General toxicology 4th stage

Heart and vascular system toxicity

Cardiovascular toxicology is concerned with the adverse effects of extrinsic and intrinsic stresses on the heart and vascular system. Extrinsic stress involves exposure to therapeutic drugs, natural products, and environmental toxicants. Intrinsic stress refers to exposure to toxic metabolites derived from nontoxic compounds such as those found in food additives and supplements. The intrinsic exposures also include secondary neurohormonal disturbance such as overproduction of inflammatory cytokines derived from pressure overload of the heart and counter-regulatory responses to hypertension.

These toxic exposures result in alterations in biochemical pathways, defects in cellular structure and function, and pathogenesis of the affected cardiovascular system. The manifestations of toxicologic response of the heart include cardiac arrhythmia, hypertrophy, and overt heart failure. The responses of the vascular system include changes in blood pressure and lesions in blood vessels in the form of atherosclerosis, hemorrhage, and edema.

Overview of Cardiac Structural and Physiological Features

Cardiac muscle, along with nerve, skeletal muscle, and smooth muscle, is one of the excitable tissues of the body. The primary contractile unit is cardiac myocyte. These are composed of contractile elements known as myofibrils, which consist of a number of thick and thin myofilaments. The thick filaments are special assemblies of the protein myosin, whereas the thin filaments primarily consist of the protein actin. Cardiac myocytes are joined end to end by intercalated disks. Within those disks, there are tight gap junctions that facilitate action potential propagation and intercellular communication.

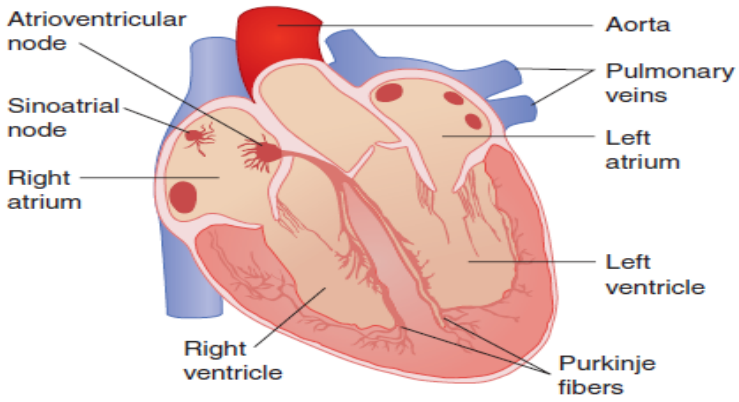


Figure 18-1. *Diagram illustrating the basic anatomy of the heart.*

The heart contains cardiac myocytes, which contribute to the majority of cardiac mass, cardiac fibroblasts, vascular cells, Purkinje cells, and other connective tissue cells. From a toxicologic perspective, the heart is vulnerable to injury because of the

limited proliferative capacity of cardiac myocytes and the promotion of cardiac fibroblast proliferation and cardiac remodeling after injury.

Electrophysiology

In cardiac myocytes, three major positively charged ions make a significant contribution to the bioelectricity of the heart; calcium (Ca2+), sodium (Na+), and potassium (K+). Each of the ions has specific channels and transporters (pumps) on the membrane of cardiac myocytes. Through the movement of these ions across the cell membrane, an action potential is generated and propagated from one cell to another, so that electric conductance is prod- uced in the heart.

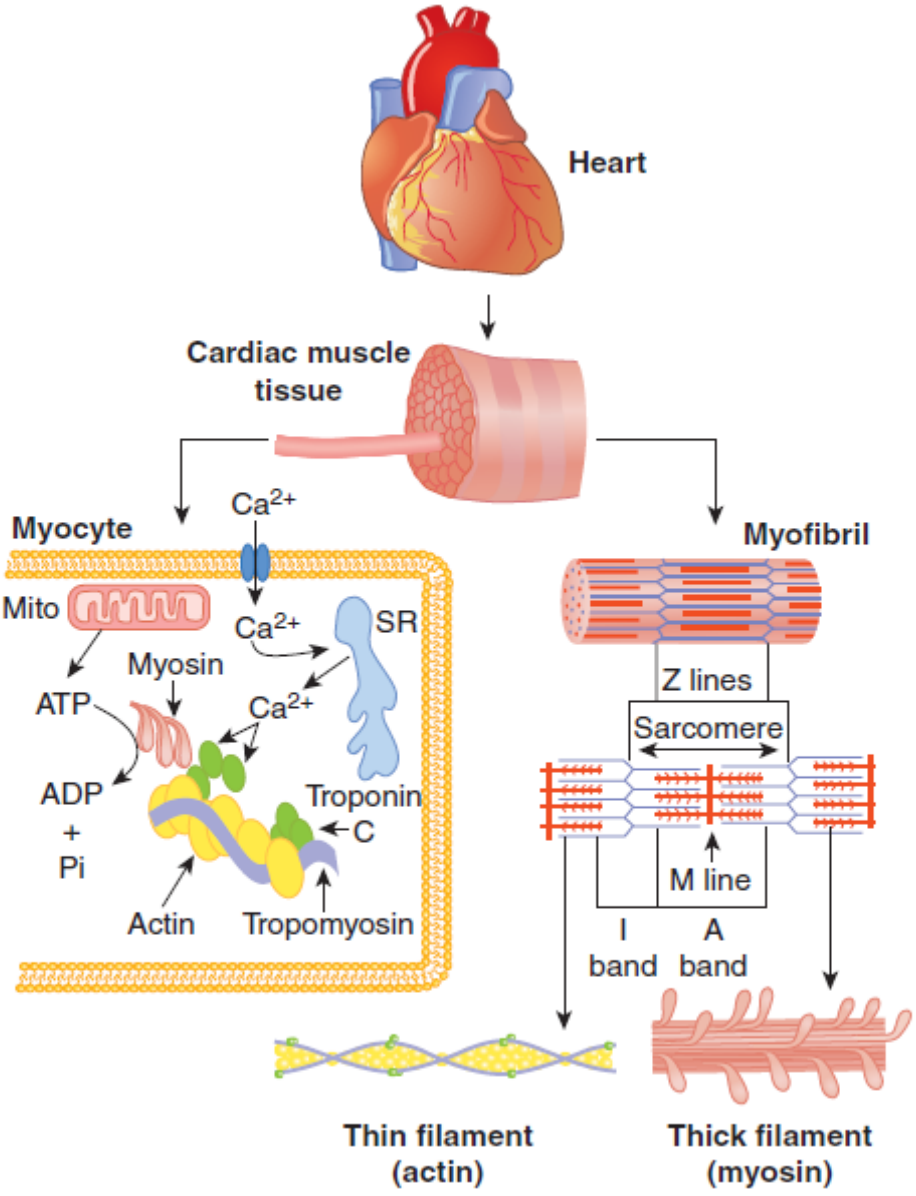


Figure 18-2. *Structural organization of cardiac muscle tissue.*

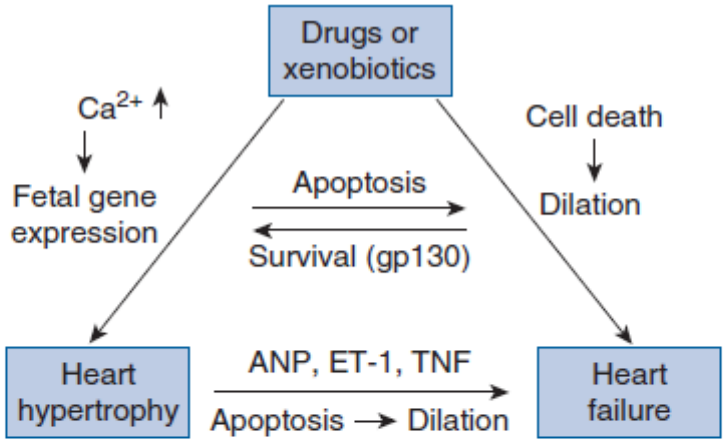
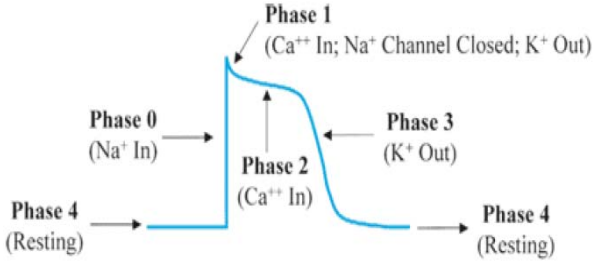
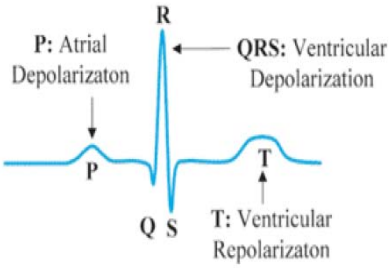


Figure 18-8. *Triangle analytical model of cardiac responses to drugs and xenobiotics.* Drugs or xenobiotics can directly cause both heart failure and heart hypertrophy. Under severe acute toxic insults, myocardial cell death becomes the predominant response leading to cardiac dilation and heart failure. In most cases, myocardial survival mechanisms can be activated so that myocardial apoptosis is inhibited. The survived cardiomyocytes often become hypertrophy through activation of calcium-mediated fetal gene expression and other hypertrophic program. If toxic insult continues, the counter-regulatory mechanisms against heart hypertrophy such as activation of cytokine-medicated pathways eventually lead to myocardial cell death through apoptosis or necrosis, dilated cardiomyopathy, and heart failure.

Action Potential





Cardiac myocytes produce an action potential when activated. In the resting state, the resting potential of a myocyte is about −60 to −90 mV relative to the extracellular fluid potential. A sudden depolarization changes the membrane potential from negative inside to positive inside, followed by a repolarization to reset the resting potential. The process of an action potential from depolarization to the completion of repolarization is divided into five phases

Phase 0 :represents a rapid depolarization due to the inward current of Na+.

Phase 1 : is associated with an immediate rapid repolarization, during which Closure of Na^+ channels and activation of outward potassium (K^+) channels, followed by an action potential plateau or

phase 2: As the Na^+ current dissipates, Ca^{2+} continues to enter the cell, giving rise to the characteristic plateau appearance.

Phase 3 :reflects a fast K+ outward current and inactivation of the plateau Ca2+inward current, and

phase 4 is the diastolic interval for the resetting of resting potential.

Electrical Conduction in the Heart

The cardiac cycle begins in pacemaker cells that spontaneously depolarize and pass a depolarizing electrical current to neighboring cells. Pacemaker cells do not contract. Spontaneous depolarization can be found in the sinoatrial (SA) node, the atrioventricular (AV) node, the bundle of His (atrioventricular bundle), and Purkinje fibers. Under physiologic conditions, SA nodal cells set the pace of the heart. If the SA node is damaged or inhibited, the next fastest depolarizing cells (AV node) assume the pacemaking activity.

Normally, the cardiac cycle begins with the spontaneous depolarization of cells in the SA node. The electrical impulse propagates through the atrial muscle and converges on the AV node. The dense fibrous tissue of the AV node causes the electrical impulse to slow down. This delayed transfer of current between the atria and the ventricles allows the atria to complete contraction before depolarization of the ventricles. The AV node impulse then is sent down the bundle of His, the bundle branches, and the Purkinje network, causing depolarization and contraction of the ventricles.

Electrical cardiac activity is regulated by the autonomic nervous system . Norepinephrine and similar sympathomimetics stimulate an increase in cardiac rate and the contractility of the myocardium. The major effect of parasympathomimetics is to decrease the rate of depolarization with only a slight decrease in ventricular contractility.

Contractility

myocyte contraction occurs when an action potential causes the release of Ca2+ from the SR as well as the entry of extracellular Ca2+into the cell. This action

potential-triggered Ca2+ increase in the cell and myocyte contraction is called *excitation–contraction coupling* , the increase in Ca2+ concentrations in the cell allows Ca2+ to bind to troponin and tropomysin leading to some conformational change in the contractile unit of the cardiac myocyte, thin filament. This conformational change permits interaction between the actin and myosin filaments through the crossbridges (myosin heads). ATP is hydrolyzed by ATPase present in the crossbridges to release energy for the movement of the crossbridges in a ratchet-like fashion.

Cardiac Output

The primary indicator of cardiac function is *cardiac output,* which is the volume of blood pumped by the ventricles per minute. Cardiac output is dependent on heart rate and stroke volume (the amount of blood ejected by the ventricles during systole). Normal cardiac output at rest is approximately 5 L/min in an average adult human, and that value may increase three- to fourfold during strenuous exercise. Toxicants may alter cardiac output through numerous mechanisms and effects on the heart, vasculature, and/or nervous system

Stroke Volume (SV) = EDV – ESV

Cardiac Output (*Q*) = SV × HR

excitation–contraction coupling in cardiac myocytes

Upon rapid depolarization (rapid influx of Na**+** through fast channels; phase 0 of the action potential), L-type Ca**2+** channels are opened allowing a slower but sustained influx of Ca**2+** down the electrochemical gradient (phase 2 of the action potential). During the process of Ca**2+**-induced Ca**2+** release (CICR), slight elevation in intracellular-free Ca**2+** stimulates Ca**2+** release from the sarcoplasmic reticulum through ryanodine receptors . The SR provides the majority of Ca**2+** required for contraction. The mitochondria provide energy for contraction in the form of ATP. For relaxation, the SR Ca**2+** ATPase actively pumps Ca**2+** back into the SR, although some Ca**2+** may be removed by the Na**+**/Ca**2+** exchanger or by sarcolemmal Ca**2+** pumps

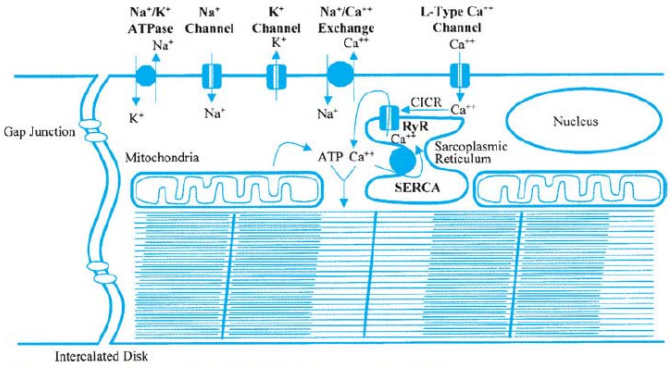


Figure 18-4. Overview of excitation–contraction coupling in cardiac myocytes.

CARDIAC TOXIC RESPONSES

The ultimate functional effect of cardiac toxic manifestations is decreased cardiac output and peripheral tissue hypoperfusion, resulting from alterations in biochemical pathways, energy metabolism, cellular structural and function, electrophysiology, and contractility of the heart.

Cardiac Arrhythmia

Cardiac rhythms under physiological conditions are set by pacemaker cells that are normally capable of developing spontaneous depolarization and responsible for generating the cardiac rhythm, the so-called automatic rhythm. A cardiac rhythm that deviates from the normal automatic rhythm is called cardiac arrhythmia ,there are several classes of tachycardia, including sinus tachycardia, atrial tachycardia, ventricular tachycardia, and torsade de pointes,In addition, subclasses such as atrial fibrillation, atrial flutter, and accelerated idioventricular rhythm provide further description of the manifestations of arrhythmia

Ischemic Heart Disease

Ischemic heart disease may be produced by various pathologic conditions and/or xenobiotics that disturb the balance of myocardial perfusion and myocardial oxygen and nutrient demand. A major cause of IHD is coronary artery atherosclerosis and the resulting arterial obstruction. Prolonged ischemia may lead to myocardial infarction, or death of myocardial cells because of lack of blood flow. Areas of the heart that are permanently damaged by myocardial infarction are replaced with scar tissue. The *cardiac remodeling* process thus includes initial myocyte loss and subsequent connective tissue cell activation and scar production, hypertrophy of remaining myocytes, altered cardiac geometry, and microcirculatory changes within the heart.

Cardiac Hypertrophy

There are two basic forms of cardiac hypertrophy **concentric hypertrophy**, which is often observed during pressure overload and is characterized by new contractile-protein units assembled in parallel resulting in a relative increase in the width of individual cardiac myocytes **eccentric hypertrophy** is characterized by the assembly of new contractile-protein units in series resulting in a relatively greater increase in the length than in the width of individual myocytes toxicologic cardiomyopathy is often manifested in the form of eccentric hypertrophy.

Heart Failure

A traditional definition of heart failure is the inability of the heart to maintain cardiac output sufficient to meet the metabolic and oxygen demands of peripheral tissues

Acute Cardiac Toxicity

Acute cardiac toxicity is referred to as cardiac response to a single exposure to a high dose of cardiac toxic chemicals. It is often manifested by cardiac arrhythmia asingle high dose of arsenic can lead to cardiac arrhythmia and sudden cardiac death exposure can directly lead to heart failure, which is different from an often-observed hypertrophic response, which may or may not progress to heart failure

Chronic Cardiac Toxicity

Chronic cardiac toxicity is the cardiac response to long-term exposure to chemicals, which is often manifested by cardiac hypertrophy and the transition to heart failure

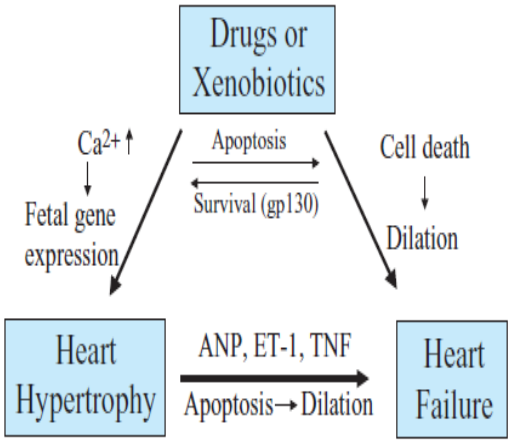


Figure 18-8. Triangle analytical model of cardiac responses to drugs and xenobiotics.

Reversible and Irreversible Toxic Responses of the heart

Cardiomyopathy was viewed not to be recoverable in the past, but there is cumulative evidence that demonstrates reversibility of cardiomyopathy. The issue related to whether or not toxicological cardiac lesions are reversible has not been explored. However, it can be speculated that there would be reversible and irreversible manifestations of the cardiac response to toxic insults. With regard to this, toxic effect on the capacity of myocardial regeneration is a major concern and myocardial regenerative toxicity determines the fate of toxicological cardiomyopathy reversible or irreversible

General Mechanisms of Cardiotoxicity

1-Interference with Ion Homeostasis

Cardiac function is dependent on tight regulation of ion channel activity and ion homeostasis. Therefore, any xenobiotic that disrupts ion movement or homeostasis may induce a cardiotoxic reaction that consists principally of disturbances in heart rhythm

Inhibition of Na^+,K^+-ATPase

Na^+,K^+-ATPase reduces intracellular Na^+ in exchange for extracellular K^+. Inhibition of cardiac Na^+,K^+-ATPase increases resting intracellular Na^+ concentrations. This in turn increases intracellular Ca^{2+} concentrations through Na^+/Ca^{2+} exchange, and the elevated intracellular Ca^{2+} and Ca^{2+} stores thus contribute to the inotropic actions of these inhibitors.

Na^+ Channel Blockade

Agents that inhibit Na^+ channels in cardiac cells alter cardiac excitability by requiring greater membrane depolarization for the opening of Na^+ channels. The effects of Na^+ channel blockade include reduction of conduction velocity, prolonged QRS duration, decreased automaticity, and inhibition of triggered activity from delayed or early after depolarizations.

K^+ Channel Blockade

Many different K^+ channels are expressed in the human heart. Blockade of K^+ channels increases the duration of the action potential and increases refractoriness .

Ca^{2+} Channel Blockade

The L-type Ca^{2+} channel contributes to excitation-contraction coupling, whereas the T-type Ca^{2+} channels contribute to pacemaker potential in the SA node. Blockade of Ca^{2+} channels in the heart produces a negative inotropic effect as a result of reductions in Ca^{2+}-induced Ca^{2+} release

2-Altered Coronary Blood Flow

Coronary Vasoconstriction

Xenobiotic-induced constriction of the coronary vasculature induces symptoms consistent with IHD. Direct effect of sympathomimetics on the coronary vasculature includes coronary vasospasm through activation of α-adrenergic receptors. When B-adrenergic receptors are blocked or during underlying pathophysiologic conditions of

the heart, the direct actions of sympathomimetics may predominate, leading to coronary vasoconstriction.

Ischemia-Reperfusion Injury

Relief of the offending cause of ischemia (e.g., thrombolytic therapy after acute myocardial infarction) provides reperfusion of the myocardium. However, depending on the duration of ischemia, a reversible contractile dysfunction remains for a day to several days after reperfusion. Reperfusion of the myocardium leads to subsequent tissue damage that may be reversible or permanent. Mechanisms proposed to account for the reperfusion injury include the generation of toxic oxygen radicals, Ca^{2+} overload, changes in cellular pH, uncoupling of mitochondrial oxidative phosphorylation, and physical damage to the sarcolemma.

3-Oxidative Stress

Reactive oxygen species are generated during myocardial ischemia and at the time of reperfusion. In patients with atherosclerosis, oxidative alteration of low-density lipoprotein is thought to be involved in the formation of atherosclerotic plaques. summarizes the adverse effects of reactive oxygen radicals generated during myocardial ischemia and reperfusion. Xenobiotics such as doxorubicin and ethanol may induce cardiotoxicity through the generation of reactive oxygen species

4-Organellar Dysfunction

sarcolemmal & Sarcoplasmic reticulum Dysfunction, and Ca^{2+} Overload

All cells contain elaborate systems for the regulation of intracellular Ca^{2+} because calcium is an important second messenger. Because extracellular Ca^{2+} concentrations are typically several orders of magnitude higher than resting intracellular free Ca^{2+}, the sarcolemmal membrane must prevent a rapid influx of Ca^{2+} and subsequent Ca^{2+} overload (sustained elevated intracellular free Ca^{2+} concentration). The principal Ca^{2+} regulatory organelle in cardiac myocytes is the sarcoplasmic reticulum (SR). Alterations of cardiac Ca^{2+} homeostasis by toxicants may perturb the regulation of cellular functions.

Mitochondrial Injury

ATP is the immediate energy source required for work in most biological systems and is obtained mainly through the oxidative phosphorylation of adenine diphosphate (ADP) in the mitochondria. Oxidative phosphorylation can be affected at various sites along the respiratory chain through the use of different chemical inhibitors, such as rotenone, cyanide, and antimycin A.

5-Apoptosis and Necrosis

Toxic insults trigger a series of reactions in cardiac cells leading to measurable changes. Mild injuries can be repaired. However, severe injuries will lead to cell death in the modes of apoptosis and necrosis.*Apoptosis* was found to be involved in cardiomyopathy , The loss of cardiac myocytes is a fundamental part of myocardial injury, which initiates or aggravates cardiomyopathy. An important mode of myocardial cell loss is apoptosis, which has been demonstrated in heart failure patients . In the early periods after myocardial infarction, ishemic injury, or toxicant-induced injury, cardiac myocyte death probably occurs through apoptotic pathways, whereas necrosis occurs at later time points after the insult. Xenobiotics that are associated with the induction of cardiac myocyte apoptosis in vitro include cocaine, daunorubicin, doxorubicin, isoproterenol, and staurosporine

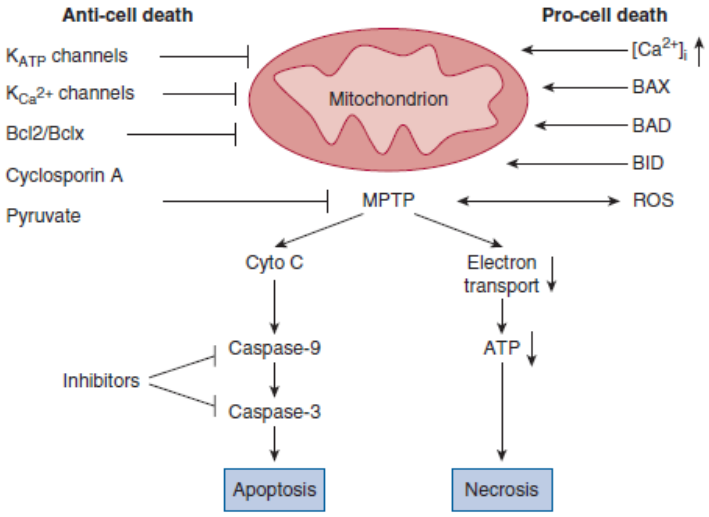


Figure 18-9. *Major factors affecting mitochondrial MPTP and myocardial cell death.* Mitochondrial cytochrome *c* release is a critical factor controlling cardiomyocyte apoptosis. Mitochondrial permeability transition pore (MPTP) opening is a determinant factor for cytochrome *c* release, as well as for electron transport collapsing leading to decreases in ATP production. The factors affecting MPTP thus are classified as pro-cell death and anti-cell death. Many other factors also affect cell death programs such as apoptosis inducing factor (AIF) released from mitochondria, but the involvement of MPTP is not evidenced.

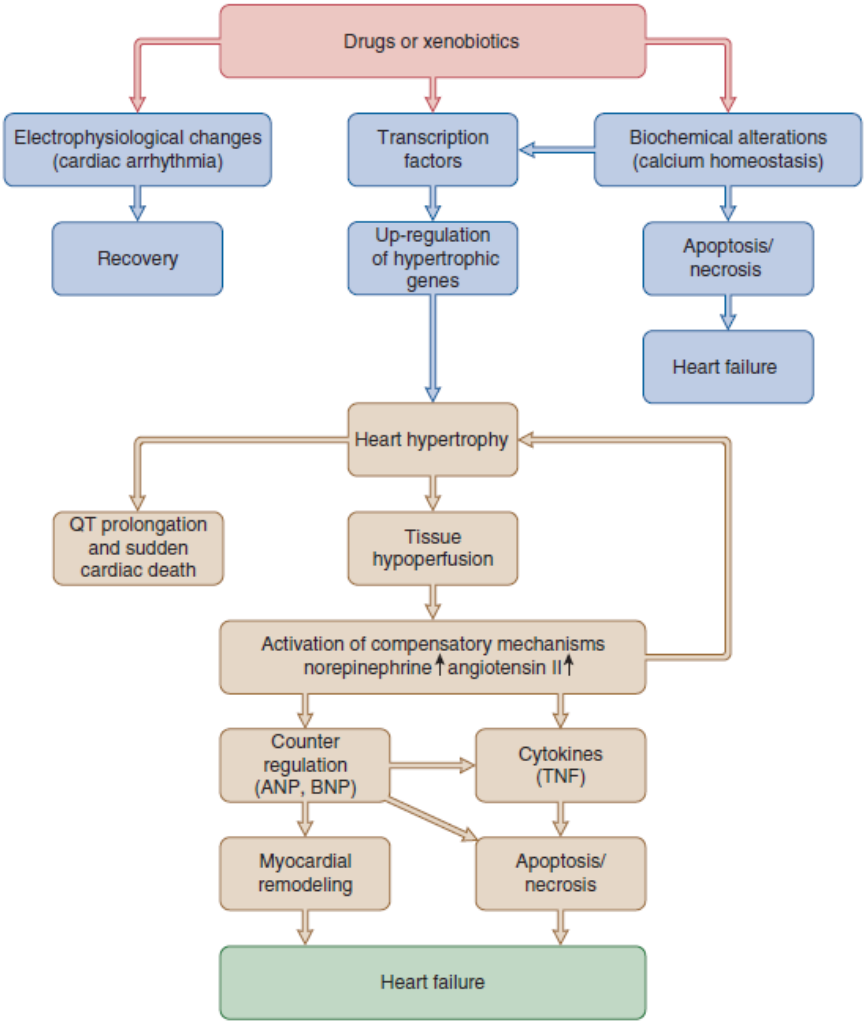


Figure 18-15. *Acute and chronic toxic exposure-induced heart failure and the transition from heart hypertrophy to heart failure.* Acute exposure to drugs or xenobiotics can cause cardiac arrhythmia, which is often observed. But if the toxic insult is so severe, myocardial apoptosis and necrosis become predominant leading to dilated cardiomyopathy and heart failure. However, the heart often survives from toxic insults through adaptive mechanisms involving upregulation of hypertrophic genes and heart hypertrophy. Heart hypertrophy increases the risk for QT prolongation and sudden cardiac death, and also activates neurohormonal regulatory mechanisms including elevation of plasma concentration of sympathetic neural transmitters and angiotensins. These compensatory mechanisms in turn activate counter-regulatory mechanisms such as ANP, BNP, and TNF-α. A long-term action of the counter-regulatory mechanisms leads to myocardial remodeling and the transition from heart hypertrophy to heart failure.

Biomarkers for Cardiac Toxicity

Myocardial injury can be divided into two major classes: structural and nonstructural injuries. The structural damage of the heart includes cell death and the associated histopathological changes such as myocardial infarction. Functional deficits often accompany the structural injury. Nonstructural damage represents functional deficits without apparent structural alterations. Myocardial structural changes and functional alterations can be indirectly measured by echocardiography and electrocardiogram in combination with stress testing. The data generated from these measurements can be considered in a broad sense as biomarkers. The fundamental principle of the biomarkers is that molecules that are released from the myocardium under various injury conditions are readily detectable from blood samples. Developing biomarkers for nonstructural injury is most challenging and demands implantation of more advanced technologies such as functional genomics and proteomics. In addition, currently available biomarkers have limitations, although they are useful.

Creatine Kinase There are three major CK isoenzymes identified; CK-MM is the principal form in skeletal muscle, CK-MB presents in myocardium CK-BB is the predominant form in brain and kidney.

Myoglobin Myoglobin is found in all muscle types and its value as a biomarker of myocardial injury

B-Type Natriuretic Peptide BNP is a cardiac neurohormone secreted by the ventricular myocardium appears to be directly correlated with the degree of ventricular wall tension.

C-Reactive Protein The acute phase reactant CRP is a marker of systemic and vascular inflammation, which appears to predict future cardiac events in asymptomatic individuals

Cardiac Troponins Cardiac troponin T (cTnT) and I (cTnI) are constituents of the myofi laments and expressed exclusively in cardiomyocytes. It is thus of absolute myocardial tissue specifi city. In healthy persons, serum cTnT or cTnI are rarely detectable. Therefore, any measurable concentrations of serum cTnT or cTnI refl ect irreversible myocardial injury such as myocardial infarction.

CARDIAC TOXIC CHEMICALS

Many substances can cause cardiac toxic responses directly or indirectly. However, only chemicals that primarily act on the heart or whose cardiac toxicity is the primary concern should be categorized as cardiac toxic chemicals. Clinically, the most recognized toxicologic cardiomyopathy is found in alcoholic heart muscle disease, which is often referred to as alcoholic cardiomyopathy , the chemicals that cause cardiac toxicity can be classified

(1) pharmaceutical chemicals, (2) natural products, and (3) environmental and industrial chemicals

Alcohol and Alcoholic Cardiomyopathy(ACM)

characterized by an increase in myocardial mass, dilation of the ventricles, wall thinning, ventricular dysfunction, and heart failure The pathogenesis of heart failure begins after an index event such as alcohol-induced cardiac muscle injury that produces an initial decline in pumping capacity of the heart. Following this initial decline, a variety of compensatory mechanisms are activated, including the adrenergic nervous system, the renin–angiotensin system, and the cytokine system. However, with time, the sustained activation of these systems can lead to secondary end-organ damage within the ventricle by activating and accelerating the left ventricle remodeling and subsequent cardiac decompensation, resulting in the transition from asymptomatic to symptomatic heart failure

It was proposed that the metabolite acetaldehyde is responsible for some of the cardiac injury associated with ethanol consumption.The metabolic enzyme responsible for the conversion of ethanol to acetaldehyde is alcohol dehydrogenase, which is absent in cardiac myocytes. Studies have indicated that the impaired liver function of alcoholics may be sufficient to generate quantities of acetaldehyde that can reach the heart .The direct effects of acetaldehyde on the myocardium include inhibition of protein synthesis, inhibition of $Ca2+$ sequestration by the SR, alterations in mitochondrial respiration, and disturbances in the association of actin and myosin.

It has been suggested that a combination of multiple factors is involved, including malnutrition,cigarette smoking, systemic hypertension, and beverage additives, in addition to a long-term consumption of alcohol in the ACM patients

Pharmaceutical Chemicals

Cardiac toxicity of pharmaceutical chemicals is a major problem in drug development and their clinical application. The pharmaceutical chemicals that cause cardiac toxic responses can be simply classified as drugs that are used to treat cardiac disease, and others that are used to treat noncardiac disease. In the category of drugs used to treat cardiac disease, cardiac toxicity is often produced by overexpression of the principal pharmaceutical effects.

Cardiac glycosides (digoxin and digitoxin)

inotropic drugs used for the treatment of congestive heart failure The mechanism of inotropic action of cardiac glycosides involves inhibition of Na+, K+-ATPase, elevation of intracellular Na+, activation of Na+/Ca2+ exchange, and increased availability of intracellular Ca2+ for contraction . Cardiac glycosides also exhibit parasympatho-mimetic activity through vagal stimulation and facilitation of muscarinic transmission The principal adverse cardiac effects of cardiac glycosides include slowed AV conduction with potential block, ectopic beats, and bradycardia

Central Nervous System Acting Drugs

Some of central nervous system (CNS)-acting drugs have considerable effects on the cardiovascular system, including tricyclic antidepressants (TCAs), general anesthetics, some of the opioids, and antipsychotic drugs.

TCAs including amitriptyline, desipramine, doxepin,imipramine, and protriptyline have significant cardiotoxic effects, particularly in cases of overdose. The effects of TCAs on the heart include ST segment elevation, QT prolongation, supraventricular and ventricular arrhythmias (including torsades de pointes), and sudden cardiac death.

Mechanism of such effect α-adrenergic blockade, TCAs cause postural hypotension, quinidine-like actions, anticholinergic effects, and adrenergic actions of these drugs, direct actions on cardiac myocytes and Purkinje fibers, including depression of inward Na+ and Ca2+ and outward K+ currents.

the risk of TCA induced cardio toxicity is significantly enhanced in children and by concomitant administration of other drugs that alter ion movement or homeostasis in the heart (e.g., the Na+ channel-blocking class I antiarrhythmic agents), or use in patients with cardiovascular disease.

Local Anesthetics In general, local anesthetics have few undesirable cardiac effects. However, when high systemic concentrations of cocaine and procainamide are attained, these chemicals may have prominent adverse effects on the heart.

Cocaine acts as a local anesthetic agent by blocking conduction in nerve fibers through reversibly inhibiting Na+ channels and stopping the transient rise in Na+ conductance. In the heart, cocaine decreases the rate of depolarization and the amplitude of the action potential, slows conduction speed, and increases the effective refractory period .The other major pharmacologic action of cocaine is its ability to inhibit the reuptake of norepinephrine and dopamine into sympathetic nerve terminals (sympathomimetic effect). Cocaine also, indirectly through its actions on catecholamine reuptake, stimulates β- and α-adrenergic receptors, leading to

increased cyclic AMP and inositol triphosphate levels. These second messengers will, in turn, provoke a rise in cytosolic Ca2+, which causes sustained action potential generation and extrasystoles, ,the net effect of these pharmacologic actions is to elicit and maintain ventricular fibrillation.

Anthracyclines and Other Antineoplastic Agents

Cardiotoxicity is recognized as a serious side effect of chemotherapy for malignant cancers, especially with well-known antitumor agents such as doxorubicin, daunorubicin, 5-fluorouracil, and cyclophosphamide. The acute effects mimic anaphylactic type responses, such as tachycardia and various arrhythmias The greatest limiting factor of the anthracyclines is associated with long-term exposure, which usually results in the development of cardiomyopathies and, in severe cases, congestive heart failure.Several major hypotheses have been suggested to account for the onset of anthracycline-induced cardiomyopathy:

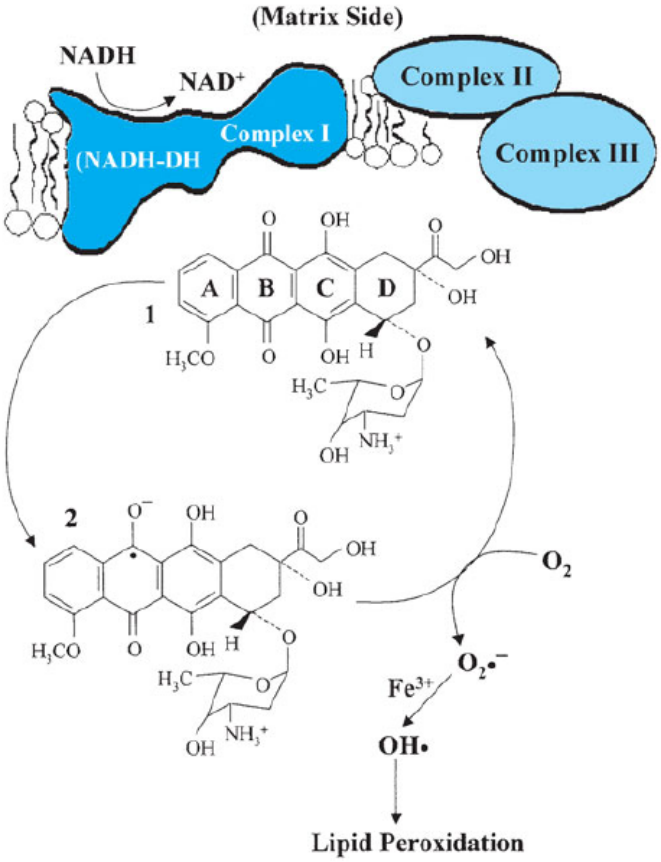


Figure 18-16. Production of superoxide anions by oxidation-reduction cycling of doxorubicin at the level of the mitochondria.

(1) oxidative stress from redox cycling or mitochondrial Ca2+ cycling, (2) defects in mitochondrial integrity and subsequent deterioration of myocardial energetics,

(3) alterations in both SR Ca2+ currents and mitochondrial homeostasis, and

(4) altered cardiac myocyte gene expression and induction of apoptosis

These ROS may then oxidize proteins, lipids, and nucleic acids and potentially cause DNA strand scission

Cyclophosphamide

High doses of cyclophosphamide given to cancer or transplant patients may lead to severe hemorrhagic cardiac necrosis. The mechanism of the cardiotoxicity of this drug is not clear, but there is suggestive evidence that the toxic metabolite of cyclophosphamide, 4-hydroperoxycyclophosphamide, may alter the ion homeostasis in cardiac myocytes, resulting in increased Na+ and Ca2+ content and reduced K+ levels

Immunosuppressants

Rapamycin and tacrolimus may produce adverse cardiovascular effects, including hypertension, hypokalemia, and hypomagnesemia. Rapamycin and tacrolimus

interact with a protein that associates with ryanodine receptors (RyRs), RyR becomes destabilized, resulting in Ca2+ leak from the SR

Antimicrobial and Antiviral Agents

Cardiotoxicity associated with the clinical use of antimicrobial and antiviral drugs is often observed in overdosage and in patients with preexisting cardiovascular dysfunction.

Aminoglycosides include amikacin, gentamicin, kanamycin,netilmicin, streptomycin, and tobramycin. Gentamicin is a representative aminoglycoside and has an inhibitory action on slow inward Ca2+ channels in heart muscle. Aminoglycosides inhibit the uptake or binding of Ca2+ at sarcolemmal sites, thus reducing the concentration of membrane-bound Ca2+ available for movement into the myoplasm during depolarization of the sarcolemma. The principle mechanism of cardiodepression by gentamicin is the dislocation of

Ca2+ from slow-channel-binding sites on the external surface of the sarcolemma, which results in a blockade of the channels.

Macrolides

include azithromycin, clarithromycin, dirithromycin,and erythromycin. Erythromycin is associated with QT prolongation and cardiac dysrhythmias characterized by polymorphic ventricular tachycardia (torsades de pointes). These effects occur primarily in patients with underlying cardiac disease.

Fluoroquinolones

Grepafloxacin, moxifloxacin,and sparfloxacin are associated with QT prolongation in perhaps a higher incidence than macrolides. In fact, grepafloxacin was voluntarily removed from the U.S. market because of the relatively high incidence of QT prolongation and risk of torsades de pointes.

Mechanism of antimicrobial that make delay or prolong QT interfere with the functioning of rectifier potassium current

Tetracycline and chloramphenicol

have been reported to depress myocardial contractility by direct cardiac myocyte interaction or an indirect effect that lowers Ca2+ concentrations in the plasma or extracellular spaces. Tetracylcines are Ca2+ chelating agents, which explain the action of tetracyclines on myocardial contractility

.**Antifungal agents**,

such as amphotericin B, may depress myocardial contractility by blocking activation of slow Ca2+ channels and inhibiting the influx of Na+.

Anti-Inflammatory Agents

A newer class of NSAIDs has been developed; including rofecoxib (Vioxx), celecoxib (Celebrex), and valdecoxib (Bextra), witch are selective inhibitors of COX-2., Vioxx was voluntarily withdrawn from the market , Vioxx increased the relative risk for cardiovascular events,such as heart attack and stroke , Bextra was removed from the market based on the potential increased risk for serious cardiovascular adverse events and increased risk of serious skin reactions (e.g., toxic epidermal necrolysis, Stevens–Johnson syndrome, erythema multiforme)
The cardiovascular events induced by COX-2 inhibitors are presumably related to thrombotic events. Studies have also indicated the link of Vioxx to long QT syndrome and the increased risk for TdP and sudden cardiac death

Antihistamines The most severe adverse effect of the second generation histamine H1 receptor antagonists (antihistamines) is their association with life-threatening ventricular arrhythmias and sudden cardiac death
Terfenadine and astemizole cause altered repolarization, notched inverted T waves, prolonged QT interval, first- and second-degree AV block, ventricular tachycardia or fibrillation, and torsades de pointes.
These antihistamines produce cardiac arrhythmias by blocking the delayed rectifier K+ channel and prolonging action potential duration in cardiac myocytes. The prolonged action potential duration promotes early after depolarizations and predisposes the myocardium to ventricular arrhythmias. However, terfenadine also inhibits L-type Ca2+ at concentrations near or below that required to inhibit delayed rectifier K+ current. Therefore, both inhibition of Ca2+ and inhibition of K+ current likely contribute to the cardiotoxic actions of terfenadine, As a result of cardiotoxicity, both astemizole and terfenadine have been removed from the United States market.

Methylxanthines (including caffeine, theobromine, and theophylline)
can be found in significant quantities in coffee, tea, chocolate, soft drinks, and other foods. Overdose of theophylline or rapid intravenous administration of therapeutic doses of aminophylline may produce lifethreatening ventricular arrhythmias; these effects may in part be explained by direct actions of theophylline on cardiac myocyte SR or by inhibition of phosphodiesterase and elevation of cyclic AMP. The cardiac effects of methylxanthines observed in vivo (including increases in cardiac output and heart rate) may also be explained by elevated catecholamines, as theophylline has been shown to increase plasma epinephrine concentrations. High concentrations of caffeine stimulate massive release of Ca2+ from the SR, an effect that is often utilized experimentally to determine SR function. Although it rarely occurs, caffeine-associated ventricular arrhythmias have been reported.

Sildenafil

Sildenafi l is a relatively specific inhibitor of phosphodiesterase-5, which is responsible for the degradation of cyclic guanosine monophosphate (cGMP; a vasodilatory second messenger). Interestingly, sildenafi l was originally developed as a potential drug for treating angina; however, it was not very effective for this purpose and was subsequently developed for treatment of erectile dysfunction, where it produces vasodilation and filling of the corpus cavernosum. The primary

concern regarding adverse effects is nonspecific inhibition of PDE3 in the heart and vasculature leading to increase CAMP and associated proplems.

Natural Products

Natural products include naturally occurring catecholamines, hormones,and cytokines, as well as animal and plant toxins

Glucocorticoids and mineralocorticoids are primarily synthesized in the adrenal glands. Naturally occurring glucocorticoids include corticosterone, cortisone, and hydrocortisone (cortisol), and the mineralocorticoid is aldosterone. Both aldosterone and glucocorticoids appear to stimulate cardiac fibrosis by regulating cardiac collagen expression independently of hemodynamic alterations. Furthermore, aldosterone and glucocorticoids induce hypertrophic growth and alter expression of Na+, K+-ATPase, Na+/H+ antiporter, and chloride/bicarbonate exchanger of cardiac myocytes

. Clinically relevant cardiac hypertrophy has been observed in premature infants undergoing dexamethasone treatment.

Thyroid hormones include thyroxine (T4) and triiodothyronine(T3).

These hormones exert profound effects on the cardiovascular system. Hypothyroid states are associated with decreased heart rate, contractility, and cardiac output; whereas hyperthyroid states are associated with increased heart rate, contractility, cardiac output,Thyroid hormones also alter expression of cardiac SR Ca2+ handling proteins including increased expression of SR Ca2+ ATPase (SERCA) and decreased expression of phospholamban, an inhibitory protein of SERCA

Animal and Plant Toxins Animal toxins in the venom of snakes,spiders, scorpions, and marine organisms have profound effects on the cardiovascular system. There are also a number of plants—such as foxglove, oleander, and monkshood—that contain toxic constituents and have adverse effects on the cardiovascular system

Environmental Pollutants and Industrial Chemicals

Solvents Industrial solvents can exert adverse effects on the heart directly or indirectly; both are related to their inherent lipohilicity. Solvents may affect cardiac physiological functions such as contraction and energy production by directly dispersing into plasma membranes. However, the effects of solvents on the heart would be more related to their actions on the neuro-hormonal regulation of cardiac function. Solvents may disrupt sympathetic and parasympathetic control of the heart as well as cause release of circulating hormones such as catecholamines, vasopressin, and serotonin, which in turn affects cardiac function

Metals and Metalloids The most common heavy metals that have been associated with cardiotoxicity are cadmium, lead, and cobalt.These metals exhibit negative inotropic and choronotropic effects and can also produce structural changes in the heart. Chronic exposure to cadmium has been reported to cause cardiac hypertrophy. Lead has an arrhythmogenic sensitizing effect on the myocardium. In addition, lead has been reported to cause degenerative changes in the heart. Cobalt has been reported to cause cardiomyopathy. The cardiotoxic effects of heavy metals are attributed to their

ability to form complexes with intracellular macromolecules and their ability to antagonize intracellular Ca2+.

Arsenic is a metalloid, which has been shown to cause cardiotoxicity directly. Arsenic has a high affinity for sulfhydryl proteins,which are involved in multiple cellular metabolism and function.

OVERVIEW OF VASCULAR SYSTEM

Vascular Physiology and Structural Features

The vascular system consists of blood vessels of varying size and different cellular composition. Blood vessels can be divided into arterial, venous, and capillary systems. In addition, the lymphatic system belongs to the vascular system, but it only carries plasma

Arterial System and Physiological Function

The arterial system is composed of the aorta, major arteries, and small arterioles. The aorta and major arteries are thick-walled structures with vascular smooth muscle, elastic, and connective tissues The tunica intima is composed of endothelial cells, facing the vessel lumen, which rest on a thin basal lamina.

The tunica media consists mainly of vascular smooth muscle cells interwoven with collagen and elastin. The tunica adventia is a layer of fibroblasts, collagen, elastin, and glycosaminoglycans

Regulatory Mechanisms of the Vascular System

The vascular system includes conduits and microcirculation. This system under physiological conditions is regulated by the demands of tissue metabolism. The mechanisms controlling vascular physiology can be divided into neural, hormonal, and local controls.

There are many hormones that control the vascular system. Catecholamines, renin–angiotensin–aldosterone, antidiuretic hormone (ADH), and atrial natriuretic peptide (ANP) are important hormones that affect the vascular system,the increase in circulating epinephrine activates the β2-adrenergic receptors localized in the coronary and skeletal muscle arteries leading to vascular smooth muscle relaxation and vasodilation. This occurs during defense and exercise, *The renin–angiotensin–aldosterone system* is critically involved in the regulation of blood pressure and volume. Renin is released from the kidney in response to reduced arterial pressure and blood volume, which catalyzes the conversion of a plasma protein angiotensinogen to angiotensin I. Angiotensin I is further converted to angiotensin II by an angiotensin-converting enzyme. AngiotensinII is a powerful arteriolar vasoconstrictor and also causes the release of aldosterone from the adrenal cortex. One of the important actions of the aldosterone is to reduce renal sodium excretion, resulting in retention of water and increase in blood volume.

ADH is released from the posterior pituitary gland under the control of the hypothalamus. ADH is a vasoconstrictor but is not present in plasma in high concentrations under physiological conditions.

ANP is released from atrial muscle cells when they are stimulated by stretch. ANP increases the excretion of sodium so that it decreases the blood volume.

Therefore, ANP regulation of blood volume is a counter-regulatory mechanism of the renin–angiotensin–aldosterone system and ADH

An important mechanism of local regulation of microcirculation is the substance released by endothelial cells, endothelium derived relaxing factor. This substance is NO generated from arginine by NOS. The mechanism of action of the endothelium-derived relaxing factor involves the increase in cyclic guanosine monophosphate (cGMP) and the subsequent activation of intracellular signaling pathways leading to relaxation of vascular smooth muscle cells. The endothelium-derived relaxing factor also suppresses platelet activation and reduces adhesion of leukocytes to endothelial cells.

VASCULAR SYSTEM TOXIC RESPONSES

Mechanisms of Vascular Toxicity

(1) alterations in membrane structure and function Vascular reactivity is regulated by the transfer of signals from the surface to the interior of the cell and/or direct modulation of the structure and function of contractile proteins. Usually, disorders of vascular reactivity involve disturbances of ionic regulation

(2) redox stress leading to disruption of gene regulatory mechanisms, compromised antioxidant defenses, and generalized loss of homeostasis,.Oxidative metabolism of plasma lipoproteins is critical in the initiation and progression of atherosclerosis. LDLs are oxidized by oxygen free radicals that are released by arterial cells. Modified LDLs attract macrophages and prevent their migration from the tissues.

(3) vessel-specific bioactivation of protoxicants Vascular toxicity also may be due to deficiencies in the capacity of target cells to detoxify the active toxin or handle prooxidant states.

(4) Vascular toxicity may be due to the accumulation of chemicals in the vascular wall. Aromatic hydrocarbons and other ubiquitous environmental contaminants partition into the lipid phase of the atherosclerotic plaques.

VASCULAR SYSTEM TOXIC CHEMICALS

Chemicals that cause vascular toxicity can also be classified into pharmaceutical chemicals, natural products, and environmental pollutants and industrial chemicals

Nicotine Nicotine is an alkaloid found in various plants and mimics the actions of acetylcholine at nicotinic receptors throughout the body. At pharmacologic concentrations, nicotine increases heart rate and blood pressure as a result of stimulation of sympathetic ganglia and the adrenal medulla.

Psychotropic Agents Trifluoperazine and chlorpromazine among the psychotropic drugs have been shown to cause intracellular cholesterol accumulation, Aside from the atherogenic effects, postural hypotension has been identified as the most common cardiovascular side effect of TCAs.

Oral Contraceptives Oral contraceptive steroids can produce thromboembolic disorders

Natural Products

Bacterial Endotoxins Bacterial endotoxins are potent toxic agents to vascular system and cause a variety of toxic effects in many vascular beds. In the liver, they cause swelling of endothelial cells and adhesion of platelets to sinusoid walls. In the lung, endotoxins produce increased vascular permeability and pulmonary hypertension

Vitamin D The toxic effects of vitamin D may be related to its structural similarity to 25-hydroxycholesterol, a potent vascular toxin. The manifestions of vitamin D hypervitaminosis include medial degeneration, calcification of the coronary arteries, and smooth muscle cell proliferation

β-Amyloid Accumulation of β-amyloid is a major lesion in the brain of Alzheimer's patients. Studies have shown that administration of β-amyloid produces extensive vascular disruption, including endothelial and smooth muscle damage, adhesion and migration of leukocytes across arteries and venules

Environmental Pollutants and Industrial Chemicals

Tobacco smoke not only exerts a direct atherogenic effect (endothelial injury, changes in lipid profiles, and proliferation of smooth muscle cells), but also facilitates thrombosis by modulation of platelet function and vascular spasm. Short-term exposure to carbon monoxide is associated with direct damage to vascular endothelial and smooth muscle cells. Injury to endothelial cells increases intimal permeability and allows the interaction of blood constituents with underlying components of the vascular wall The toxic effects of carbon monoxide have been attributed to its reversible interaction with hemoglobin. As a result of this interaction,carboxyhemoglobin decreases the oxygen-carrying capacity of blood, eventually leading to functional anemia. In addition, carbon monoxide interacts with cellular proteins such as myoglobin
and cytochrome *c* oxidase and elicits a direct vasodilatory response of the coronary circulation

Metals and Metalloids The vascular toxicity of food- and waterborne elements (selenium, chromium, copper, zinc, cadmium, lead, and mercury) as well as airborne elements (vanadium and lead) involves reactions of metals with sulfhydryl, carboxyl, or phosphate groups. Metals such as cobalt, magnesium, manganese, nickel, cadmium, and lead also interact with and block calcium channels. Intracellular calcium-binding proteins, such as CaM, are biologically relevant targets of heavy metals, including cadmium, mercury and lead.

Lead has been shown associated with essential hypertension in a large percentage of patients . Elevated blood pressure has also been observed during childhood lead poisoning. The direct vasoconstrictor effect of lead may be related to the putative hypertensive response.This effect can be complemented by the ability of lead to activate the renin–angiotensin–aldosterone system. Lead also directly affects vascular endothelial and smooth muscle cells. For instance, lead inhibits the repair process in damaged endothelial cells and modulates spontaneous release of fibrinolytic proteins from subendothelial cells through intracellular calcium-independent pathways . Acute lead-induced neuropathy may be due to cerebral capillary dysfunction Inorganic lead alters arterial elasticity and causes sclerosis of renal vessels.