Introduction to the Toxicology of the Cardiovascular System

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1. Principle Components and Functions of the Cardiovascular System

- Heart - Varies among vertebrate species with complete separation of the two sides of the heart (left and right) being present in birds and amphibians.
  - The right atrium accepts poorly oxygenated blood from the body. The right ventricle pumps blood into pulmonary artery on its way to the lungs. The oxygenated blood then enters the pulmonary vein which dumps into the left atrium. The left atrium pumps blood into the left ventricle which then pumps it into the aorta on its way to the systemic circulation (includes coronary arteries that supply the heart itself, the head, including the brain, and all the organs and tissues of the body.
- The myocardium = the heart muscle, including the atrial and ventricular walls, and the papillary muscle.
- The valves include the atrioventricular (right, left), pulmonary, and aortic.
- Ion gradients (polarization) are established and maintained in the heart muscle and in specific nodes within the heart that help regulate the cardiac rhythm. The gradients (polarization) exist because Na⁺ and Ca²⁺ are pumped out of the myocardial cells (into the extracellular compartment) and K⁺ pumped into the myocardial cells (intracellular compartment). Slow Ca²⁺ flux is particularly important in the sinoatrial and the atrioventricular nodes. The ion gradients are achieved by the action of Na⁺/K⁺ ATPase (Na⁺/K⁺ pump), and by Ca²⁺-ATPase that pumps Ca²⁺ out of the cells.
- When the Na⁺ channels open, Na⁺ rushes in (causing temporary depolarization). The flow of electrons toward the more positive area of the cell (due to the charge associated with the sodium atoms) propagates the depolarization reaction along the membrane and other Na⁺ channels open, continuing the process through the heart. Shortly after the entry of Na⁺, K⁺ begins to leave the myocardial cell via K⁺ channels, thereby beginning the process of repolarization. The influx of Na⁺, however, also triggers an influx of Ca²⁺ as well as its release from intracellular storage sites (e.g. the sarcoplasmic reticulum). The increased free Ca²⁺ in the myocardial cells increases coupling between the contractile actin and myosin fibers of the cell which results in shortening of myocardial fibers (myocardial cells are hooked together in fibers).
- The usual pacemaker of the heart is the sinoatrial node, an area that depolarizes spontaneously and thereby initiates depolarization that progresses through the heart
- The propagation of the impulse through the heart is normally facilitated by special conductile fibers in the heart (Purkinje fibers) and impeded by certain areas of slower conduction (such as between the atria and the ventricles) so that the heart "rhythmically squeezes the blood along" within the lumen, making it an extremely efficient pump
- The electrocardiogram reflects the electrochemical activity in the heart that is associated with this sequence of depolarizations (which bring about systole = time of contraction) as well as repolarization events (occurs during diastole = time of relaxation; provides time for the heart to fill and the muscle to repolarize as it gets ready for the next depolarization event).
- The movement of valves is largely passive (especially the aortic and pulmonary; similar to a parachute) as they prevent backward movement of the blood - one way flow.
- The pulmonary circulation (and right heart) is low pressure, while the systemic circulation (and left heart) is high pressure. Volumes of flow in both sides are the same.
- Birth defects that result in abnormal structure and disease states that alter the structure of valves or the overall size of the heart such that blood flow becomes more turbulent result in heart murmurs.

- Arteries
  - Aorta and major arteries - large tubes with considerable elastin.
Following contraction of the heart, and in conjunction with closure of the aortic and pulmonary valves, the aorta and pulmonary artery are distended by the influx of blood during systole, and the elasticity of the vessels maintains pressure in the system during diastole.

**Arterioles**
- Small "precapillary" vessels with muscular walls: contraction alternates so that various capillary beds take turns receiving blood over time. The arterioles thus conserve the overall volume of blood in the vasculature, thereby making less work for the pump.
- Smooth muscle in the walls of arterioles and bronchi contract or relax in response to adrenergic agonists (epinephrine and norepinephrine).
  - e.g. vessels to the skin contract, coronary vessels and bronchi dilate

**Capillaries**
- The smallest porous blood vessels in the body; porous and allow extracellular fluid to leak into the tissues.
- Site of delivery of water, electrolytes, oxygen, glucose, amino acids, fatty acids, and other nutrients, plus removal of waste products, carbon dioxide, excess acid, etc.

**Venules**
- Some muscle, but much less than the arterioles.
- Help regulate pressure in capillaries.

**Veins**
- Carry poorly oxygenated blood back to the heart at greatly reduced pressure as compared to the arteries.
- Some of the veins (e.g. in legs) contain valves to prevent backpressure or reverse flow
- Vena cava
  - The anterior and posterior vena cava come together as the oxygen-depleted blood flows into the right atrium.

**Lymphatics**
- Extremely low pressure, one-way system flowing toward the heart.
- Lymphatics pick up fluid that does not make it back into the capillaries and flow into larger lymphatics that coalesce into the thoracic duct.
- The thoracic duct terminates where it empties into the vena cava.

**Endothelium**
- Cells that line blood vessels.
- Metabolically active, produce and respond to a variety of hormones (e.g. prostaglandins).

### 2. Cardiovascular System Dysfunction

**Forms of cardiac dysfunction**
- Tachycardia = excessively rapid heart rates
- Bradycardia = excessively slow heart rates
- Arrhythmia = usually implies excessively irregular heart rhythm
  - Exception - Sinus arrhythmia is the normal variation in heart rhythm; controlled by the normal pacemaker of the heart (sinoatrial node).
  - Heart block - Termination of the conduction of the impulse through the heart; other areas usually take over as an alternate "pacemaker" of the heart.
  - Premature excitation (usually spontaneous discharges of electrochemical activity, often accompanied by contraction, lack of coordination with other aspects of the cardiac cycle may greatly diminish the efficiency of pumping), e.g. premature ventricular contractions.
  - Flutter - A rapid arrhythmia - atrial flutter is generally less serious than ventricular flutter.
  - Fibrillation - Irregular depolarizations with no more than "quivering of the heart" - ineffective pumping - often rapidly fatal - e.g. ventricular fibrillation.

**Congestive heart failure (CHF)**
- Left heart failure - Back up of blood into the lungs, potential for pulmonary edema.
- Right heart failure - Back up of blood into the systemic circulation, potential for accumulation of fluid in the abdominal cavity = ascites.
- CHF may result from:
  - Interference with conduction of impulses through the heart (acute or chronic)
  - Lesions in the heart valves
  - Lesions in the myocardium

**Cardiogenic shock**
- Shock is defined as acute peripheral circulatory failure due to derangement of circulatory control or loss of circulating fluid.
- Cardiogenic shock is brought about by suddenly impeded pump failure: example, heart attack due to sudden occlusion of blood flow to the myocardium, or massive doses of cardiotoxic agents.
Forms of vascular dysfunction

- Excessive contraction of peripheral or cardiac arterioles (e.g. excessive doses of drugs that are derivatives of catecholamines).
- Excessive relaxation of peripheral arterioles (e.g. due to a high dose of a drug that acts as a blocker of catecholamine receptors) - can lead to circulatory shock.
- Increased permeability of capillary beds resulting in loss of fluid and insufficient blood volume for effective return of blood to the heart (e.g. bacterial endotoxins associated with some forms of food poisoning (e.g. Escherichia coli) or gut infections (e.g. Salmonella), or with a range of toxic substances (e.g. arsenic, antimony, several types of poisonous plants, high doses of heavy metals, etc.).

3. Drugs and Toxicants that Affect the Heart: Examples of Agents that Influence Excitability

- **Catecholamines**
  Cause formation of cyclic AMP in the heart that acts as a potent second messenger, triggering myocardial contraction in part through release of intracellular Ca++ stores.

- **Cocaine**
  - Mechanism of concern is inhibition of re-uptake of catecholamines.
  - Result is excessively stimulated myocardium, with severe tachyarrhythmias and often death.

- **Verapamil**
  Drug that blocks sodium channels, decreasing intracellular Ca++ concentrations, such that contractile activity decreases.

- **Cardiac glycosides** (e.g. digitalis)
  - Poisonous plant toxin and drug that inhibits Na⁺/K⁺ ATPase, such that intracellular sodium concentrations increase; Na⁺ is exchanged for Ca²⁺ (from outside the cell, as well as from intracellular depots in the sarcoplasmic reticulum and the mitochondria).
  - The excess intracellular free Ca²⁺ increases coupling of actin and myosin, which at low doses can help congestive heart patients, but which at high doses can cause many types of cardiac arrhythmias resulting in CHF or cardiogenic shock.

- **Quinidine**
  An antiarrhythmic drug that inhibits Ca²⁺ uptake by the sarcoplasmic reticulum.

- **Japanese Yew** (*Taxus*) (common ornamental plants; also wild species of yew)
  Alkaloids block electrochemical conduction through the heart.

- **Diethyl Ether and Halogenated Alkanes**
  - Examples include ether and chloroform (both formerly used widely as anesthetics), and fluorocarbons (e.g. trichlorofluoromethane, a constituent of Freons, used in refrigeration and air-conditioning equipment).
  - Effect = greatly exaggerated sensitivity of the heart to catecholamines - results in tachyarrhythmias.
  - Chronic exposure to certain haloalkanes has been associated with cardiomyopathies.

- **Examples of Agents that Cause Cardiomyopathy (degenerative or necrotic lesions in the muscle of the heart).**
  - Alcohol (ethanol) (cardiomegaly = enlarged heart, with lipid droplets in the myocardium), which may be complicated by acetaldehyde (metabolite of ethanol) effects, because acetaldehyde slows the heart at low concentrations and may increase the release of catecholamines at high doses.
  - Overdose with certain catecholamines, e.g. isoproterenol.
  - Ionophore toxicoses.
  - **Cassia** (poisonous plant) toxicoses.
  - Allergic reactions associated with hypersensitive myocarditis.
    - Some penicillin reactions.
    - Some sulfonamide reactions.
    - Methyl-dopa induced cardiomyopathy.
  - **Cobalt (Co)**
    - Acute high dose or chronic low dose exposure can cause cardiomyopathy in laboratory rodents and human beings.
    - Chronic Co toxicosis can cause vacuolation of Purkinje fibers and a slow heart rate.
  - **Lead (Pb)**
    - Exposure *in utero* may pose the greatest risk.
    - Degenerative lesions and increased sensitivity to norepinephrine have been noted in the hearts of children exposed to high doses of lead.
  - Antineoplastic drugs.
    - Doxorubicin.
    - Daunorubicin.
    - These drugs cause production of oxygen free radicals.
    - Lesions in human beings or laboratory animals include enlargement of the heart (dilation), atrophy and degeneration of the cardiac myofibers, edema, and fibrosis.
4. Drugs and Toxicants That Affect the Blood Vessels: Examples

- **Lead**
  Causes changes in elasticity of blood vessels by affecting the vascular ground substance. May cause sclerosis of renal vessels. Has caused hypertension in poisoned birds (pigeons).

- **Cadmium (Cd)**
  Increases synthesis of angiotensinogen, a precursor to angiotensin.

- **Estrogen-containing oral contraceptives**
  Increases synthesis of angiotensinogen, a precursor to angiotensin.

- **Ergot alkaloids**
  - Stimulate catecholamine receptors in peripheral vessels.
  - Result in gangrene and loss of extremities (fingers, toes, hooves, tails).

5. Drugs and Toxicants That Affect the Blood Volume: Examples

- **Diuretics**
  - Stimulate urine flow - Decreased blood volume and may alter electrolyte concentrations.

- **Agents that cause renal failure and severe fluid loss due to the combined effects of the inability to concentrate urine and sometimes vomiting (may be confused with vasoactive agents).**
  - Excessive doses of nonsteroidal anti-inflammatory drugs.
  - Excessive doses of sulfonamides.
  - Gentamicin overdose.

- **Glycyrrhizin**
  Aldosterone-like substance in licorice, ingestion of large doses can cause fluid retention and sustained hypertension.

**References**

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