

CHAPTER 22

PHARMACOLOGIC BLOCKADE OF RAS

- Effects of ACE-I and ARBs
- Rationale of RAS Blockade in CAD
 - Antiatherogenic activity
 - Antiischemic effects
 - ASO plaque stabilization
 - Antothrombotic action
 - Antiarrhythmic activity
 - Antiremodeling effects

Pharmacologic agents which inhibit the renin angiotensin system (RAS) namely converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARBs) are gaining increasing importance in the management of patients with coronary artery disease. The main role of this pharmacologic group is cardiovascular protection and prevention of future cardiovascular events (strokes, heart failure, myocardial infarction, cardiovascular and total mortality) particularly in high risk patients. They produce their beneficial effect by a number of actions addressing the different components of the cascade of events that lead to the development of acute coronary syndromes. They have antiatherosclerotic, antiischemic and antithrombotic and plaque stabilizing effects.

There are two current approaches of clinical value for interfering with RAS. (1) angiotensin- converting-enzyme inhibition (ACE -I). (2) angiotensin- receptor - blockade (ARB).

1. ACE -Inhibitors

- ACE inhibitors produce their pharmacologic action by limiting the production of All. Also through inhibition of Kininase II (the same enzyme as ACE), an enzyme responsible for the breakdown of bradykinin, they interfere with bradykinin degradation and increase bradykinin level in tissue.
- A potential limitation of ACE-I is the production of All through other enzymatic pathways such as chymase, tonin and cathepsin, either directly from angiotensinogen or from AI. This might attenuate the effectiveness of ACE -inhibition.
- ACE-I have the advantage of increased bradykinin. The beneficial effects of bradykinin include vasodilatation, inhibition of platelet aggregation, increased prostacyclin and NO production.
- Furthermore, a potential limitation of ACE-I is the loss of the negative feedback produced by All on renin production, since All inhibits renin secretion. An increased renin may stimulate excess AI production which might overcome the ACE-I activity.

2. Angiotensin Receptor Blockers

- ARBs are specific for type I All (AT₁) receptor, while type 2 (AT₂) receptor remains active and stimulated by All. AT₂ receptors mediate a cardioprotective role: vasodilation, inhibition of cell growth, apoptosis, stimulate bradykinin and NO production.
- ARBs have the theoretical advantage over ACE -I through achieving a more effective blockade of RAS. They block receptors responsible for most of the harmful effects of All i.e. vasoconstriction, cellular hypertrophy and proliferation.

EFFECTS OF ACE-I AND ARBs

1. *Vasodilation*. arterial and to a less extent venodilation through:
 - Direct effect (interfering with All vasoconstriction).
 - Attenuation of sympathetic activity.

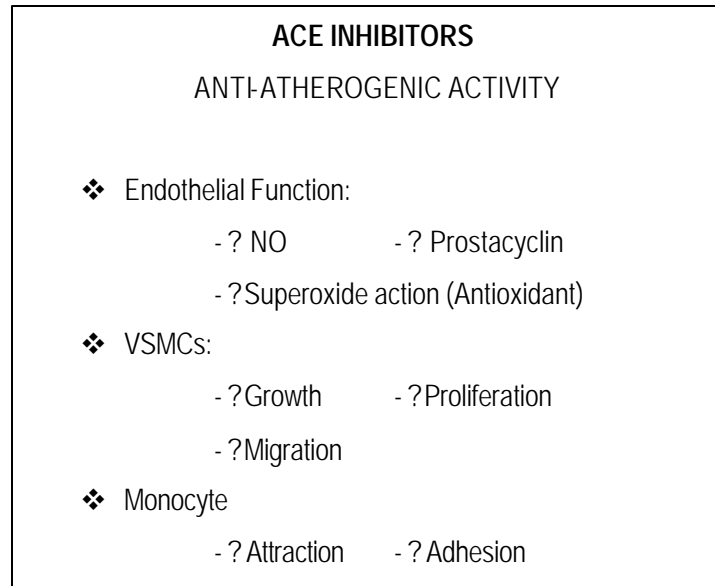
- Improved endothelial function and stimulation of NO and prostacyclin release (both are vasodilators).
- 2. *Bradycardia* through diminished sympathetic activity and increased vagal tone.
In spite of vasodilation and fall in blood pressure, heart rate is not increased by RAS blockade.
- 3. *Sodium excretion and potassium retention* secondary to reduction in aldosterone production.
- 4. *Increased free water loss* by blocking All mediated vasopressin (ADH) release. This action helps to correct dilutional hyponatremia in patients with heart failure.
- 5. *Other actions* not related to blood pressure, blood volume or electrolyte effects:
 - a. Antioxidants: decreased production of superoxide anion.
 - b. Decreased cardiac and VSM cells hypertrophy.
 - c. Decreased cellular hyperplasia.
 - d. Anti-inflammatory actions which contribute to the antiatherosclerotic potential of ACE-I and ARBs.
 - e. Antiplatelet and fibrinolytic actions- decreased PAIs and increased TPA activity.
 - f. ACE-I are liable to produce cough and rarely angioedema secondary to accumulation of bradykinin.

RATIONALE OF RAS BLOCKADE IN CAD

- Antiatherogenic activity.
- Antiischemic effects.
- ASO plaque stabilization.
- Antithrombotic action.
- Antiarrhythmic activity.
- Antiremodeling effects.

Anti-atherogenic Activity

- Studies in experimental animals showed that RAS blockade can decrease the cholesterol content and the size of atherosclerotic plaques.
- By acting on endothelial cells, VSMCs and monocytes; three important players in the atherosclerotic process, RAS blockade will have anti atherogenic activity.
 1. Improvement in endothelial function: ACE-I increase NO and prostacyclin production from endothelial cells and decrease superoxide generation.
 2. Inhibition of VSMCs growth, proliferation and migration, which are important steps in formation of atherosclerotic plaques.
 3. Inhibition of monocytes attraction and adhesion to vessel wall.



Anti-ischemic Effects

- ACE-Is were shown to attenuate the subjective and objective evidence of myocardial ischemia during treadmill testing. They decrease the nitroglycerin requirements and improve exercise tolerance.
- The possible mechanisms of the anti ischemic activity of RAS blockade are:
 1. Hemodynamic:
 - Decrease myocardial oxygen demand through a negative inotropic effect and through a decrease in cardiac loading conditions. Decrease in after-load secondary to arterial vasodilation and reduction in preload due to venodilatation.
 - Increase in myocardial oxygen supply secondary to coronary vasodilatation.
 2. Structural effects:
 - Cardiac: regression of cardiac hypertrophy and LV dilatation will decrease myocardial oxygen requirements.
 - Vascular: improvement in endothelial function will improve the coronary circulation.
 3. Neurohormonal modulation:
 - Reduction in sympathetic stimulation after ACE-I will relieve coronary arteries vasoconstriction, decrease oxygen requirements and improve coronary perfusion.

Atherosclerotic Plaque Stabilization

ACE-I therapy can produce atherosclerotic plaque stabilization through the following mechanisms:

1. Change plaque structure:
 - Attenuation of the inflammatory process and decrease in inflammatory cells.

- Reduction in plaque thrombogenicity (decrease in PAH and tissue factor).
2. Improvement in endothelial function:
 - ACE-I improve the flow-mediated dilatation of coronary arteries.
 - Decrease oxidative stress.
 - Increase NO synthase (enzyme responsible for NO generation from amino acid arginine) expression.
 3. Systemic anti-inflammatory effects:
 - Reduction in inflammatory markers – IL6, MCP-1, CRP.
 4. Reduction in wall stress:
 - Through blood pressure reduction.

Anti-thrombotic Action

ACE-I have both a systemic and a local anti-thrombotic activity through:

1. Decrease in PAI-1 activity.
2. Reduction in plasma fibrinogen.
3. Decreased platelet activation and aggregation.
4. Reduction in tissue factor generation.

Anti arrhythmic Activity

- All has proarrhythmic potentials particularly during ACS through the following mechanisms:
 1. Direct coronary vasoconstriction and decreased coronary blood flow.
 2. Increased cardiac filling and wall stress.
 3. Enhances sympathetic tone and effects of circulating catecholamines.
 4. Stimulate aldosterone production, promoting potassium excretion leading to hypokalemia.
 5. Direct electrophysiologic effects on cardiac myocytes.
- There is experimental and clinical evidence of an anti arrhythmic effect of ACE inhibitors.
- ACE-I reduce ventricular repolarization inhomogeneity (QT dispersion) after MI.
- ACE-I decrease the incidence of atrial fibrillation in patients with impaired LV function secondary to AMI.
- ACE-I reduce sudden cardiac death and all cause mortality.
- Incidence of ventricular fibrillation tends to be lower in patients treated with ACE-I after MI.

Anti remodeling Effects

- RAS blockade can slow, attenuate and stop the LV remodeling process.
- Ventricular remodeling following myocardial damage is initially a compensatory process to maintain cardiac pumping function. It is triggered by neurohormonal activation.

- Inappropriate and excessive neurohormonal activation with change in cardiac myocyte genetic program lead to the deleterious effects of remodeling which progress in a vicious circle ending in cardiac death.
- Remodeling involves:
 - (1) Loss of cardiac myocytes through both necrosis (inflammatory death) and apoptosis (programmed cell death).
 - (2) Excess collagen tissue formation and excessive cardiac fibrous tissue are both reparative to replace the lost myocytes and reactive in the interstitial perivascular spaces.
 - (3) Change in type of myosin protein to a more fetal form secondary to regression in the myocyte genetic program, the fetal type consumes less energy but contracts with less strength.
 - (4) Ventricular dilatation and thinning secondary to myocyte loss and excess collagen tissue and myocardial scarring.
 - (5) Myocardial hypertrophy
- Many of the previous remodeling processes are initiated and maintained by excessive RAS activation.
- ACE inhibitors have both acute and chronic benefits, limiting the changes that can occur during acute ischemia namely myocardial injury and impairment of endothelium –dependent vasodilatation.
- RAS blockade proved effective in attenuating the remodeling process, it decreased LV dilatation and prolonged survival.
- Tissue specific ACE inhibitors (e.g. ramipril, perindopril, and tandolapril) may have more anti-remodeling benefit over non tissue-specific ones.