications and ultimately death if the condition is not well managed, vasopressor medications administered during treatment may help to prevent low blood

pressure. However, studies have shown that use of pressors during hemorrhagic shock is somewhat limited to treatments in Europe and not necessarily in the United States.

A review by Beloncle, *et al*., in the *Annals of Intensive Care* evaluated results of studies that provided vasopressor medications to patients in hemorrhagic shock and showed that among many studies, administration of these drugs during the early phases of shock was beneficial.[58] Although fluid administration is a key component of controlling hemodynamic status among patients with severe hemorrhage, vasopressor administration, at least during the early stages of shock, could assist with management of hypotension. Although there are several studies that support this theory, the review noted that there is still insufficient evidence to entirely support this practice.

Septic shock is a form of distributive shock that develops following infection and results in life-threatening hypotension. The condition often begins as a form of infection at a certain point in the body, followed by septicemia, in which the infection enters the bloodstream and spreads to other body locations. Septic shock describes a state in which the infection has affected the patient's ability to perfuse vital organs and significant hypotension is present. Septic shock causes hypotension, often despite adequate fluid resuscitation and, without proper management, can lead to organ failure and death. It can develop in any patient; however, it is more commonly seen among patients who are very young, the elderly, and those who are immunocompromised.

Pressors play a key role in the management of septic shock. The *Surviving Sepsis Campaign*, the results of which were published in the journal *Critical Care Medicine,* has recommended use of vasopressors as part of

hemodynamic support and adjunctive therapy in the management of septic shock.[59] The guidelines recommend the use of the drugs norepinephrine and epinephrine and supply target arterial pressures as part of guidelines for improving blood pressure levels among patients who experience hypotension during sepsis in addition to other measures of circulatory support. In addition to control of hypotension, the patient with septic shock typically needs antimicrobial drugs to control the infection, correction of hypoxia or hypoxemia if it has developed, which often involves mechanical ventilation, and adequate organ perfusion, which is supported through fluid administration and use of pressor medications.

Cardiogenic shock describes a condition in which the affected patient experiences decreased cardiac output and tissue hypoxia despite adequate blood volume in the intravascular space. The affected patient typically has sustained hypotension and reduced cardiac output, but often has not experienced a drop in blood volume. The signs and symptoms of cardiogenic shock are related to tissue hypoperfusion and poor cardiac output, including altered mental status, cool and pale extremities, oliguria, and cyanosis.[34] This state of shock develops after some form of cardiac dysfunction, such as cardiac arrhythmia, valve dysfunction, or coronary artery disease.

Vasoactive drugs, including pressors and inotropic medications are often given to patients experiencing cardiogenic shock to resolve some hypotension. Patients with inadequate tissue perfusion and hypotension as a result of cardiogenic shock often receive medications to increase the mean arterial pressure to between 60 and 65 mmHg.[34] Because cardiogenic shock develops as a result of some form of cardiac dysfunction, medication administration may also be aimed at improving cardiac output. For example, cardiogenic shock may develop following a myocardial infarction, in which

the heart muscle has experienced severe ischemia and tissue necrosis. Administration of agents that improve cardiac output during the state of cardiogenic shock may help to meet some of the oxygen demands needed during this time and can improve coronary blood flow.

It is important to note that pressors must be used with a strict amount of control, typically within the intensive care setting or in a situation in which the clinician is able to constantly monitor the patient's vital signs and response to the drugs' effects. When appropriate monitoring is not available, the side effects of some of these drugs can cause harmful and possibly irreversible negative effects to the patient.

Cardiac Contractility and Output

Cardiac contractility describes the strength and force of the heart's contraction during systole. There are various factors that can affect cardiac contractility and that can ultimately lead to a decrease in cardiac output, including cardiovascular disease conditions such as hypertension, ischemic heart disease, or cardiomyopathy, the use of some types of drugs, such as beta blockers, or stimulation of the parasympathetic nervous system.[22] Alternatively, drugs that are positive inotropes can increase contractility. Other external effects that may cause greater cardiac output, even if only temporarily, might be increased stress levels or anxiety, as well as physical exercise.

The stroke volume describes the amount of blood that is pumped out of the heart with each contraction. According to Starling's Law, the heart will have a greater stroke volume when it has a larger amount of filling pressures.[23] If cardiac contractility is increased, stroke volume is therefore increased; alternatively, when the heart is not pumping efficiently, the stroke volume is

decreased and there is less output of blood with each heartbeat, which can lead to decreased oxygenation of the body's tissues and organs and shock.

Cardiovascular failure and shock results when the heart is unable to pump enough blood to sustain the needs of the tissues and surrounding organs to receive enough oxygen or nutrients. Without treatment, this ischemia may cause permanent complications and could even lead to death. Inotropes are those drugs that improve circulation and oxygen delivery by increasing cardiac output. They are most often administered in critical care environments for use among significantly ill patients who are at risk of severe hemodynamic compromise from poor cardiac contractility.

The most commonly used inotropes that are administered to improve cardiac output are classified as catecholamines, which occur naturally in the body and have hormonal properties. Some of the most commonly used endogenous inotropes administered to improve cardiac contractility include dopamine, norepinephrine, and epinephrine. Synthetic forms are also available and include dobutamine and dopexamine.

Dopamine has positive vasoactive effects in that it works by increasing cardiac contractility and it has a vasoconstrictive effect. It improves cardiac contractility at low to moderate doses when it works as a dopamine receptor agonist. Dopamine is a neurotransmitter normally produced by the body and it acts as a precursor to norepinephrine. Its effects ultimately depend on the dosage prescribed, as well as the patient's condition. Dopamine given in low doses typically stimulates the receptors that produce vasodilation of the renal and mesenteric arteries. Alternatively, higher doses of dopamine stimulate cardiac output and produce vasoconstriction.[34]

Dopamine is given as a continuous intravenous infusion based on the patient's weight. A moderate dose of dopamine, which can be administered to improve cardiac output in cases of cardiogenic or septic shock, is typically 5 to 15 mcg/kg/min. The dose can be increased every 10 to 30 minutes at intervals of 1 to 4 mcg/kg/min, depending on patient response. Higher doses of 20 to 50 mcg/kg/min may also improve blood pressure by stimulating vasoconstriction.[34]

Norepinephrine is a catecholamine normally produced by the body that stimulates alpha and beta receptors. This stimulation improves cardiac contractility and increases the heart rate, which leads to improved cardiac output. Norepinephrine (Levophed®) is also used for management of severe hypotension that is so significant that it is life threatening. In cases of cardiac arrest, norepinephrine is administered as an initial infusion at a rate of 8 to 12 mcg/min, which can be increased or decreased, based on the effects on the patient. Its continuous infusion rate is typically lower and ranges from 2 to 4 mcg/min.[34]

According to the Surviving Sepsis Campaign, *norepinephrine is the first choice of vasopressor therapy for patients experiencing septic shock*. It should be initially administered to achieve a mean arterial pressure of 65 mmHg. If norepinephrine is ineffective in achieving this state alone, then epinephrine should be added for blood pressure support.[59]

Epinephrine, also called adrenaline, is often added to norepinephrine to resolve hypotension or it may be used in place of dopamine when dopamine is otherwise ineffective. Like norepinephrine, epinephrine stimulates alpha and beta-adrenergic receptors to improve cardiac output and to increase blood pressure. In cases of cardiac arrest, epinephrine can be given via

various routes, depending on what is available, including intravenous, endotracheal, and intracardiac doses. It may be given intravenously as an IV push dose of 0.5 to 1 mg every 3 to 5 minutes; if IV access is not available and the patient is intubated, epinephrine can be administered via endotracheal tube at a dose of 2 to 2.5 mg, given every 3 to 5 minutes.[64]

Dobutamine increases cardiac output and primarily affects the beta receptors; it is classified as a sympathomimetic amine. Dobutamine, along with dopamine, is one of the main drugs used to improve cardiac contractility in cases of septic shock. When a patient has decreased cardiac output as a result of shock, dobutamine may be administered as a continuous infusion, particularly during early portions of treatment. It is administered at a rate between 0.5 and 1 mcg/kg/min initially, and then increased to 2 to 20 mcg/kg/min, depending on patient response.[64]

Systemic Vasculature

Decreased blood pressure develops during shock, although the affected patient may or may not experience vasodilation as a cause of hypotension. Some vasopressor medications increase blood pressure levels because they impact the systemic vasculature and cause it to constrict. This counteracts the effects of vasodilation, in which the enlarged diameter of the blood vessels can lead to low pressures and poor peripheral perfusion.

When shock occurs, the affected individual experiences inadequate organ perfusion, often as a result of low intravascular fluid volume. In cases of cardiogenic shock, poor cardiac output is often a causative factor for shock development; however, this type of shock also causes poor vascular resistance, which leads to hypotension. The blood vessels dilate in response to the condition and, while hypovolemia is often not present in cases of

cardiogenic shock, the patient still experiences hypotension and poor tissue perfusion, often because of vasodilation. Vasopressors are therefore often administered to constrict systemic vasculature, which will ultimately improve blood pressure and tissue perfusion.

By constricting the systemic vasculature, vasopressors are able to improve blood flow and improve blood pressure. Therefore, these drugs have actions that stimulate the smooth muscles found in the walls of the blood vessels to contract. Stimulation of this contraction occurs with the interaction of certain substances with adrenergic receptors in the blood vessels. Specific drugs are designed to stimulate these adrenergic receptors, which then causes smooth muscle contraction. The alpha-receptors in the blood vessels are responsible for vasoconstriction, while the beta-receptors are often responsible for vasodilation. Drugs that have an affinity for the alpha-receptors are those that produce vasoconstriction; when the vessels constrict, vascular resistance is increased.

Drugs that are alpha-receptor agonists are therefore those that are commonly administered to increase vascular resistance, causing vasoconstriction and improved blood pressure. This is especially important during states of shock when hypotension causes such poor perfusion of the peripheral tissues and organs that organ failure can quickly result. Catecholamines, including norepinephrine and epinephrine are examples of drugs that are alpha-receptor agonists and that cause vasoconstriction. In addition to these examples described, other examples of drugs used as pressors that increase vascular resistance include metaraminol and ephedrine.

Metaraminol (Aramine®) is a pure alpha-1 agonist that directly affects the alpha-1 receptors in the blood vessels to cause vasoconstriction. It is known as a sympathomimetic amine that has effects on both systolic and diastolic blood pressure levels. It has a relatively short half-life, but it is administered through an intravenous infusion. Unlike some other types of vasopressor drugs, metaraminol can be administered through a peripheral infusion and does not necessarily require central line placement. A typical dose of the drug is given as a 0.5 to 5 mg IV bolus.[99] Alternatively, metaraminol may be administered as a continuous infusion; it should be added to IV fluid, such as with sodium chloride solution, and adjusted to be administered at a rate between 15 and 100 mg to maintain adequate blood pressure.[100]

Ephedrine is another drug that is classified as a sympathomimetic amine; it has various uses in clinical medicine, from use as a bronchodilator to a decongestant medication. Ephedrine may also be given to control blood pressure levels among some patients experiencing hypotension due to vasodilation. As with metaraminol, ephedrine may also be given through a peripheral IV and does not necessarily require central line access, making it beneficial for rapid administration when needed. It is indicated for use in cases of hypotension where central line access is not available. It is administered in doses between 3 and 9 mg, which can be repeated PRN.[99] The drug has the potential to cause tachyphylaxis, which describes a condition where there is a rapid decrease in response to the drug with repeated administrations, so its effects should be monitored accordingly.

Before giving vasoactive drugs, the healthcare provider should ensure that the patient also receives adequate fluid. Administering medications to cause vasoconstriction to improve blood flow will not have an effect if the patient is deficient in fluid volume to begin. Vasopressors should be administered

concomitantly with intravenous fluids; often, during states of shock, the patient requires fluid resuscitation, which involves administration of very large amounts of fluid to offset hypovolemia. Monitoring of vital signs, including blood pressure, heart rate, and cardiac output are each necessary and should be ongoing throughout the period of vasopressor administration.

Thrombolytic Therapy

Thrombolytic therapy is initiated when a patient suffers from complications of blood clots, in particular, conditions such as stroke or myocardial infarction. In addition to these critical conditions, blood clots that develop within the blood vessels can lead to myriad of other complications, including pulmonary embolism if a blood clot lodges within the pulmonary vasculature, deep vein thrombosis when the blood clot implants in one of the deep veins in the legs or the pelvis, or clotting of central lines and dialysis catheters, which prevents the administration of some essential medical procedures or administration of important drugs and fluids.

Normally, clotting processes are necessary and beneficial to prevent excess hemorrhage following an injury. This coagulation is very important to not only maintain normal blood flow but to also contain blood loss when a blood vessel is injured. When a patient has coagulation problems, blood may either clot too much, putting the patient at risk of developing blood clots in abnormal locations, or blood may not clot quickly enough and the patient may bleed unnecessarily. This most often is caused due to an absence of coagulation factors that normally contribute to blood clot formation. The body has a delicate balance of factors that contribute to both coagulation and anticoagulation, with specific substances involved on either end of the spectrum of clotting processes.

With normal coagulation, platelets and certain proteins within plasma gather at the site of injury to form a blood clot to stop the bleeding. Once the bleeding has stopped and the area has started to heal, the blood clot typically dissolves on its own. The platelets, also called thrombocytes, are actually fragments of cells that contribute to clot formation when necessary. Plasma proteins known as clotting factors also contribute to clot formation when necessary. The clotting factors are numbered and are given different names between each; they range from clotting factor I (fibrinogen) to XIII (fibrin-stabilizing factor). These factors are normally inactive within the blood until an injury occurs and they are called to action to participate in the clotting process.

When a blood vessel is injured, vasoconstriction initially occurs at the site of injury, which reduces blood flow in an attempt to prevent excess hemorrhage. Platelets arrive at the site of injury where they adhere to the endothelial surface of the damaged blood vessel through the glycoproteins found on their cell membrane surfaces. Once they have arrived and begin to collect at the injury site, they release adenosine diphosphate, which attracts more platelets to the area. Eventually, enough platelets collect at the site so that a clot can form, strengthened by the presence of fibrin, which develops with the release of clotting factor I (also known as fibrinogen). This process signals the beginning of the clotting cascade.

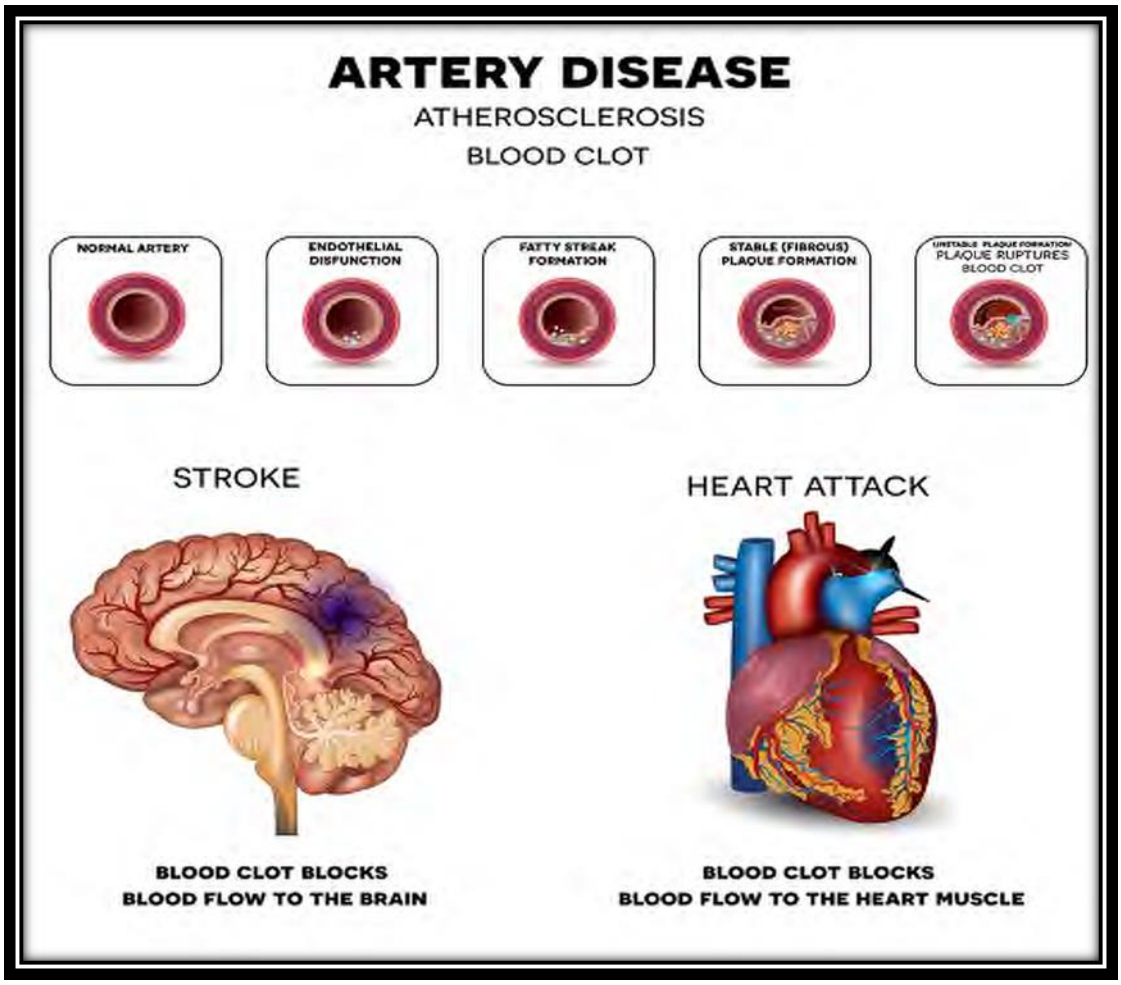
The clotting cascade is what initiates the work of clotting factors that are present. As stated, clotting factors are circulating in the blood but are typically inactive until an injury occurs; it is with an injury that the clotting cascade commences and the clotting factors are activated. The intrinsic and extrinsic pathways describe the process of the clotting cascade that alters certain clotting factors and changes them from their inactive to active forms.

It is called a pathway because as each clotting factor becomes activated another clotting factor in the process is activated. The production of fibrin creates strong threads of tissue, which stabilize the clot and strengthen it, but also prevent the clot from growing to become too large or to extend into other tissue areas where it is not needed.

As mentioned, a blood clot normally breaks down and dissolves on its own when it has developed as a result of blood vessel damage. When the body prevents hemorrhage by creating a blood clot, it normally also breaks down that blood clot within 1 to 2 days by causing lysis of the fibrin chains within the clot in a process known as fibrinolysis.[26] The main substance within the body that causes fibrinolysis is plasmin, which is an activated form of the plasma protein plasminogen. Plasminogen is changed into its active form through plasminogen activators released from the endothelial cells, most commonly tissue-type plasminogen activator and urokinase-type plasminogen activator. With the disturbance of coagulation processes, the body may develop a measure of abnormalities related to clot dissolution, which can potentially lead to a hypercoagulable state.

Blood clots are more likely to form in areas where blood flow is slowed and is sluggish. An example of this occurs when a patient who is recovering from surgery is immobilized and does not get out of bed for several days. The blood flow in the peripheral tissues is slowed from lack of skeletal muscle movement. This slowing of blood flow through the vascular system then places the affected patient at a risk of blood clots, which is often why measures are implemented following surgery to improve blood flow in the peripheral tissues and to prevent blood clot formation.

Excessive effort from the clotting factors in the blood, when they have been activated, can promote thrombus formation in an area of sluggish blood flow and the body may not lyse the clot through its normal channels. Without the body's efforts toward clot dissolution, the clot can grow large enough to occlude a blood vessel and impede blood flow. The types of clots formed may vary, depending on their areas of formation. For example, a blood clot that develops within an artery will be different in composition than one that forms in a vein, since the artery is a resistance vessel that carries oxygenated blood.



A blood clot that breaks off from its initial site of development and travels through the bloodstream to lodge in another vessel in a different location is known as a thromboembolism. The area where the blood clot implants will cause varying effects based on the location; a blood clot that lodges in a blood vessel in the brain causes a stroke while a blood clot in one of the coronary arteries causes a myocardial infarction. Once the blood clot lodges within a certain vessel, it occludes blood flow and prevents any more blood from flowing past its area of implantation. The tissue on the other side of the clot no longer receives the oxygen and nutrients that it needs from the blood and it becomes ischemic. Eventually, tissue necrosis can develop when the tissues are deprived of oxygen for so long that they die.

Blood clots may also form as a result of heart disease primarily because of development of atherosclerotic plaque. Instead of a specific injury that would require blood clotting measures, such as with laceration of a blood vessel, atherosclerotic plaque that has built up in the arteries contains some elements that are more likely to cause blood clots. This material is exposed to blood flow as it passes through the affected vessel and past the areas of atherosclerotic lesions. The components of the atherosclerotic plaque that would tend to produce a thrombus then extend further into the lumen of the blood vessel, increasing the potential for plaque rupture and a break in the affected area.

The thrombus may connect to the vessel wall at the site of the atherosclerosis; when this occurs, the clot builds and becomes larger when platelets aggregate around the site and fibrin strengthens the clot. Eventually, the clot can become large enough that it occludes the blood vessel and impedes blood flow, causing tissue ischemia in the distal tissues. If the clot does not attach in the area where it initially broke off, it may then

travel through the bloodstream as a thromboembolus and may lodge in another area to cause the described complications, such as myocardial infarction or stroke.

A patient with coagulation issues and who is at greater risk of blood clots may develop deep vein thrombosis (DVT) when a blood clot travels through the veins and lodges in a particular area, obstructing blood flow and causing pain and swelling. Venous blood clots often develop because of venous stasis or due to inherent problems with the affected patient's anticoagulation system. If a blood vessel is injured, such as when a vessel is cut during surgery, the body releases inflammatory cytokines, which increase the coagulable state. When venous stasis is apparent, there is diminished blood flow through the venous system; consequently, blood is not returned as quickly back to the heart where it can receive more oxygen and the cardiovascular cycle of receiving oxygenated blood and returning deoxygenated blood is disrupted. This tissue hypoxia further stimulates the clotting cascade and activates certain clotting factors, setting off the pathway for blood clots to form.

As stated, blood clots that form in the venous system are more likely to lodge in the deep vessels of the lower legs or in the lower abdomen and pelvis, causing DVT. These blood clots, when they become thromboembolic, may also travel through the circulatory system to the lungs to lodge in the pulmonary artery and to cause pulmonary embolism, characterized by shortness of breath, coughing, and hemoptysis.

It is clear that blood clots can lead to significant complications when they develop and treatment is often aimed at preventing clots from forming, particularly among high-risk individuals who have known clotting disorders

and are in hypercoagulable states. Prevention is aimed at controlling platelet activity to prevent excess accumulation at sites of injury and to interfere with the process of the clotting cascade so that blood clots do not form where they are not needed. However, this places the affected patient at risk of hemorrhage if he or she is taking drugs that interfere with clotting; if an injury does occur, the patient may not produce enough of a response to create a blood clot and may bleed unnecessarily.

On the other hand, when blood clots do develop they can be dangerous and debilitating. For the patient who has not been able to prevent blood clot formation, whether because risk factors were not identified or whether a clot developed despite measures to prevent its accumulation, other medications will be required to manage the clot, dissolve it, and prevent it from causing further complications.

Blood Clots

Thrombolytic drugs are the main types of medications utilized to get rid of blood clots through their dissolution. In comparison to some other types of drugs that are prescribed to control blood clots, such as anti-platelet drugs, which interfere with platelet aggregation, or hemorheologics, which decrease platelet aggregation and reduce blood viscosity, thrombolytics are drugs designed to dissolve existing clots that have formed. Thrombolytics are therefore not considered to be preventive drugs to be given for high-risk patients in case they may develop blood clots. Instead, they are typically administered in emergent situations where a blood clot has not only developed, but has often caused such ischemia that the affected patient requires drugs for clot dissolution to prevent further ischemia and irreversible effects of the condition.

Thrombolytic drugs are typically administered intravenously so that they can work rapidly. Different types of drugs work in different ways. Some are designed to dissolve blood clots when they are injected and travel through the bloodstream to the site of the clot to break it up and to restore blood flow. In some other cases, the physician may insert a catheter into the affected blood vessel near the area of the clot and may inject the medications near the site of the clot to begin dissolving the obstruction.

Alteplase is a type of thrombolytic used to dissolve blood clots when they develop; it is classified as tissue plasminogen activator, recombinant (tPA). Alteplase is indicated for administration during emergency situations where blood clots have caused obstruction to the point that the affected patient is in a life-threatening situation, such as with a myocardial infarction. It is indicated for use in myocardial infarction with ST elevation (STEMI). Alteplase (Activase®) may also be indicated for cases of ischemic stroke and for pulmonary embolism.[27] When thrombosis develops and a patient suffers hemodynamic compromise, the patient's condition should be evaluated quickly and thrombolytic drugs administered rapidly. Administration of these types of drugs can quickly lyse the blood clot and can improve blood flow, potentially reversing some of the damaging effects of ischemia. Alteplase should be given as soon as possible after the affected patient begins to experience symptoms; and, the best results occur when the drug is administered within six hours of symptom onset.

Alteplase works in a manner similar to what the body does when it normally lyses a blood clot. Plasminogen is activated to become plasmin, which affects the strands of fibrin that make up the blood clot to break it down. Alteplase converts some of the trapped plasminogen within the clot into plasmin so that it will work against the fibrin portion of the clot and induce fibrinolysis.

As a result, the fibrin strands are broken down and the clot dissolves.[28] The actual dose administered varies, depending on the condition that has developed.

Alteplase administered for management of myocardial infarction is given as a 15 mg IV push dose over 1 to 2 minutes, followed by 0.75 mg/kg infusion over 30 minutes, followed by 0.5 mg/kg continuous infusion over the next 60 minutes in patients who weigh less than 67 kg.[65] The actual time of dose administration may actually take place over a longer period than what is listed here, depending on the patient's condition and the urgency of the situation. Alteplase may also be administered as a 3-hour infusion, in which case the doses are increased more slowly and are given over a longer period of time.

Because alteplase works to break down clots that have developed, it can also increase a patient's risk of hemorrhage and bleeding after the drug is administered. Alteplase should be closely monitored with administration. Contraindications to the drug include a history of intracranial hemorrhage, brain tumor, recent surgery or trauma, and internal bleeding.[28] It should also not be administered with other drugs or substances that would increase the risk of bleeding, such as with vitamin K or heparin. Its administration requires frequent patient monitoring for changes in hemodynamic status, including changes in blood pressure and neurologic changes. The clinician should avoid any invasive procedures within several hours to days of administration of alteplase, if possible, such as starting an intravenous line or placing a nasogastric catheter.

Alteplase is actually structurally identical to tPA, which is a naturally occurring fibrinolytic agent that is normally found in the endothelial cells

within the blood vessels. tPa initially binds to fibrin that is found on the surface of the blood clot and activates plasminogen. Plasmin is then formed and released, where it breaks apart the fibrin molecules, which causes clot dissolution. Normally tPA is selective for dissolution of fibrin that is found specifically within clots, however, it also has the potential to activate plasminogen found in other areas, which can lead to abnormal bleeding.[67] tPA is indicated for use in the management of clots associated with acute myocardial infarction, those that cause thrombotic stroke, and in pulmonary embolism.

Beyond alteplase, there are other medications that work in a manner very similar to tPA and that are classified as tissue plasminogen activators. These include retaplase (Retavase®), which is a synthetic derivative of recombinant tPA that is indicated for treatment of acute myocardial infarction and pulmonary embolism. It is a potent drug that is administered through intravenous bolus.

Tenecteplase (TNK-tPA) is another tissue plasminogen activator used for management of myocardial infarction. It should be administered as soon as possible, preferably within 30 minutes of onset of a heart attack. TNK-tPA is administered as an intravenous bolus and the dose is based on patient weight, ranging from 30 to 50 mg, given as IV push over 5 seconds.

Another thrombolytic medication used to dissolve blood clots and to prevent complications from vessel occlusion is streptokinase. It is primarily administered when blood clots have developed in cases of myocardial infarction, pulmonary embolism, or stroke. A discussion of the discovery of streptokinase is recorded in an article in the *Texas Heart Institute Journal.* Dr. William Smith Tillett, an associate professor of medicine at Johns

Hopkins University, first discovered streptokinase in 1933. Tillett noted that streptococci that were in test tubes that contained human plasma tended to clump together, while those in test tubes that contained human serum did not. Through his observations, he noted that there was a component found in plasma that caused the response of the streptococci, a component that was not found in serum.[66]

What Tillett hypothesized was that the fibrinogen found in the human plasma would be absorbed onto the surface of streptococci and the plasma would then be free from fibrinogen. This latter point was important in that whenever streptococci were added to samples of human plasma, clots would not form because the plasma samples were devoid of fibrinogen, having been absorbed into the streptococci.

Streptokinase has been developed as an extracellular protein that comes from the culture of beta-hemolytic streptococci. Once administered, streptokinase forms a complex with plasminogen to convert it to its active form of plasmin. Streptokinase also supports the breakdown of fibrinogen and clotting factors V and VII.[68] Streptokinase is not specific for plasminogen found only in clots and it may bind with plasminogen that not only is found within clots, but also with circulating fibrinogen.[67] This increases the risk of hemorrhage, which is elevated even more than when tPA is used for medical treatment.

Anistreplase (Eminase®) is made up of a complex of streptokinase and plasminogen. When compared to streptokinase, anistreplase has more fibrin specificity and can actively dissolve clots that are causing impaired circulation. As with other thrombolytic drugs, anistreplase increases the risk of bleeding for the patient because of its ability to break down fibrin. It is

only indicated for the treatment of acute myocardial infarction; a typical dose is as an intravenous bolus of 30 units, given over 2 to 5 minutes.[68]

Urokinase is an agent used for fibrinolysis. It is found in the urine and is produced by the kidneys. It can be directly extracted from urine, but it is also sold in a commercially available form that is created from tissue cultures using recombinant DNA techniques.[68] As with other thrombolytics listed here, urokinase can cause considerable hemorrhage because of its effects on fibrin clots. Urokinase has often been used for breaking up clots that form within central venous catheters but it is indicated for the management of pulmonary embolism. When given for pulmonary embolism, urokinase is administered as an intravenous infusion with a loading dose of 4400 IU/kg ideal body weight (IBW) over 10 minutes, followed by 4400 IU/kg IBW over 12 hours.[89]

The healthcare provider should carefully consider the appropriate use of thrombolytic therapy as indicated in certain conditions, however, the use of these drugs may need to be limited in patients who have experienced injuries as a result of trauma. Because thrombolytic drugs can cause bleeding, they should be used with care in situations where bleeding is already present, and, if necessary, other options considered in their place.

Vasoconstriction

Vasoconstriction describes the process of narrowing of the blood vessels. Typically, this process improves blood pressure levels and slows blood flow. Constriction and dilation of blood vessels is primarily controlled through the smooth muscles that are found in different layers of the blood vessel walls. Circulation is mainly affected by factors such as the amount of blood flow, peripheral vascular resistance, and blood pressure. When vasoconstriction

occurs, it can impact all of these factors, which ultimately leads to a decrease in circulation.

The circulatory system is technically divided into three different systems: the systemic circulatory system, the pulmonary circulatory system, and the coronary circulatory system. The systemic system consists of the left ventricle, which pumps blood into systemic circulation, as well as the aorta, and the arteries and veins that supply blood to and retrieve blood from the peripheral tissues and the brain. Alternatively, the pulmonary circulation is made up of the right side of the heart, which pumps blood to the lungs, as well as the pulmonary artery, the pulmonary capillaries that circulate near the lungs, and the pulmonary vein, which returns oxygenated blood from the lungs back into the heart.

The coronary circulation is made up of the vessels that supply blood to the myocardium. The left main coronary artery begins at the base of the aorta and branches out into smaller arteries that encircle the heart. The right main coronary artery also begins at the base of the aorta, where it surrounds the heart and branches off into smaller vessels as well. Each of the coronary arteries and their branches serve different portions of the heart muscle. For example, the right coronary artery branches into the posterior descending artery, which supplies blood to the back of the heart. Any areas of circulation, including the systemic, coronary, or pulmonary circulatory systems can develop vasoconstriction. Because each of these systems provides blood to their respective areas of the body, vasoconstriction can lead to varied symptoms and complications when blood flow is slowed and restricted.

The mean arterial pressure (MAP) is actually another name for average blood pressure, which is the force of blood against the interior lumens of the blood vessels. The MAP is mainly controlled by the sympathetic nervous system which activates the smooth muscles through release of norepinephrine, which interacts with adrenergic receptors. Ultimately, this process leads to an increase in calcium ions within the smooth muscle cells of the blood vessel walls. As an alternative mechanism, the parasympathetic nervous system causes vasodilation of the blood vessel walls; this process is part of the body's natural mechanism of controlling blood pressure.

Vasoconstriction can also be caused by other body mechanisms as well. Certain receptors present on the aorta and on other large vessels near the heart respond to changes in pressure and can increase the heart rate and blood pressure by causing sympathetic stimulation. Stimulation of the renin-angiotensin system also causes vasoconstriction and the release of the hormone aldosterone to ultimately increase blood volume and to control blood pressure. Finally, other factors, such as the body's response to cold temperatures; exposure to certain environmental chemicals or influences, such as nicotine in tobacco; and dietary intake of salt can all affect blood vessel diameter and can lead to vasoconstriction.[90]

Vasoconstriction can have both positive and negative effects on circulation. On one end of the spectrum, vasoconstriction reduces blood flow and can greatly restrict the amount of blood and oxygen supplied to the body's tissues. The process can also raise blood pressure to the point that it is too high, which can be dangerous for some people who cannot tolerate such increased levels. Alternatively, vasoconstriction acts as a mechanism for controlling blood flow to specific areas where it is needed most. When blood flow is required more in one area of the body over another, blood is shunted

to the area and blood vessels in other, outlying areas constrict so that blood flow is reduced. Vasoconstriction is also important for the body to retain heat and for controlling blood loss when hemorrhage occurs.

Certain conditions can lead to vasodilation that continues unabated and that needs to be controlled to prevent deleterious effects. Nitric oxide is a potent vasodilator; its release by some autonomic nerves causes the blood vessels to dilate and it prevents vasoconstriction. Increased amounts of nitric oxide are released as part of the inflammatory response to promote blood flow; however, too much nitric oxide may cause a persistent state of vasodilation, which can alter blood pressure and systemic blood flow.

Beta-2 receptors, found in the smooth muscles, also cause vasodilation. When certain substances stimulate these receptors, they can lead to increased vasodilation that may require medical intervention to control. There are various other factors, both endogenous and environmental, that can promote continued vasodilation. Therefore, medications used to stimulate vasoconstriction and to control these factors are often aimed at preventing those mechanisms that lead to vasodilation.

Smooth Muscle Contraction

Smooth muscle contraction within the blood vessels causes the vessels to constrict, thereby decreasing total lumen size. This constriction leads to increased systemic vascular resistance and an increase in blood pressure. As described, the systemic vascular resistance (SVR) describes the resistance of the walls of the blood vessels within systemic circulation, but not necessarily including pulmonary circulation.

Smooth muscle contraction and increased vascular resistance must occur in combination with increased cardiac output, otherwise the blood flow to the tissues may still not be adequate. If vasoconstrictors work to decrease blood vessel lumen size and to increase blood pressure, they still cannot adequately perfuse the tissues if blood flow has not increased through output from the heart. If cardiac output is not simultaneously increased along with smooth muscle contraction of the blood vessels, the affected individual may only experience vasoconstriction and decreased blood flow that only circulates at a slower pace.

Furthermore, if blood pressure is increased through vasoconstrictor drugs and vascular resistance is increased in some areas of the body by a certain amount and is increased in other areas by a lesser amount, the blood will perfuse to those areas where there is a smaller increase in systemic vascular resistance because the increased blood pressure is greater than the vascular resistance in those areas.[91] This change in vascular resistance is how many vasoconstrictor drugs exert their effects; when the smooth muscle contractions alter the vascular resistance in a certain area, the body ensures that blood flow is upheld to the critical organs, such as the brain and the heart.

Drugs that promote smooth muscle contraction are typically sympathomimetic drugs, which are those that have alpha-adrenergic agonist effects. Remember that adrenergic receptors are those that are affected by the effects of catecholamines, such as epinephrine and norepinephrine. Alpha receptors are located at various points in the body, including within the smooth muscle cells of the vascular system. When sympathomimetic drugs bind to these receptors and stimulate them, it causes vasoconstriction through smooth muscle contraction.

Alpha adrenoceptors consist of alpha-1 and alpha-2 receptors. Sympathomimetic drugs may be selective to one specific type of these receptors or they may bind to both. Most of the smooth muscles found in the blood vessels contain alpha-1 receptors. The alpha-agonist drugs tend to constrict both arteries and veins, although the effects of vasoconstriction are more noticeable in the arteries. Because the arteries are resistance vessels and because they are the oxygen-carrying vessels in the body, vasoconstriction of these vessels has a greater impact on blood pressure and perfusion.

Common drugs that are used to stimulate adrenoceptors include those that are similar to the naturally produced catecholamines, including epinephrine, norepinephrine, and dopamine. Epinephrine can be administered exogenously, although it is also produced by the body and is released from the adrenal medulla, where it improves cardiac output and raises blood pressure. Norepinephrine is secreted from the sympathetic nervous system, where it interacts not only with alpha-receptors, but also with beta-receptors on the myocardium. However, it is stimulation of alpha-1 receptors in the tissues of the vascular system that increases systemic vascular resistance to produce vasoconstriction.

Dopamine is a neurotransmitter that has inotropic effects on the cardiac muscle. When given in higher doses, dopamine also can stimulate vasoconstriction due to its effects on systemic vascular resistance. All of these drugs have an impact on blood pressure levels and induce vasoconstriction because of their adrenoreceptor agonist properties. Other drugs that are alpha-adrenergic agonists and that also raise blood pressure by stimulating vasoconstriction through smooth muscle contraction include methoxamine and phenylephrine.

Methoxamine is a synthetic form of the catecholamines that has similar activity and is selective for alpha-receptors, although it tends to prefer alpha-1 receptors to alpha-2 receptors. Methoxamine raises peripheral vascular resistance to increase blood pressure when it stimulates alpha-1 receptors. The drug is commonly used during anesthesia administered during surgical procedures.[92] It effectively increases systemic vascular resistance and is quite potent when compared to some other types of drugs used for similar purposes; however, it should not be used for patients who have severe cardiovascular disease.

In addition to its designated use in controlling blood pressure through vasoconstriction, methoxamine may be implemented for management of paroxysmal supraventricular tachycardia. It is available as an intramuscular or intravenous dose. When given for control of blood pressure, a typical dose is 5 to 20 mg IM or 3 to 5 mg IV.[93] Healthcare providers who administer methoxamine for blood pressure treatment should be aware of the patient's cardiac history; although the drug does not directly affect the heart, it could cause bradycardia in larger doses.

Phenylephrine is an alpha-receptor agonist that has significant vasoconstricitve effects. It is most well known for its effects as a decongestant (Sudafed®, Neo-Synephrine®) because it causes vasoconstriction of the blood vessels in the nasal passages. However, it is also used for treatment of hypotension and vascular failure associated with shock states. As with other types of vasoconstrictor drugs, phenylephrine causes a decrease in the diameter of the blood vessel lumen because of its effects on alpha-1 receptors in the smooth muscle cells of the vessel wall. The drug is poorly absorbed as an oral tablet, so it is more likely given either subcutaneously, intramuscularly, or intravenously. Subcutaneous or IM

doses may be given every 1 to 2 hours as needed for blood pressure control; typical doses given through these routes are approximately 2 to 5 mg per dose. When given IV, it may be infused as a bolus or as a continuous infusion. A bolus dose is approximately 0.2 mg; a continuous infusion maintenance dose is 40 to 60 mcg/min.[94]

When administering drugs that increase vascular resistance and control blood pressure, the healthcare provider should continue to monitor the patient's vital signs throughout the duration of the drug therapy. Although it may initially appear that the drug is working when the patient's blood pressure rises to within normal limits, blood pressure levels should continue to be monitored to prevent too high of pressures and the opposite effects of the drug. Furthermore, administration of vasoconstrictors could cause poor peripheral perfusion as the body attempts to maintain blood flow to the vital organs. The healthcare provider should monitor signs of adequate peripheral circulation, such as warm extremities and absence of cyanosis, to determine that systemic circulation has not been compromised.

Arterial Pressure

As previously discussed, mean arterial pressure (MAP) is another term used to describe the average blood pressure in the arteries. The MAP is determined by SVR and total cardiac output. It is increased by various factors that support increased SVR and increased cardiac output, including greater preload. When vasodilation occurs and there is more room within the vascular system for blood to flow, the blood pressure drops; the greater diameter of the vessels means less pressure of blood flow against the internal walls of the arteries. If blood pressure drops too low, the patient is at risk of many negative effects associated with hypotension, and

medications may be necessary to induce vasoconstriction and to correct the situation.

Drugs that increase arterial pressure may also be known as pressors because of their mechanism of action in improving blood pressure levels. Drugs that are administered to increase arterial pressure are designed to improve blood pressure levels and to treat hypotension, which can cause many negative effects to the patient. By managing hypotension through increasing arterial pressure, these drugs improve blood flow, increase circulation of oxygen and nutrients to the peripheral tissues, and ensure that vital organs receive the oxygen that they need.

Sympathomimetic drugs are those that promote vasoconstriction through contraction of smooth muscle tissue; alternatively, vasoconstriction may also occur through certain drugs that increase arterial pressure. These drugs are non-sympathomimetic drugs or they may be synthetic versions of naturally occurring hormones, including vasopressin analogues.

Vasopressin, also known as anti-diuretic hormone, is a naturally occurring hormone secreted from the posterior pituitary in the brain. It is responsible for regulating fluid levels through the kidney and has an impact on blood pressure levels associated with increased fluid volume; additionally, it acts as a vasoconstrictor to reduce the size of blood vessel lumens, ultimately narrowing the blood flow pathway. The body releases vasopressin when receptors in the walls of the atria sense a change in total blood volume. These sensors are stretch receptors that normally inhibit release of vasopressin when stimulated; however, when hypovolemia develops, the receptors are less likely to fire and the body releases more vasopressin.

Stimulation of the renin-angiotensin system also promotes the release of vasopressin when angiotensin II is created, thereby controlling fluid levels in the vascular system. When released, vasopressin then increases production of corticotropin, a hormone produced by the anterior pituitary gland that stimulates the adrenal cortex. The adrenal cortex is responsible for creating cortisone, which plays a role in blood pressure regulation.[96]

Vasopressin works within the kidneys and in the blood vessels. Certain vasopressin-type receptors are located in each of these areas: vasopressin-1 are found in the vascular system while vasopressin-2 receptors are found in the renal system. Vasopressin works in the kidneys to increase fluid reabsorption into circulation by stimulating the vasopressin-2 receptors there. Additionally, it has a vasoconstrictive effect in the blood vessels when it stimulates vasopressin-1 receptors.[95]

Exogenous vasopressin is often prescribed for patients who suffer from diabetes insipidus to control fluid loss through urination. It is also used in cases of cardiogenic shock where the patient is experiencing extreme vasodilation that leads to severe hypotension, despite administration of other drugs to counteract the situation, including norepinephrine and fluid resuscitation measures. When given in higher doses during these situations, vasopressin stimulates smooth muscle contraction, which causes vasoconstriction and an increase in arterial pressure. It has also been used in other clinical situations to treat hemorrhage associated with esophageal varices, as part of anesthesia administration for patients undergoing cardiopulmonary bypass, and as part of treatment for cardiac arrest.

Because of vasopressin’s effects on mean arterial pressure, it has also been used as an option for treatment during cardiopulmonary resuscitation for

cardiac arrest. Vasopressin has been shown to improve myocardial blood flow as well as blood flow to the brain, which made it a potential alternative to epinephrine used during resuscitation. A review by Mitra, *et al*., in the *Indian Journal of Critical Care Medicine* considered evidence for use of vasopressin treatment for patients experiencing cardiac arrest. The review found that among patients who experienced asystole and received vasoactive drugs as part of treatment, more patients were later received at the hospital and eventually dismissed when they had received vasopressin during resuscitation as compared to those who received epinephrine.[97]

Despite these and other studies that have shown the benefits of vasopressin during emergency use, ACLS guidelines are changing to omit use of vasopressin in place of epinephrine during cardiac resuscitation. The current guidelines still allow for vasopressor use among patients with severe hypotension, including those patients experiencing shock that is refractory to other treatments. The recommended dose for the management of vasodilatory shock is 0.1 to 0.4 units/min, given intravenously, which has been shown to improve hypotensive states in 85 % of patients who have otherwise not responded to norepinephrine administration.[98]

Vasopressin should be used with caution in patients who have heart disease, as its administration can increase myocardial oxygen demands and could place more stress on the heart. Patients with previous vascular disease should also be closely monitored to assess for complications associated with fluctuations in blood pressure. Finally, because vasopressin impacts the kidneys and stimulates vasopressin-2 receptors there, it should be used with caution in patients diagnosed with renal disease to avoid hypersensitivity reactions.

Vasodilator Drugs

Vasodilators are agents that improve blood flow by increasing the size of the blood vessels. These drugs may stimulate arterial dilation, which changes levels of blood pressure, or venous dilation, which can increase the venous return of blood to the heart. The flow of blood through the different chambers of the heart and into circulation is affected by various mechanisms both within and outside of the heart's structure. Receptors within the heart stimulate the blood vessels to expand or contract, while changes in pressure within certain areas of the myocardium can alter blood flow.

Preload describes the amount of stretch in the ventricles at the end of diastole. Because it occurs at the end of diastole, preload is actually also the phase just before the beginning of the next round of blood movement by the ventricles during systole. The more that the ventricles are stretched with blood, the greater the amount of preload. Alternatively, afterload describes systemic vascular resistance, which has been defined as the amount of resistance against which the heart must pump blood. Both preload and afterload can affect the heart's ability to contract normally, as well as how blood is pumped into circulation and its abilities to traverse through the cardiovascular system.

Vasodilator medications are prescribed for various conditions that contribute to heart disease, including for the management of hypertension, pulmonary hypertension, and heart failure. Often, the goals of vasodilator therapy are to reduce the amounts of preload or afterload, or even both levels. The various medical conditions that lead to an increase in vascular resistance that require vasodilation can cause a number of symptoms and complications among affected patients. For instance, uncontrolled hypertension can lead to vessel damage and the potential for stroke, while

vasospasm that leads to angina causes pain, myocardial ischemia, and potential myocardial infarction if blood flow is not promptly restored.

Vasoconstriction is associated with various medical conditions for which vasodilator medications are prescribed. Pulmonary hypertension describes a state of increased blood pressure within the pulmonary vasculature. It most often develops when the small blood vessels that surround the lungs become blocked or occluded. The walls of the blood vessels may constrict due to inflammation, they may tighten as a result of some type of disease process, or they may develop small blood clots that cause vessel occlusion. The heart has a harder time pumping blood through these vessels and because of the narrowed diameter of the vessel lumens, blood pressure rises in this area. The heart may eventually become weakened due to the increased effort; heart failure may be more likely to develop among persons who have pulmonary hypertension because the prolonged increase in energy requirements of the heart causes its condition to deteriorate.

Pulmonary hypertension typically causes symptoms of fatigue, shortness of breath, and a diminished ability to complete routine activities of daily living without requiring rest breaks. Among some people, it may also cause chest pain and tachycardia. Pulmonary hypertension is actually classified according to 5 different forms of the condition:[101]

- *Group 1*:
  Group 1 pulmonary arterial hypertension is thought to have no known cause or is considered to be caused by use of certain drugs or exposure to toxins; or occurs as the result of some types of diseases, such as certain connective tissue diseases, HIV infection, or congenital heart disease.

- *Group 2*
  Group 2 pulmonary hypertension is typically caused by conditions affecting the left side of the heart, such as mitral valve disease or chronic hypertension.

- *Group 3*
  Group 3 pulmonary hypertension is associated with lung diseases and infections, including chronic obstructive pulmonary disease (COPD) or interstitial lung diseases that have caused scar tissue to develop within the lungs.

- *Group 4*
  Group 4 pulmonary hypertension is caused by blood clots that occlude the pulmonary vessels and that affect pulmonary circulation.

- *Group 5*
  Group 5 pulmonary hypertension is caused by other disorders, including blood or metabolic disorders.

Pulmonary hypertension is just one type of clinical condition that can lead to increased vascular resistance and poor cardiac function. Obviously, based on the different types of pulmonary hypertension and their causes, vasodilator medications will not be effective for all types. For instance, pulmonary hypertension that has developed as a result of blood clots would more likely require anti-platelet drugs or thrombolytics to dissolve the blood clots and would not necessarily be affected by vasodilator medications. When pulmonary hypertension does develop because of conditions that cause chronic vasoconstriction — typically when it is classified as group 1 or group

2 pulmonary hypertension — the symptoms and complications may be relieved with administration of vasodilator agents.

Drugs prescribed for vasodilation often induce changes in the systemic vasculature in one of several ways. They reduce systemic vascular resistance, decrease arterial blood pressure, or reduce venous blood pressure. Note that many drugs administered as vasodilators will impact the blood vessels through more than one of these mechanisms, as many of them overlap.

Systemic Vascular Resistance

The systemic vascular resistance can be calculated if the cardiac output and the mean arterial pressures are known. Recall that the mean arterial pressure (MAP) is often used as another name for average arterial blood pressure measurement during one cardiac cycle and systemic vascular resistance (SVR) is the amount of resistance against blood flow of the walls of the blood vessels, excluding the vessels of pulmonary circulation. The formula for calculating systemic vascular resistance is useful for understanding how each of the variables involved affect blood flow and tissue oxygenation. The formula for calculating SVR is as follows:

$$SVR = MAP \div CO$$

Utilizing this formula reminds the user that each variable is dependent on the other and that an increase in one variable will lead to a change in the others in the formula. Total systemic vascular resistance is affected by increased or decreased levels of cardiac output. If the mean arterial pressure is high, then the SVR will be higher as well. Changes made in cardiac output

when medications are administered will then affect the SVR and should be noted.

Vasodilators are important for reducing SVR when it has become elevated, whether due to changes in the level of cardiac output or because of increased MAP. As stated, systemic vascular resistance may also be elevated due to increased blood viscosity or increasingly turbulent blood flow; increasing the diameter of the affected blood vessels in these situations then can improve blood flow and can improve cardiac output.

The mechanisms between the different types of drugs may also differ, depending on the blood vessels most affected. Some vasodilators work primarily on the arteries, while others focus on the veins. There are some drugs that also affect both arteries and veins to produce vasodilation and to increase vessel diameter. Whether a certain drug affects the veins, the arteries, or both is known as its selectivity, which describes how a specific drug acts at a certain site in the body, in comparison to its effects on other sites.

The selectivity of a drug impacts how it will affect the body at its specific location. For instance, a drug that focuses primarily on vasodilation of the arterioles will increase oxygen delivery through blood flow that has just come from the heart. Alternatively, a drug that primarily affects the veins will impact blood flow and venous return. Medications that improve SVR are those that mostly work to impact the arteries, which are the vessels involved in vascular resistance.

Dilating the arteries will decrease systemic vascular resistance by first decreasing cardiac afterload, or the force that the heart works against when

pumping blood.[25] Decreased afterload then leads to a decrease in cardiac workload and places less stress on the heart.

Renin inhibitors are one class of drug that act as vasodilators to reduce high levels of blood pressure. Renin inhibitors affect the renin-angiotensin-aldosterone system by inhibiting the release of renin. This then decreases angiotensin II formation, a substance that normally leads to vasoconstriction. By inhibiting the release of renin, these drugs dilate the arteries and veins, reduce arterial pressure, and decrease preload and afterload levels.

Aliskiren (Tekturna®) is a renin inhibitor that is indicated for the treatment of hypertension. It has a relatively long half-life and so is taken as a dose once daily. Aliskiren not only inhibits renin secretion to reduce vasoconstriction, but it also prevents the release of aldosterone, which can increase blood pressure. A typical dose is 150 mg PO, taken once daily, although this dose may be increased, depending on the patient's blood pressure response. The total dose should not be more than 300 mg per day.[103] Renin inhibitors, while effective, should be used with caution in patients who have kidney disease, as aliskiren increases the risk of renal function impairment in some people. Because it causes vasodilation, the patient taking aliskiren should be counseled about the signs and symptoms of hypotension and should be monitored for complications of low blood pressure.

Arterial Blood Pressure

The process of lowering the arterial blood pressure involves lowering systemic vascular resistance, as the arteries are resistance vessels. Because the arteries and arterioles are those vessels that carry oxygenated blood

away from the heart and to the rest of the body, they are also the vessels that have a greater amount of resistance from the pressure of the heart's contractions and the force of blood. Dilation of the arterial vessels causes a decrease in systemic vascular resistance, a widening in the diameter of the vessel lumen, and a decrease in arterial blood pressure.

Many pharmacological agents that lower arterial blood pressure will also lower venous pressure as well. However, there are some drugs that specifically focus only on lowering arterial blood pressure and those that work more selectively within the arteries and affect those vessels first, but they also have an impact on venous circulation.

Vasodilators are prescribed for various conditions that lead to high blood pressure and increased pressure within the cardiovascular system. Some drugs, depending on how they are prescribed, are better suited for different conditions as compared to others because of their mechanisms of action. For instance, drugs that are administered for the management of hypertension are more often known as arterial dilators that cause a decrease in arterial pressure, since the arteries are more affected by high blood pressure than the veins. Arterial dilators may be prescribed for other conditions that primarily affect the arteries and the veins, including conditions such as angina or heart failure, although venous dilators also can have an impact on these conditions.

Calcium channel blockers are one example of drugs that are primarily used to lower arterial pressure and they have little to no effect on venous dilation. As previously described, calcium channel blockers exert their effects by disrupting the movement of calcium through channels into the cells. Calcium plays a significant role in the cells by regulating cell activity and behavior,

such as through neuron excitability, muscle contraction, or metabolism. The movement of calcium and the control of calcium ion concentrations within the cells are very tightly regulated by the body because of calcium's important effects. Calcium channels allow calcium ions to carry electrical charges into excitable cells, which cause signaling of various activities. Calcium channels are evident in a variety of cells, including myocardial cells and in smooth muscle cells.[102]

Nicardipine (Cardene®) is a type of calcium channel blocker that primarily affects the arteries to lower arterial blood pressure through its vasodilation effects. Nicardipine works by inhibiting movement of calcium ions across the cell membrane during depolarization, which also makes it a good choice in the treatment of some types of cardiac arrhythmias. The drug also effectively dilates the coronary arteries, induces vasodilation, and increases myocardial oxygen delivery.[103] It is typically administered for the management of hypertension and for cases of stable angina. Nicardipine may be administered as an oral tablet or it can be given intravenously. A typical oral dose of the drug is approximately 20 mg PO three times a day, which may be increased periodically, based on the patient's response, up to 60 mg PO twice a day.

Clevidipine (Cleviprex®) is another type of calcium channel blocker that may be used for management of hypertension. It is indicated for use when oral blood pressure drugs are not available. As with nicardipine, clevidipine manages the influx of calcium ions into the cells during depolarization in the smooth muscles in the arteries. This action causes a decrease in arterial vascular resistance, arterial relaxation, and a decrease in arterial blood pressure. Clevidipine is only given intravenously, and it is typically administered as a continuous infusion, although it may be given

intermittently as well. As a continuous infusion, clevidipine is given at a rate of 1 to 2 mg/hr, which may be increased as needed to control blood pressure levels; average patient use is 4 to 6 mg/hr.[103]

Because calcium channel blockers induce vasodilation as part of their mechanisms of action, they should be monitored carefully among some patients who are prone to developing hypotension as an effect of the drug working too well. Due to their effects on calcium ions and their electrical activity, these drugs may also cause cardiac arrhythmias in some patients and they should be monitored for those outcomes as well.

Although most drugs used to dilate arterial vessels tend to have an impact on venous dilation as well as arterial dilation, hydralazine is one example of a medication that specifically targets arterial blood pressure. Hydralazine (Apresoline®) is prescribed primarily for the treatment of hypertension, as it is a vasodilator that relaxes the smooth muscles in the arteries. It is also beneficial for patients with heart failure, as the drug tends to reduce afterload, which decreases the work of the heart. Hydralazine can be given as an oral agent, in which it is taken on a daily basis at a dose between 10 and 50 mg PO four times a day to control blood pressure levels. For care of patients with heart failure, the drug may be administered at 10 to 25 mg PO twice a day, but not to exceed 75 mg PO three times a day.[103]

Hydralazine is also used during cases of hypertensive crisis, when a patient presents for care with such dangerously high levels of blood pressure that he is at risk of stroke. When administered for hypertensive crisis, hydralazine is given intravenously; an initial bolus of 10 to 20 mg is given every 4 to 6 hours.[103] The dose should be changed to an oral route as soon as the patient is able to take it.

Pulmonary hypertension, while a form of high blood pressure, still presents differently than "standard" hypertension of the systemic vasculature. Pulmonary hypertension may also be treated with drugs designed to lower arterial blood pressure through their actions as vasodilators. Pulmonary hypertension, as it affects the pulmonary arteries and is classified as pulmonary hypertension Group 1, is defined as a pulmonary arterial pressure over 25 mmHg or a pulmonary capillary wedge pressure of less than 15 mmHg.[104] Drugs prescribed to treat pulmonary hypertension therefore are those whose mechanisms of action are designed to target arterial blood pressure reduction.

Prostacyclin is a naturally occurring type of prostaglandin produced by the endothelial cells in the body that is normally responsible for controlling some vasodilation and inhibiting platelet aggregation. There is some evidence that suggests that prostacyclin production may be decreased in patients who suffer from Group 1-type pulmonary hypertension. A review in the journal *Respiratory Medicine* discussed the use of prostacyclin and prostaglandin analogs for treatment of pulmonary hypertension under the approach that patients with pulmonary hypertension are more likely to respond to exogenous prostacyclin and its counterparts because of the potential decrease in naturally-occurring levels of prostacyclin among these patients, which could be the cause of poor vasodilation and increased arterial pressures in the pulmonary vasculature.[104] Exogenous prostaglandins are often administered as part of treatment for pulmonary hypertension, as these drugs act as potent vasodilators to improve blood flow to the lungs and to enhance blood oxygen levels.

The first drug to be approved by the U.S. Food and Drug Administration (FDA) for the treatment of pulmonary hypertension was epoprostenol, a

synthetic type of prostaglandin that can be administered to do the work of some of the endogenous prostaglandins in the body. Epoprostenol (Flolan®, Veletri®) is potent and effective as a vasodilator; it also inhibits platelet aggregation to prevent blood clots that could also affect pulmonary blood flow. The drug is given intravenously and administered at a rate of 2 ng/kg/min, which can be increased by 2 ng/kg/min every 15 minutes, depending on its effects.[105] Epoprostenol is only administered through a central venous catheter and it must be monitored carefully with use to ensure that the patient does not experience a drop in blood pressure. Because epoprostenol has platelet-aggregation effects, the patient should also be carefully monitored for signs of bleeding.

Some patients with pulmonary hypertension may benefit from administration of inhaled prostaglandin analogs. These drugs, instead of being administered intravenously, are inhaled through a nebulizer to travel directly to the lungs. Iloprost (Ventavis®) is an example of a prostaglandin that is available in an inhaled form; it has vasodilator effects and it inhibits platelet aggregation in a manner similar to prostacyclin. In its inhaled form, iloprost is administered at a dose of 2.5 mcg one time; it may be repeated if well tolerated. A maintenance dose of the medication is 5 mcg, given 6 to 9 times throughout waking hours.[105] The doses cannot be administered more often than 2 hours apart. This inhaled form of prostaglandin has been shown to improve arterial blood pressure levels, as well as improve exercise capacity and functional status in patients with pulmonary hypertension.[104]

Exogenous prostacyclin and prostaglandin analogs are very effective in lowering arterial blood pressure related to pulmonary hypertension. These drugs, because of their blood pressure lowering effects, may cause dizziness or lightheadedness in the patients who take them. However, because they

are potent, they can also improve quality of life for those who need them to control blood pressure levels and to manage hypertension.

Venous Blood Pressure

Dilation of the venous blood vessels causes an increase in the size of the venous lumen of the affected blood vessel, leading to a drop in venous pressure. Some drugs are administered specifically to control blood pressure associated with the venous system. The venous blood pressure describes the amount of blood pressure within the veins (as compared with the pressure in the arteries). It also describes the amount of pressure in the atria. Venous blood pressure is normally much lower in comparison to arterial blood pressure. The right atrium has an approximate venous blood pressure of 5 mmHg, while the average venous blood pressure in the left atrium is 8 mmHg.

When discussing venous blood pressure levels and the amount of venous return, the term *capacitance* is often included as part of discussion. Venous capacitance describes the veins' abilities to increase the volume of blood that it holds without causing a large increase in blood pressure. The veins serve as the main capacitance vessels in the body. Much of the volume of blood is found in the veins at any one given time and blood flow to different regions of the body will be regulated through the movement of blood through the veins.

When the veins are constricted, blood flow is reduced and there is a decrease in total venous volume. This increases the amount of venous blood pressure, which affects cardiac output. Alternatively, vasodilation of the veins results in increased venous volume and lowered blood pressure.

Reduction in the amount of venous blood pressure ultimately results in a decrease in preload, which reduces the work of the heart.

Venous blood pressure may be measured in different locations and the term is used to describe more than one particular area. For instance, portal venous pressure refers to the amount of pressure found in the portal vein, while jugular venous pressure is an indirect measure of venous pressure as seen in the neck over the internal jugular vein. Central venous pressure (CVP), also referred to as right atrial pressure, is the amount of venous pressure entering the right atrium from the vena cava. Measurement of the central venous pressure is important to understand the amount of pressure in the blood that enters the heart from circulation, because it impacts how well the heart is able to pump the blood back into circulation after the blood has been oxygenated.

In comparison to arteries, veins bring blood back to the heart in a process known as venous return. This process is often facilitated through outside mechanical forces, such as with the movement of skeletal muscles or with breathing. Because of this, veins have less of an ability to contract and to minimize their diameter as compared to arteries; however, they do have the capacity to stretch and can extend their size to accommodate more blood when needed. Unfortunately, this stretching can also contribute to low blood pressure levels when blood pools in the veins and is not returned to the heart at an adequate rate.

An increase in venous pressure can also occur when there is an increase in blood volume within the veins. Depending on how compliant the veins are, such as through their ability to stretch and dilate, an increase in venous volume also increases venous blood pressure. Alternatively, when venous

compliance is decreased and the lumen of the vein is fixed and does not dilate, venous pressure is also increased.[107]

The smooth muscles of the veins are stimulated to contract through the sympathetic nervous system in a manner similar to contraction of the arteries. A change in the sympathetic nervous system can increase or decrease the tone of the vessel wall and can lead to vasodilation or vasoconstriction of the venous system. Drugs that are designed to lower venous blood pressure are those that relax the venous blood vessels, improve their capacitance, and ultimately lower venous blood pressure levels as well as central venous pressure.

Venous dilators are typically administered for the management of conditions such as angina or heart failure. Drugs that are venous dilators often have combination mechanisms of arterial and venous dilation, although there are some whose actions are more focused primarily on venous dilation only.

By decreasing venous blood pressure, venous dilator drugs reduce preload, which decreases demands on the heart. Some patients with angina benefit from decreased preload because it reduces oxygen demands of the myocardial tissue and decreased stress on the ventricles. The decrease in preload reduces the stroke volume and cardiac output, which then also decreases afterload on the left ventricle.[107] Among patients with heart failure, venous dilators may be prescribed to decrease capillary hydrostatic pressure, which will in turn reduce edema formation. These drugs are therefore administered for management of heart failure not only to control blood pressure levels, but also to prevent excess fluid buildup in the peripheral tissues.

Heart failure, as previously discussed, leads to a decrease in cardiac output and failure of the heart to keep up with the demands for oxygenated blood by the tissues. A decrease in cardiac output due to heart failure causes the heart rate to slow and blood is more likely to back up into venous circulation. This results in an increase in CVP because of the increase in blood volume. Venous constriction may also develop from the administration of certain drugs that cause the blood vessels to constrict as part of treatment for other conditions, such as with administration of epinephrine or dopamine. Venous constriction in these situations can also lead to an increase in venous circulation when the diameter of the venous lumen is smaller.[108]

One of the more common types of drugs used specifically used as venodilators are nitrodilators, which are often administered for management of pain associated with angina. Nitrodilators work in a manner similar to the body's release of nitric oxide (NO), which relaxes smooth muscles and leads to vasodilation and ultimately, a decrease in venous blood pressure. Nitroglycerin is an example of a drug that has been used for decades in the treatment of angina because it is a potent vasodilator. Other examples of drugs that act specifically as venodilators include sodium nitroprusside (Nitropress®) and isosorbide mononitrate (Imdur®).

Sodium nitroprusside is a vasodilator drug that works to relax the walls of the veins, which decreases venous blood pressure, reduces preload, and decreases afterload. It is used in cases of hypertensive crisis as well as in the management of complications associated with heart failure. Nitroprusside is always administered as an intravenous infusion. Because it is sometimes given during periods of hypertensive crises, it may be administered emergently. A regular adult dose is 0.25 to 1 mcg/kg/min IV,

with a maximum of 10 mcg/kg/min.[103] The drug is usually given as a continuous infusion; and, the exact rate of infusion depends on the patient's response to the drug and should be continuously reevaluated during the course of administration.

Isosorbide mononitrate is another type of nitrodilator that is also used for the treatment of angina. It causes a decrease in preload and afterload, as well as a decrease in left ventricular end-diastolic pressure and systemic vascular resistance. By decreasing venous blood pressure, isosorbide mononitrate can improve blood flow and can resolve symptoms of angina. It may be given as an oral preparation, to be taken daily among patients who suffer from stable angina. A typical dose of the drug is 30 to 60 mg/day PO, which may be increased to every 3 days, as needed; the maximum dose should not be over 240 mg per day.[103]

Vasodilator drugs may cause orthostatic hypotension among certain patients when dilated veins cause blood to pool in the lower extremities when the affected patient is lying supine at rest. Upon standing, the brain does not initially receive as much blood because the blood has collected in other areas within the venous system. The affected person may then experience dizziness or syncope with position changes unless blood flow is allowed to catch up. As with administration of other types of drugs used to manage blood flow through the cardiovascular system, patients who take venous dilators should be closely monitored for ill effects associated with hypotension.

Summary

With increasing rates of cardiovascular disease, the types and mechanisms of cardiac drugs continue to expand to meet the needs of those who suffer

from these illnesses. Each year, medications are tested and evaluated for their effects on cardiovascular disease, and changes are made in policies and protocols of administration that are based on research outcomes.

The pharmaceutical industry also continues to release and market new drugs designed to manage complications of cardiovascular disease. The healthcare provider who works with patients that suffer from cardiac complications must be cognizant of changes in dosage, routes of administration, and potential side effects of these drugs, as well as their indications for use, to best treat the people who need these drugs the most.

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1. **Angina is a condition where a patient experiences**

    a. chest discomfort.
    b. insufficient blood and oxygen to the heart muscle.
    c. pain only upon exertion.
    d. Answers a., and b.

2. **Vasoactive drugs, including pressors and inotropic medications are often given to patients experiencing**

    a. hypertension.
    b. cardiogenic shock to resolve some hypotension.
    c. chest pain.
    d. kidney failure.

3. **Thrombolytic drugs are typically administered**

    a. subcutaneously.
    b. intramuscularly.
    c. intravenously.
    d. sublingually.

4. **One particular type of beta-blocker, _____ showed significant results in decreased overall patient mortality when used among those with heart failure.**

    a. inderal
    b. carvedilol
    c. lidocaine
    d. nitroglycerin

5. **True or False: Indapamide, a thiazide diuretic, has been shown to have some calcium channel blocking effects in the arteries.**

    a. True
    b. False

6. **Nitroglycerin is a nitrate medication that causes**

    a. relaxation of the smooth muscles of the blood vessels.
    b. vasodilation.
    c. improved blood flow.
    d. All of the above

7. Loop diuretics typically are quite effective in their actions to

a. control fluid levels.
b. treat heart failure.
c. prevent dehydration.
d. Answers a., and b.

8. If a blood vessel is injured the body releases _____, which increase the coagulable state.

a. blood clot factors
b. inflammatory cytokines
c. enzymes
d. potassium

9. Examples of beta blockers that specifically target cardiac beta-adrenergic receptors include all, *except*

a. atenolol.
b. esmolol.
c. lidocaine.
d. metoprolol.

10. True or False: Clotting factors are circulating in the blood but are typically inactive until an injury occurs.

a. True
b. False

11. Which of the following is/are one of the major types of diuretic drugs:

a. Loop diuretics.
b. Thiazide diuretics.
c. Potassium-sparing diuretics.
d. All of the above

12. The alpha-receptors in the blood vessels are responsible for

a. vasoconstriction.
b. vasodilation.
c. relaxation of coronary arteries only.
d. Answers b., and c.

13. The beta-receptors are often responsible

a. vasoconstriction.
b. vasodilation.
c. constriction of coronary arteries only.
d. Answers a., and c.

14. True or False: To facilitate urinary excretion, loop diuretics increase movement of fluid and electrolytes from the kidney tubules.

a. True
b. False

15. Calcium channel blockers have little to no effect on venous dilation and primarily are used to

a. lower arterial pressure.
b. increase arterial pressure.
c. alleviate peripheral venous pressure.
d. Answers a., and c.

16. Streptokinase

a. is an extracellular protein that comes from the culture of beta-hemolytic streptococci.
b. forms a complex with plasminogen to convert it to its active form of plasmin.
c. supports the breakdown of fibrinogen and clotting factors V and VII.
d. All of the above

17. Hydralazine is

a. used to treat hypertension
b. a vasodilator that relaxes the smooth muscles in the arteries
c. beneficial for patients with heart failure, as the drug tends to reduce *pre*load.
d. Answers a., and b.

18. Beta-2 receptors

a. are found in the smooth muscles.
b. cause vasoconstriction.
c. lead to increased vasodilation.
d. Answers a., and c.

19. Anistreplase is made up of a complex of streptokinase and plasminogen, which is only indicated for

a. acute myocardial infarction.
b. deep vein thrombosis.
c. pulmonary blood clot.
d. arterial blood clot to the brain.

20. True or False: Because alteplase works to break down clots that have developed, it can also increase a patient's risk of hemorrhage and bleeding after the drug is administered.

a. True
b. False

21. Vasoconstriction describes the process of

a. low peripheral vascular resistance.
b. dilation of blood vessels.
c. narrowing of the blood vessels.
d. increased circulation.

22. Pulmonary hypertension typically causes symptoms of

a. fatigue.
b. shortness of breath.
c. diminished physical ability.
d. All of the above

23. Constriction and dilation of blood vessels is *primarily* controlled by

a. increasing and decreasing blood pressure.
b. the smooth muscles in the blood vessels.
c. peripheral vascular resistance.
d. the heart rate.

24. Which of the following is part of the systemic circulatory system?

a. The left main coronary artery
b. The pulmonary artery
c. The aorta
d. The right side of the heart

25. The pulmonary circulatory system includes

a. the left side of the heart.
b. the myocardium.
c. the aorta.
d. the right side of the heart.

26. The right coronary artery branches into the posterior descending artery, which supplies blood

a. to the back of the heart.
b. into the systemic circulation system.
c. to the brain.
d. to the aorta.

27. The mean arterial pressure (MAP) is another name for

a. vasoconstriction and dilation.
b. the circulation system.
c. average blood pressure.
d. high blood pressure.

28. The MAP is *mainly* controlled by which of the following?

a. The adrenergic receptors
b. The sympathetic nervous system
c. The parasympathetic nervous system
d. Vasodilation of the blood vessel walls

29. Vasodilation of the blood vessel walls is caused by

a. the release of norepinephrine.
b. the sympathetic nervous system.
c. the parasympathetic nervous system.
d. an increase in calcium ions.

30. Stimulation of the renin-angiotensin system also causes vasoconstriction and the release of

a. the hormone aldosterone.
b. the hormone epinephrine.
c. the hormone eplerenone.
d. the hormone vasopressin.

31. True or False: The effects of vasoconstriction from alpha-agonist drugs are more noticeable in the veins.

a. True
b. False

32. Healthcare providers who administer methoxamine for blood pressure treatment should review a patient's cardiac history because

a. methoxamine directly affects the heart.
b. reduces mean arterial blood pressure.
c. it causes vasodilation.
d. it could cause bradycardia in larger doses.

33. Vasopressin is a naturally occurring hormone secreted from

a. the kidneys.
b. parasympathetic nervous system.
c. sympathetic nervous system.
d. the posterior pituitary in the brain.

34. The heart's ability to contract normally can be affected by

a. preload only.
b. afterload only.
c. preload and afterload.
d. None of the above

35. The formula for calculating systemic vascular resistance (SVR) is as follows:

a. SVR = MAP ÷ CO
b. SVR = MAP + CO
c. SVR = MAP
d. SVR = CO

36. _____ most often develops when the small blood vessels that surround the lungs become blocked or occluded.

a. Pulmonary hypertension
b. Vasospasm
c. Cardiac arrhythmia
d. Myocardial infarction

37. When the heart and surrounding tissue lack appropriate blood flow, they are said to develop _____.

a. angina
b. ischemia
c. tissue necrosis
d. hypertension

38. A condition known as atherosclerosis is most often associated with _____.

a. myocardial infarction
b. unstable angina
c. stable angina
d. tissue necrosis

39. True or False: Vasoconstriction can have both positive and negative effects on circulation.

a. True
b. False

40. According to the Canadian Cardiovascular Society grading scale, Class I angina occurs

a. only when at rest.
b. at rest or during moderate exercise.
c. at any time regardless of physical activity.
d. only during strenuous physical activity.

41. Vasospasm of the coronary artery most often occurs in vessels that are

a. poorly oxygenated.
b. "hardened" by atherosclerosis.
c. not "hardened" by atherosclerosis.
d. after a coronary vessel becomes occluded.

42. Other factors that can lead to vasoconstriction include

a. cold temperatures.
b. nicotine in tobacco.
c. intake of salt.
d. All of the above

43. "Variant angina" is more likely to occur

a. as a result of exertion or exercise.
b. during the early morning hours.
c. during cessation of tobacco use.
d. in warm temperatures.

44. Acetylcholine is a neurotransmitter that eventually contributes to _____ through its release of nitric oxide.

a. vasodilation
b. vasospasm
c. variant angina
d. None of the above

45. True or False: Some patients who suffer from coronary artery vasospasm suffer from vasoconstriction with the release of acetylcholine.

a. True
b. False

46. Nitroglycerin is or may be administered

a. after symptoms of angina have developed.
b. prophylactically - before angina symptoms have developed.
c. only as a short-acting agent.
d. Answers a., and b.

47. _____ is a common calcium channel blocker that is used for the management of angina due to coronary vasospasm.

a. Isosorbide dinitrate
b. Amlodipine
c. Acetylcholine
d. Clopidogrel

48. Clopidogrel may be a beneficial drug to administer for those patients

a. with acute chest pain due to unstable angina.
b. who are about to have an invasive procedure.
c. with signs of bleeding.
d. who cannot tolerate aspirin.

49. In general, arrhythmias occur as conduction abnormalities in the heart's _____.

a. circulation system
b. electrical system
c. endothelial layer
d. blood vessels

50. Normally, the electrical conduction impulses begin in

a. the sinoatrial (SA) node.
b. the atrioventricular (AV) node.
c. the triangle of Koch.
d. the non-nodal tissue.

51. The _____ is the main connection through which electrical impulses pass between the atria and the ventricles.

a. sinoatrial (SA) node
b. bundle of His
c. triangle of Koch
d. atrioventricular (AV) node

52. The _____ is called the "pacemaker" of the heart.

a. sinoatrial (SA) node
b. bundle of His
c. posterior pituitary
d. atrioventricular (AV) node

53. The heartbeat is regular and synchronized on the right and left sides of the heart because of

a. the triangle of Koch.
b. the atria and the ventricles.
c. the Purkinje fibers.
d. atrioventricular (AV) node.

54. The _____ is most often used when selecting medication to control the arrhythmia.

a. Myron Prinzmetal classification system
b. Canadian Cardiovascular Society grading scale
c. Vaughan-Williams classification system
d. None of the above

55. _____, a sodium channel blocker used to decrease conduction velocity, may also increase the risk of *torsades de pointes*.

a. Atenolol
b. Procainamide
c. Esmolol
d. Atropine

56. Common drugs used for the management of increased conduction velocity within the heart are

a. beta-blockers.
b. potassium channel blockers.
c. calcium channel blockers.
d. sodium channel blockers.

57. _____ is used for the management of supraventricular arrhythmias and it is administered prophylactically.

a. Atropine
b. Isoproterenol (Isuprel®)
c. Epinephrine
d. Atenolol (Tenormin®)

58. True or False: Epinephrine is used in the clinical setting for management of bradycardia but not to treat emergency, life-threatening cardiac arrhythmias.

a. True
b. False

59. Cardiac arrhythmias occur when cardiac cells

a. transfer certain ions across the cell membranes.
b. depolarize.
c. depolarize at an inappropriate rate or time.
d. have a slight difference in voltage.

60. Re-entry occurs when an electrical signal in a heart cell

a. does not complete a normal circuit.
b. depolarizes and then repolarizes.
c. depolarizes at an inappropriate rate or time.
d. is set up for the next impulse to pass it.

61. Abnormal automaticity occurs when electrical impulses are sent

a. by the sinoatrial (SA) node.
b. and then the cell repolarizes.
c. at an inappropriate rate or time.
d. by cardiac cells other than the SA node.

62. In order for a cardiac cell to depolarize, the voltage inside the cell must be _____ the voltage outside the cell.

a. equal to
b. different from
c. faster than
d. slower than

63. An ectopic beat is described as any heartbeat that originates

a. outside the aorta.
b. outside the atrioventricular (AV) node.
c. outside the sinoatrial (SA) node.
d. in the cardiac cell membrane.

64. When cells outside the sinoatrial (SA) node try to originate electrical impulses,

a. slower than normal arrhythmias result.
b. bradycardia occurs.
c. depolarization does not occur as quickly.
d. All of the above.

65. True or False: Ventricular tachycardia is an example of an arrhythmia that may develop as a result of re-entry that impacts the ventricles.

a. True
b. False

66. Procainamide can be administered

a. in oral form in the United States.
b. for paroxysmal supraventricular tachycardia (PSVT).
c. to patients with previous myocardial infarction.
d. to patients with potassium imbalances.

67. Captopril is given as an oral agent to control blood pressure levels

a. 2 to 3 times daily until blood pressure levels are normal.
b. once a day in the beginning.
c. for a period not exceeding 2 weeks.
d. but cannot be administered with other drugs.

68. True or False: Captopril doses may be prescribed in doses as high as 150 mg.

a. True
b. False

69. Indapamide is a drug that

a. should only be taken once daily.
b. should be taken in the morning.
c. may cause hypotension among some patients.
d. All of the above

70. Clonidine and alpha-methyldopa are sympatholytic drugs that

a. may not be used with other drugs.
b. are used for the management of hypertension.
c. are not safe for patients with kidney disease.
d. can increase arterial pressure.

CORRECT ANSWERS:

1. Angina is a condition where a patient experiences

d. Answers a., and b.

2. Vasoactive drugs, including pressors and inotropic medications are often given to patients experiencing

b. cardiogenic shock to resolve some hypotension.

3. Thrombolytic drugs are typically administered

c. intravenously.

4. One particular type of beta-blocker, _____ showed significant results in decreased overall patient mortality when used among those with heart failure.

b. carvedilol

5. True or False: Indapamide, a thiazide diuretic, has been shown to have some calcium channel blocking effects in the arteries.

a. True

6. Nitroglycerin is a nitrate medication that causes

d. All of the above

7. Loop diuretics typically are quite effective in their actions to

d. Answers a., and b.

8. If a blood vessel is injured the body releases _____, which increase the coagulable state.

b. inflammatory cytokines

9. Examples of beta blockers that specifically target cardiac beta-adrenergic receptors include all, *except*

c. lidocaine.

10. True or False: Clotting factors are circulating in the blood but are typically inactive until an injury occurs.

a. True

11. Which of the following is/are one of the major types of diuretic drugs:

d. All of the above

12. The alpha-receptors in the blood vessels are responsible for

a. vasoconstriction.

13. The beta-receptors are often responsible

b. vasodilation.

14. True or False: To facilitate urinary excretion, loop diuretics increase movement of fluid and electrolytes from the kidney tubules.

a. True

15. Calcium channel blockers have little to no effect on venous dilation and primarily are used to

a. lower arterial pressure.

16. Streptokinase

d. All of the above

17. Hydralazine is

d. Answers a., and b.

18. Beta-2 receptors

d. Answers a., and c.

19. Anistreplase is made up of a complex of streptokinase and plasminogen, which is only indicated for

a. acute myocardial infarction.

20. True or False: Because alteplase works to break down clots that have developed, it can also increase a patient's risk of hemorrhage and bleeding after the drug is administered.

a. True

21. Vasoconstriction describes the process of

c. narrowing of blood vessels.

22. Pulmonary hypertension typically causes symptoms of

d. All of the above.

23. Constriction and dilation of blood vessels is *primarily* controlled by

b. the smooth muscles in the blood vessels.

24. Which of the following is part of the systemic circulatory system?

c. The aorta

25. The pulmonary circulatory system includes

d. the right side of the heart.

26. The right coronary artery branches into the posterior descending artery, which supplies blood

a. to the back of the heart.

27. The mean arterial pressure (MAP) is another name for

c. average blood pressure.

28. The MAP is *mainly* controlled by which of the following?

b. The sympathetic nervous system

29. Vasodilation of the blood vessel walls is caused by

c. the parasympathetic nervous system.

30. Stimulation of the renin-angiotensin system also causes vasoconstriction and the release of

a. the hormone aldosterone.

31. True or False: The effects of vasoconstriction from alpha-agonist drugs are more noticeable in the veins.

b. False

32. Healthcare providers who administer methoxamine for blood pressure treatment should review a patient's cardiac history because

d. it could cause bradycardia in larger doses.

33. Vasopressin is a naturally occurring hormone secreted from

d. the posterior pituitary in the brain.

34. The heart's ability to contract normally can be affected by

c. preload and afterload.

35. The formula for calculating systemic vascular resistance (SVR) is as follows:

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62. In order for a cardiac cell to depolarize, the voltage inside the cell must be _____ the voltage outside the cell.

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65. True or False: Ventricular tachycardia is an example of an arrhythmia that may develop as a result of re-entry that impacts the ventricles.

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b. are used for the management of hypertension.

References Section

The reference section of in-text citations include published works intended as helpful material for further reading. Unpublished works and personal communications are not included in this section, although may appear within the study text.

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