Lecture-5- **د.رياض الموسوي**

Heart Failure

G- Inotropic Drugs

A. Digitalis

They are a group of chemically similar compounds (cardiac glycosides) that can increase the contractility of the heart muscle and, therefore, are widely used in treating HF; the most widely used agent is **Digoxin.**

Mechanism of action:

1-Regulation of cytosolic calcium concentration:

Free cytosolic calcium concentrations at the end of contraction must be lowered for cardiac muscle to relax. The Na+/Ca2+-exchanger plays an important role in this process by extruding Ca2+ from the myocyte in exchange for Na+ (Figure 16.8). The concentration gradient for both ions is a major determinant of the net movement of ions. By inhibiting the ability of the myocyte to actively pump Na+ from the cell, cardiac glycosides decrease the Na+ concentration gradient and, consequently, the ability of the Na+/Ca 2+-exchanger to move calcium out of the cell. Further, the higher cellular Na+ is exchanged by extracellular Ca2+ by the Na+/Ca2+-exchanger increasing intracellular Ca2+. Because more Ca2+ is retained intracellularly, a small but physiologically important increase occurs in the free Ca2+ that is available at the next contraction cycle of the cardiac muscle. It follows that if the Na+/K+ ATPase is extensively inhibited, the ionic gradient becomes so disturbed that dysrhythmias can occur.

2-Increased contractility of the cardiac muscle: Administration of digitalis glycosides increases the force of cardiac contraction, causing the cardiac output to more closely resemble that of the normal heart. The resulting improved circulation leads to reduced sympathetic activity, which then reduces peripheral resistance. Together, these effects cause a reduction in heart rate. Vagal tone is also enhanced, so the heart rate decreases and myocardial oxygen demand diminishes.

Indications:-

1- Severe left ventricular systolic dysfunction after initiation of ACE inhibitor and diuretic therapy.
2- HF with atrial fibrillation.

Pharmacokinetics: All digitalis glycosides possess the same pharmacologic actions, but they vary in potency and pharmacokinetics. **Digoxin** is very potent, with a narrow margin of safety (low therapeutic index) and long half-life of around 36 hours**. Digoxin** is mainly eliminated by the kidney, requiring dose adjustment based on creatinine clearance. Digoxin has a large volume of distribution, because it accumulates in muscle. A loading dose regimen is employed when acute digitalization is needed. **Digitoxin** has a much longer half-life and is extensively metabolized by the liver before excretion in the feces, and patients with hepatic disease may require decreased doses.

S.E:-

1- Cardiac effects: The common cardiac side effect is arrhythmia, characterized by slowing of atrioventricular conduction associated with atrial arrhythmias. A decrease in intracellular potassium is the primary predisposing factor in these effects.

2- Gastrointestinal effects: Anorexia, nausea, and vomiting are co b. mmonly encountered adverse effects.

3- Central nervous system effects: These include headache, fatigue, confusion, blurred vision, alteration of color perception, and halos on dark objects.

Factors predisposing to digitalis toxicity:

1- Electrolytic disturbances: Hypokalemia can precipitate serious arrhythmia. Reduction of serum potassium levels is most frequently observed in patients receiving thiazide or loop diuretics, and this usually can be prevented by use of a potassium-sparing diuretic or supplementation with potassium chloride. Hypercalcemia and hypomagnesemia also predispose to digitalis toxicity.

2- Drugs: Quinidine, verapamil, and amiodarone, , can cause digoxin intoxication, both by displacing digoxin from tissue protein-binding sites and by competing with digoxin for renal excretion. As a consequence, digoxin plasma levels may

increase by 70 to 100 percent, requiring dosage reduction. Potassium-depleting diuretics, corticosteroids, and a variety of other drugs can also increase digoxin toxicity. Hypothyroidism, hypoxia, renal failure, and myocarditis are also predisposing factors to digoxin toxicity.

Digitalis toxicity can be managed by discontinuing cardiac glycoside therapy, determining serum potassium levels (decreased K+ enhances potential for cardiotoxicity), and if indicated, giving potassium supplements. In general, decreased serum levels of potassium predispose a patient to *digoxin* toxicity. *Digoxin* levels must be closely monitored in the presence of renal insufficiency, and dosage adjustment may be necessary. Severe toxicity resulting in ventricular tachycardia may require administration of antiarrhythmic drugs and the use of antibodies to *digoxin* (digoxin immune Fab), which bind and inactivate the drug.

H- β-Adrenergic agonists

B-Adrenergic stimulation improves cardiac performance by causing positive inotropic effects and vasodilation. Dobutamine is the most commonly used inotropic agent other than digitalis. Dobutamine leads to an increase in intracellular cyclic adenosine monophosphate (cAMP), which results in the activation of protein kinase. Slow calcium channels are one important site of phosphorylation by protein kinase. When phosphorylated, the entry of calcium ion into the myocardial cells increases, thus enhancing contraction. Dobutamine must be given by intravenous infusion and is primarily used in the treatment of acute HF in a hospital setting.

I- Phosphodiesterase inhibitors

Amrinone and milrinone are phosphodiesterase inhibitors that increase the intracellular concentration of cAMP. This results in an increase of intracellular calcium and, therefore, cardiac contractility, as discussed above for the β-adrenergic agonists. Long-term amrinone or milrinone therapy may be associated with a substantial increase in the risk of mortality. However, short-term use of intravenous milrinone is not associated with increased mortality, and some symptomatic benefit may be obtained when it is used in patients with refractory HF.