Heart toxicity:

Cardiovascular toxicology is concerned with the adverse effects of extrinsic and intrinsic on the heart and vascular system.

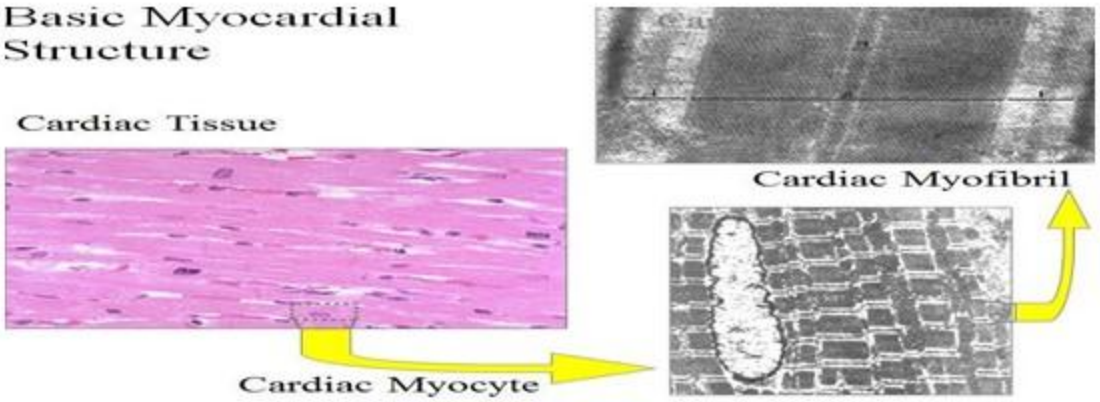
- Extrinsic stress involves exposure to therapeutic drugs, natural products, and environmental toxicants.

- Intrinsic stress refers to compounds exposure to toxic metabolites derived from nontoxic compounds such as those found in food additives and supplements. In addition secondary neurohormonal disturbance such as overproduction of inflammatory cytokines derived from pressure overload of the heart and counter-regulatory responses to hypertension.

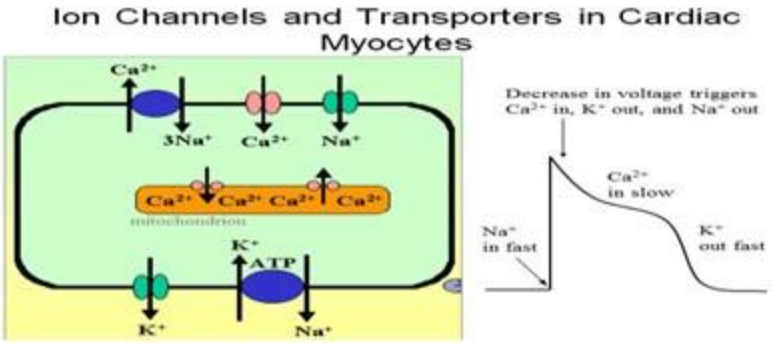
The manifestations of toxicological response of the heart include cardiac arrhythmia, hypertrophy, and heart failure. The responses of the vascular system include changes in blood pressure and lesions in blood vessels in the form of atherosclerosis, hemorrhage, and edema.

Overview of Cardiac Structural and Physiological Features:

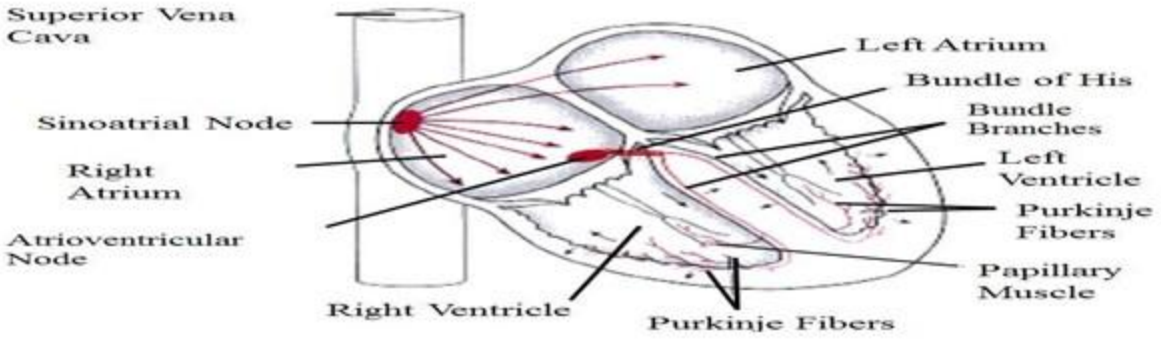
Cardiac muscle is one of the excitable tissues of the body.



The heart is vulnerable to injury because of the limited proliferative capacity of cardiac myocytes and the injury promotion of cardiac fibroblast proliferation and cardiac remodeling after injury.



Basic Cardiac Electrophysiology



Electrical Conduction in the Heart:

If the SA node is damaged or inhibited, the next fastest depolarizing cells (Av node) assume the pacemaking activity.

Cardiac output:

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

General Mechanisms of Cardiotoxicity:

Any xenobiotic that disrupts ion movement or homeostasis may induce a cardiotoxic reaction that consists principally of disturbances in heart rhythm

1• Inhibition of Na, K –ATPase:

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

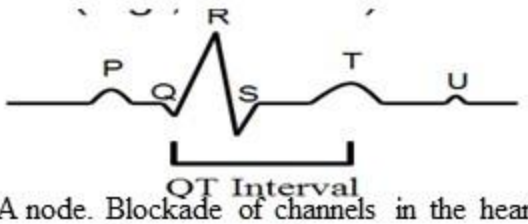
• Na+ channel Blockade:

Agents that inhibit Na^{+} channel(Class I Antiarrhythmics, local anesthetics) in cardiac cells alter cardiac excitability by requiring greater membrane depolarization for the opening of Na' channels. These effects of Na channel blockade include reduction of velocity, prolonged QRS duration, decreased automaticity, and inhibition of triggered activity from delayed or early after depolarizations.

K+ Channel Blockade:

Many different medication effects on K channels in human heart (Class III antiarrhythmic, Vasodilator agents). Blockade of K expressed in the channels increases duration of the action potential and increases refractoriness.

Ca^{2+} Channel Blockade:



The L-type Ca^{2+} channel (Amlodipine, Diltiazem, Felodipine, Nisoldipine, Verapamil) contributes to excitation-contraction coupling, whereas the T-type Ca^{2+} channels contribute to pacemaker potential in the SA node. Blockade of 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

A- Coronary Vasoconstriction:

Xenobiotic induced constriction of the coronary vasculature induces symptoms consistent with IHD. The activation of α-adrenergic receptor caused coronary vasospasm. Besides, B- adrenergic receptors are blocked (Propranolol · Metoprolol · Atenolol · Carvedilol) leading to coronary vasoconstriction.

B- **Ischemia-Reperfusion Injury:**

Relief of the offending cause of ischemia (e.g., thrombolytic therapy after acute myocardial infarction) provides reperfusion of the myocardium. Reperfusion of the myocardium leads to subsequent tissue damage that may be reversible or permanent, depending on the duration of ischemia. Mechanisms proposed to account for the reperfusion injury include the generation of toxic oxygen radicals, Ca overload change in cellular pH uncoupling of mitochondria oxidative phophorylation, 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 atherosclerosis plaques. Xenobiotics such as doxorubicin and ethanol may induce cardiotoxicity through the generation reactive oxygen species.

4- **Organellar Dysfunction**

• Sarcoplasmic reticulum Dysfunction and Ca overload. The principal Ca_2 regulatory organelle in cardiac myocytes is the sarcoplasmic reticulum (RS). Alterations of cardiac Ca_2 homeostasis by toxicants may perturb the regulation of cellular functions.

• Mitochondrial Injury:

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**: regulation and series of toxic insults trigger reactions in cardiac cells leading to changes. Mild injuries can be repaired or, sever injuries will lead to cell death in the modes of apoptosis and necrosis. Apoptosis caused loss of cardiac myocytes attributed to myocardial injury. In the early periods after myocardial infarction, ischemic injury, or toxicant-induced injury, cardiac myocyte death probably occurs through apoptotic pathways, where necrosis occurs at later time after the insult. Xenobiotics that are associated with the induction of cardiac

myocyte apoptosis, in vitro include cocaine, daunorubicin, doxorubicin, isoproterenol, staurosporine.

CARDIAC TOXIC CHEMICALS

The chemicals that caused cardiac toxicity can be classified according: 1)Pharmaceutical chemicals

2) Natural products, and (3) Environmental and industrial chemicals.

Alcoholic Cardiomyopathy (ACM):

Is characterized by an increase in myocardial mass, dilation of the ventricles walls thinning, ventricular dysfunction, and heart failure. The pathogenesis of heart failure by alcohol-induced cardiac muscle injury that lead to decline in pumping capacity of the heart, that following a variety of compensatory mechanisms are activated including the adrenergic nervous system, the renin-angiotensin system, and the cytokine system. With time, can lead to 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.

The metabolite acetaldehyde is responsible for some of the cardiac injury associated with ethanol consumption. When sufficient quantities of acetaldehyde that reach to the heart .The effects of acetaldehyde on the myocardium include:

a. inhibition of protein synthesis,

b. inhibition of Ca2+ sequestration by the SR,

c. alterations in mitochondrial respiration.

d. disturbances in the association of actin and myosin.

There are multiple factors is involved, including malnutrition, cigarette smoking, systemic hypertension.

1. Pharmaceutical Chemicals:

The cardiac toxic responses for drugs that are used to treat cardiac disease, and others that are used to treat noncardiac disease. In the drug used to treat cardiac disease, cardiac toxicity is often 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 the inotropic action of cardiac glycosides involves inhibition of Na^+ and K^+-ATPase, elevation of intracellular Na^+, activation of Na^+/Ca^{2+} exchange, and increased availability of intracellular Ca^{2+} for contraction. Cardiac glycosides also exhibit parasympatho-mimetic activity through vagal stimulation and glycosides muscarinic transmission. The principal adverse cardiac effects of cardiac include slowed AV conduction with potential block 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, and imipramine 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, and sudden cardiac death. In addition, as a result of peripheral α-adrenergic blockade, TCAs cause postural hypotension—the most prevalent cardiovascular effect, the actions (quinidine-like actions, anticholinergic effects, and adrenergic) of these drugs, direct actions on myocytes and Purkinje fibers including depression of inward Na^+ and Ca^{2+} and outward K^+ current.

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 the heart (e.g., Na^+ channel-blocking class I antiarrhythmic agents) or use patients with cardiovascular disease.

• Local Anesthetics:

In general, local anesthetics undesirable cardiac effects. cocaine and procainamide, 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.

• Cocaine is ability to inhibit the reuptake of norepinephrine and dopamine in to sympathetic nerve terminals (sympathomimetic effect).

• Cocaine also indirectly through its actions by stimulates β-α adrenergic receptors, leading increased cyclic AMP and inositol triphosphate levels. These second messengers will in turn, provoke a rise in cytosolic which causes sustained action potential generation and extracystoles, the net effect of these pharmacological actions is to elicit and maintain ventricular fibrillation.

• Anthracyclines and other Antineoplastic Agents:

The 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 is associated with long-term exposure.

The onset of anthracycline-induced cardiomyopathy:

(1) Oxidative stress from redox cycling or mitochondrial Ca^{2+} cycling,

(2) Defects in mitochondrial integrity and subsequent deterioration of myocardial energetics.

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

(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 cardioloxicity of this drug is evidence that the toxic metabolite of cyclophosphamide. Hydroperoxycyclophosphamide may alter the ion homeostasis in cardiac myocytes, resulting in increased Na^{+} and Ca^{2+} content and reduced K^{+} levels.

Antimicrobial and antiviral agents:

is often observed in over dosage and in patients with preexisting cardiovascular dysfunction.

***Aminoglycosides**:

Gentamicin is representative aminoglycosides and has inhibitory action on slow Ca^{2+} channels in heart muscle. Aminoglycosides inhibit the uptake or binding of Ca^{2+} at sarcolemmal sites, thus reducing the concentration of membrane-bound Ca^{2+} available for movement into the myoplasm during depolarization of the sarcolemma. The principle mechanism of cardio depression gentamicin is the dislocation of Ca^{2+} 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 is associated with QT prolongation and cardiac dysrhythmias characterized by polymorphic ventricular tachycardia. 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 because this effect

Tetracycline and chloramphenicol:

have been reported to depress myocardial contractility by direct cardiac myocyte interaction or an indirect effect that lowers Ca^{2+} concentrations in the plasma or extracellular spaces, Tetracylcines are Ca^{2+} 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 Ca^{2+} channels and inhibiting the influx of Na^{+}.

Anti-Inflammatory Agents:

Newer class of NSAIDs has been developed: including rofecoxib (vioxx) celecoxib (Celebrex) and valdecoxib (Bextra). They are selective of inhibitors 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 and 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 and inhibit PGI2 (prostacyclin) are presumably related to thrombotic events. Studies have also indicated link of Vioxx to long QT syndrome and the increased risk for and sudden cardiac death.

Antihistamines:

The adverse effect of the second generation histamine H_1 receptor antagonists (antihistamines) is their association with life-threatening ventricular arrhythmias and sudden cardiac death.

Terfenadine and astemizole:

Cause altered repolarization, which notched inverted T waves, prolonged QT interval, first-and second degree AV block, that caused ventricular tachycardia or fibrillation. These antihistamines produce cardiac arrhythmias by blocking delayed rectifier K^+ channel and prolonging action potential duration in cardiac myocytes. The prolonging potential duration promotes early after depolarization and predisposes the myocardium to ventricular arrhythmias. However, terfenadine also inhibit L-type Ca^{2+} at concentrations near or below that required to inhibit delayed rectifier K^+ current. Therefore, both inhibition of Ca^{2+} and inhibition of K^+ current likely contribute to the cardiotoxic actions of terfenadine. Both astemizole and terfenadine have been removed from the United States market.

Immunosuppressants: Rapamycin and tacrolimus may produce adverse cardiovascular effects, including hypertension, hypokalemia, and hypomagnesemia. Rapamycin and tacrolimus caused Ca^{2+} leak from the SR

Methylxanthines: (including caffeine, theobromine, and theophylline), can be found in significant quantities in coffee, tea, chocolate, soft-drinks, and other foods. Theophylline has been used for many decades for the treatment of asthma. Overdose of theophylline or rapid intravenous administration of therapeutic doses of aminophylline may produce life-threatening ventricular arrhythmias by direct actions of theophylline on cardiac myocyte SR or by inhibition of phosphodiesterase and elevation of cyclic AMP. In addition it caused elevated catecholamines, as theophylline has been shown to increase plasma epinephrine concentrations.

High concentrations of caffeine stimulate massive release of Ca^{2+} from the SR, an effect that is often utilized experimentally to determine SR function, caffeine-associated ventricular arrhythmias have been reported.