Total Renin-Angiotensin – Aldosterone System (RAAS) Blockade

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A B S T R A C T

Enhanced activity of the RAAS is observed in chronic HTN and CHF, especially in the background of Na restriction and diuretic use. Blocking this neuro-humoral pathway at various levels viz: a) in the formation of AII from AI by ACE inhibition, b) the receptors of AII blockade, c) the aldosterone receptors blockade, and d) renin inhibition would be the most rational and scientific way of managing the patients of HTN and/or CHF apart from the already well established beta blockade. Large number of trials and observational data involving drugs that inhibit RAAS have demonstrated improved survival and better quality of life in these patients. This article aims at giving a comprehensive review of the current status of RAAS blockade in the treatment of HTN and CHF. It is concluded that RAAS inhibition is beneficial in these patients especially the high-risk category and those with diabetes.

INTRODUCTION OF RAAS

Even after 100 years of the discovery of renin, our knowledge of RAAS continues to expand. Renin, a protease enzyme, stored and secreted from the renal juxta-glomerular cells located in the wall of the afferent arteriole which is contiguous with the macula densa portion of the same nephron, converts the Angiotensinogen, an alpha 2 globulin of hepatic origin, to Angiotensin I (AI), a deca-peptide. This inactive substance AI is then converted to Angiotensin II (AII), an octopeptide by an enzyme called angiotensin converting enzyme (ACE) (Fig.1).[1] The AII is a very active, powerful vasoconstrictor with many other effects on various organs including adrenal cortex, brain, intestine and heart. The ACE itself is a protease with two zinc groups present in plasma (circulating ACE) but mainly bound to tissues (tissue ACE). This converting enzyme not only converts AI to AII but also inactivates bradykinin, hence the name kininase. Moreover, not all AII is generated as a result of the activity of ACE, non-ACE pathways involving chymase-like serine proteases can also form AII and do the same job. AII exerts all its effects though its receptors, which are mainly of two types viz., AII type 1 (AT1) and AII type 2 (AT2) receptors. Both the receptors respond to AII. From the physiological point of view, it is the AT1 receptors that mediate all the principal responses to AII. AT1 receptors are further divided into AT1a (more important) and AT1b subtypes. The principal effects of AII are vasoconstriction, myocyte hypertrophy, stimulation of contraction and antinatriuresis, regarded as adverse on the diseased heart and failing circulation. Most of these are mediated though the activation AII type 1 receptor (AT1). The activation of AII type 2 receptor (AT2) which is expressed in low concentrations in kidney, heart and mesenteric blood vessels, possibly stimulates vasodilatation via bradykinin and nitric oxide (NO) and perhaps has other effects that oppose those of activation of AT1 receptor.

Aldosterone release either in response to AII though the stimulating effects of the latter on adrenal cortex, has major effects on electrolyte balance. It retains sodium (Na) and helps to excrete potassium (K) by inhibition of Na – K exchange in the distal renal tubule. Water is retained along with Na. Aldosterone,

Table 1: Angiotensin II Mediated Injury[2]

General Effects

Causes vasoconstriction.

Expands plasma volume (increases aldosterone and antidiuretic hormone).

Increases tissue collagen deposition and fibrosis.

Atherosclerosis

Up-regulates production of vascular cell adhesion molecule proteins.

Causes chemotaxis of leukocytes.

Increases platelet adhesiveness.

Increases plasminogen activator inhibitor type 1.

Renal Effects

Promotes sodium retention.

Shifts pressure natriuresis toward higher blood pressure.

Increase renal transformin growth factor β.

Cardiac effects

Within the cardiac wall promotes left ventricular hypertrophy and congestive heart failure through cardiac and vascular myocyte hypertrophy, fibroblast proliferation, and endothelial cell apoptosis.
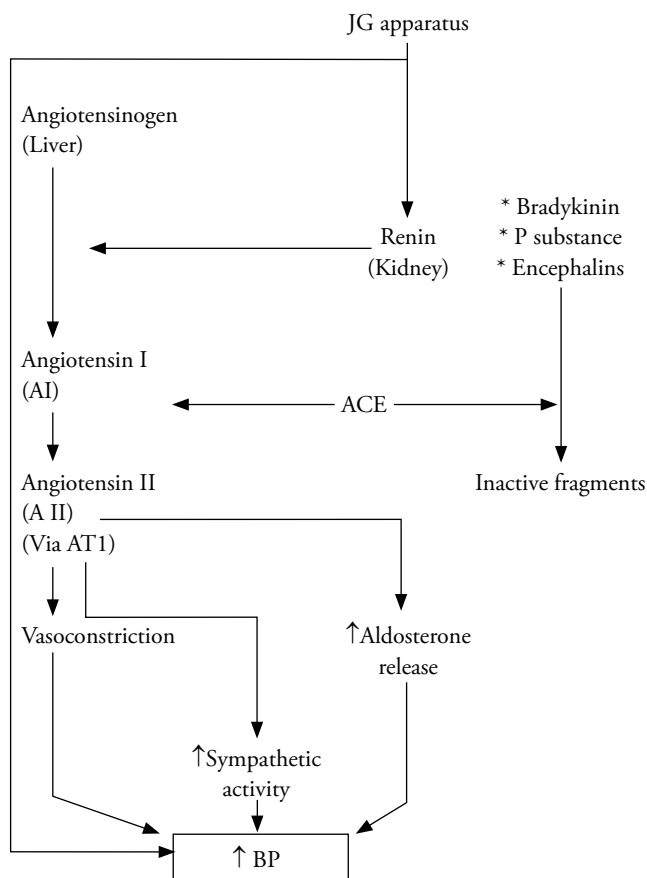
Fig. 1: Schematic diagram of RAAS

Table 2 : Actions of bradykinin[3]

Organ	Cellular effect	Consequences
Gut	Ca^{++} mobilization	Slow contraction (brady: slow; kinin: movement)
Vascular endothelium	Formation of NO, prostacyclin	Vasodilatation; antiplatelet aggregation endothelial protection.
Respiratory tract	Formation of prostaglandins	Cough, angioedema
Terminal neurons	Release of norepinephrine	Arrhythmias

some of it locally produced may adversely alter the structure of myocardium by promoting cardiac fibrosis. Aldosterone also promotes endothelial dysfunction. In heart failure (HF) for instance, plasma aldosterone rises upto 20 times in response to increased AII. Aldosterone is thus the final link in the overactive RAAS with increased AII levels which in turn has injurious effects on various tissues (Table l).[2] Increased aldosterone levels consequent to increased AII activity have injurious effects on vessels, heart and electrolytes.

Since there is production of AII via alternate, non-classical pathways also (through non-renin effects on angiotensinogen or non-ACE effects on AI), the ACE inhibition in long-term cannot be expected to bring down the AII levels or consequently

aldosterone levels which will continue to exert their widespread harmful effects.[1]

Lastly, kallikrein-kinin system and bradykinin is a parallel pathway since ACE is also responsible for the degradation and inactivation of bradykinin. Both AI to AII conversion and inactivation of bradykinin formed from its precursor kininogen are mainly facilitated by ACE (kininase). ACE inhibition can therefore be expected to prevent the formation of AII and degradation of bradykinin as a result of which bradykinin levels rise and AII levels are reduced. Bradykinin has some beneficial effects on endothelium and increases the production of nitric oxide (NO) resulting in vasodilatation (Table 2).[3]

TOTAL RAAS BLOCKADE

Uncontrolled overactivity of RAAS resulting in increased levels of AII is found in all forms of hypertension (HTN) and heart failure (HF). Hence blocking the RAAS in different steps in its pathway could be the most rational way of managing HTN and/ or HF. These could at various levels as follows:

1. Renin inhibition
2. ACE inhibition
3. AII receptor blockade
4. Aldosterone blockade

One more blockade i.e. at the level of release of renin from JG apparatus in the kidney viz., adrenergic blockade (beta-blockers) is well known and is actually a step in the prevention of RAAS overactivity.

Renin inhibition

Inhibition of the action of renin to cleave the decapeptide AI from angiotensinogen include some that must be given intravenously such as Enalkiren and orally effective agents including Remikiren and Zankiren. They not only inhibit the production of AI and AII but also prevent the reactive rise in renin release following the use of ACEIs and ARBs. They are not in clinical use as yet and whether in future they will be of clinical benefit remains speculatory.

ACE inhibition

The first ACE inhibitor Captopril was described in 1977 and since then ACE inhibitors (ACEIs) have become the cornerstone of the treatment of heart failure, hypertension and in cardiovascular protection. ACEIs act on the crucial enzyme that generates AII. Many carefully designed trials have shown that ACEIs give both primary and secondary protection from cardiovascular disease thereby interrupting the vicious circle from risk factors to LVF as many sites (Fig. 2)[3].

There are three classes of ACEIs:

a. Class I active drug: Captopril type, Suphydryl-containing zinc ligand

b. Class II pro-drugs: Enalapril and like ones mostly lipid soluble, carboxyl-containing zinc ligand. They require to be converted into active drug for their action. Fosinopril contains phorphyl zinc ligand.

c. Class III water soluble: Lisinopril, active drug

The list of currently used ACEIs is given in the Table 3.

ACE INHIBITORS
Dzau-Braunwald model

$\ominus$ = ACE inhibitor effect
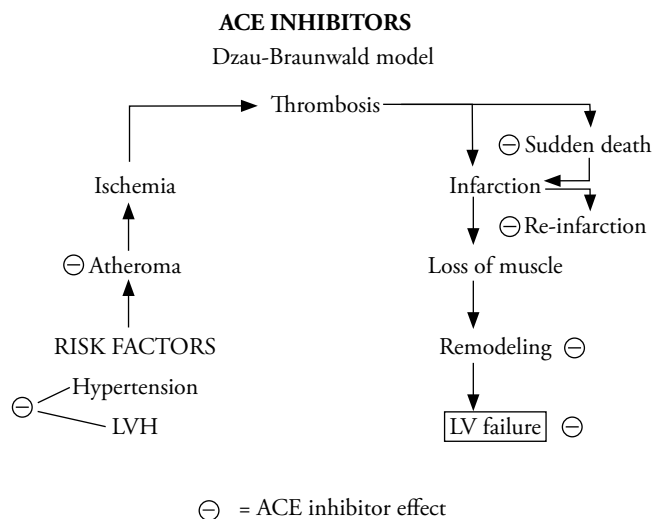
Fig. 2 : Dual role of ACEIs both preventing and treating cardiovascular disease

Table 3 : Currently used ACEIs and their doses[4]

| Drugs	Duration of action (h)	Recommended daily dose (mg)
Benazepril	16-24	5-40
Captopril	6-12	25-150
Enalapril	18-24	5-40
Fosinopril	24	10-4
Lisnopril	24	5-40
Moexipril	12-24	7.5-15
Perindopril	24	4-16
Quimapril	18-24	5-80
Ramipril	18-24	1.25-20
Trandelopril	24	1-4

Mechanism of action of ACEIs

Although the blockade of ACE within the pulmonary circulation to eliminate AII is primary antihypertensive effect of ACEIs, it is observed that though there is an initial fall in plasma AII when an ACEI is given to hypertensive patients, this effect lasts only for several weeks. By 6 months the plasma AII level returns to normal while the BP remains controlled. This is due to the combined effect of transient reduction of AII and the accumulation of bradykinin, a potent vasodilator. AII production occurring through nonclassical pathways (non-renin and non-ACE) is not blocked by ACEIs.

Various trials[5-7] to date have shown that the ACEIs control HTN, reverse left ventricular hypertrophy (LVH), prevent stroke, and reduce coronary artery disease to a degree similar to diuretics and Beta blockers. Besides, ACEIs have been shown to reduce morbidity and mortality from congestive HF (CHF) especially after acute MI. Progression to chronic renal failure due to HTN, diabetes (DM) and primary glomerulonephritis is slowed down by ACEIs independent of their antihypertensive effects[8] (HOPE). ACEIs also have been shown to improve endothelial function. The major trials showing the beneficial role of ACEIs in HTN are HOPE[8] and ANBP2[9] and AASK Trials.[10] In the presence of
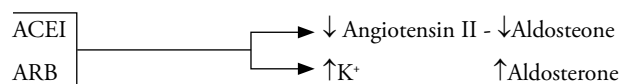
Fig. 3: Mechanism of 'aldosterone escape' with ACEI or ARB therapy
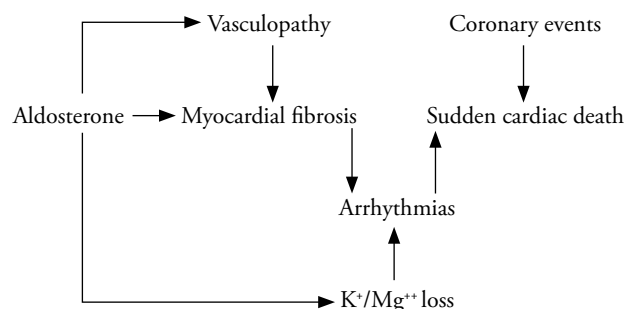
Fig. 4: Mechanism of various deleterious effects of aldosterone

both DM & HTN, ACEIs are the preferred initial drugs to treat HTN.[11]

Side effects and Contraindications of ACEIs

One of the most troublesome and fairly common side effects of ACEIs is cough, the incidence is anywhere from 5.5 to l5% in the various studies, the least being in HOPE study.[8] A low dose combination of ACEI and a calcium-channel antagonist like Nifedipine is said to lessen the problem of cough. Hypotension, hyperkalemia and renal side effects with reversible renal failure can all occur with ACEIs but are not common. Bilateral renal artery stenosis, pregnancy and already existing hyperkalemia are real contraindications to ACEIs.

### Angiotensin II receptor blockade

Angiotensin II receptor blockers (ARBs) of which the prototype is Losartan, specifically block the Angiotensin II of the receptor subtype AT1. The other subtype AT2 receptor is not blocked and can still respond to increased concentration of AII. Unopposed AT2 receptor activity through some unknown mechanisms leads to the formation of protective bradykinin and vasodilatation which could be cardioprotective. Presently all the available ARBs are useful in the treatment of HTN.[4] ARBs reduce hypertensive blood pressures by blocking AII's effects:

i. To increase the peripheral vascular resistance.

ii. To increase aldosterone and ADH secretion expanding the plasma volume.

iii. To increase tone in the sympathetic nervous system.

In addition to reducing systemic HTN, ARBs directly block the effect of AII at the tissue level throughout the body. All the currently available ARBs are efficacious in the treatment of HTN as monotherapy as well as combination with a diuretic. They differ in their duration of action and receptor-binding characteristics. Losartan is a relatively short-acting drug and is best given in twice-daily schedule. Other ARBs are long-acting and can be given once daily. It is speculated that ARBs and ACEIs produce additive antihypertensive effects but this aspect remains to be studied carefully to document such synergism. However, the additive therapy may be beneficial in some cases of refractive CHF but not in HTN.

Table 4 : Currently used ARBs[4]

Drug	Daily dose range (mg)
Candesartan	8-32
Eposartan	400-800
Irbesartan	150-300
Losartan	50-100
Telmisartan	40-80
Valsaratan	80-320
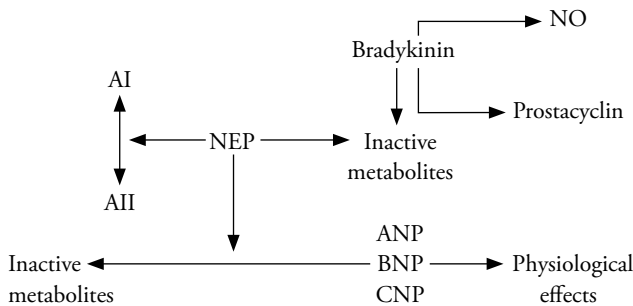
Fig. 5 : Concept of vasopeptidase inhibition (ANP: Atrial natriuretic peptide, BNP: brain NP, CNP: C-type NP)

ARBs have renoprotective and antiproteinuric effects similar to ACEIs although long-term studies are lacking. ARBs also cause regression of LVH like ACEIs and are less hyperkalemic. Effectiveness of ARBs in CHF and after MI has been well documented. In the ELITE study ARBs were better tolerated than ACEIs but latter provided a superior overall benefit.[12]

Side-effect profile of ARBs is excellent. Pregnancy and bilateral renal artery stenosis remain strong contraindications for ARBs as with ACEIs.

Aldosterone-Blockade

ACEI therapy only partially suppresses aldosterone production and 'aldosterone escape' occurs in upto 40% of patients with CHF. The plasma aldosterone levels can be 20-fold higher in untreated patients with chronic CHF compared to normal controls. It was presumed that with ACEI therapy alone or in combination with ARB, these rising aldosterone levels can be controlled, but this actually does not happen and in many cases the aldosterone levels return back to baseline by 43 weeks even with maximum dose of both agents (RESOLVD trial).[13] AII is a potent stimulant for aldosterone production and increased levels of K^+ as seen after chronic ACEI therapy, also is a powerful secretagogue for aldosterone. This means that it is impossible to get rid of aldosterone by blocking ACE or AII (Fig. 3).[14] Moreover aldosterone escape might even promote release of AII via a positive feedback loop that stimulates ACE in the vasculature.

Effects of Aldosterone: Traditionally in CHF, elevation of aldosterone levels lead to excessive Na-retention and expansion of ECF and K^+ loss. By contributing to electrolyte imbalances especially K^+ and Mg^{++} loss, aldosterone increases the propensity of the myocardium for lethal arrhythmias and sudden cardiac death.

Newly discovered effects of aldosterone include endothelial dysfunction (vasculopathy), myocardial fibrosis and cardiac remodeling and decreased baroreceptor sensitivity (Fig. 4). Aldosterone may induce endothelial dysfunction and may promote atherosclerotic events through reduction of NO bioavailability. Various animal studies support this.[14]

The first proof that aldosterone promotes myocardial fibrosis in man came when it was shown that spironolactone reduced plasma PIII NP (procollagen type III aminoterminal peptide) levels in CHF as seen in RALES trial.[15] This is an indirect marker of myocardial collagen turnover in man.

Aldosterone has been shown to inhibit baroreflex sensitivity in healthy human volunteers.

Clinical evidence of Aldosterone Blockade

Aldosterone blockade has been shown to be very effective in reducing the morbidity and mortality in CHF patients who were already receiving all the conventional drugs including digoxin, diuretics and ACEIs in both the major trials RALES[15] and EPHESUS.[16] Aldosterone-blockade by eplerenone (a selective aldosterone blocker) has a role in the treatment of essential HTN; it has a mild diuretic effect in addition. Thus it has been shown to have antihypertensive effect in low-renin, elderly hypertension and high renin HTN patients. Eplerenone also appears to protect target organs viz., it reduces LVH and micro-albuminuria in diabetics. Thus eplerenone is a useful add-on antihypertensive therapy and well documented therapy in chronic CHF patients (EPHESUS).[16]

Miscellaneous drugs in RAAS blockade:

Vasopeptidase inhibitors: These drugs inhibit ACE and the neutral endopeptidase (NEP) which normally degrades numerous endogenous natriuretic peptides. Thereby the effects of ACEI viz., decrease in AII and increase in bradykinin – are combined with increases in natriuretic peptides (Fig. 5).[18] The most widely studied of these agents is Omapatrilat.[17,18] The others in the investigative stage are Fasidotril, Sampatrilat and Ecadotril.

CONCLUSION

The concept of total RAAS blockade is a firm and rational step forward in the treatment of HTN and CHF. Definite benefits both in terms of morbidity and mortality have been shown in various mega, randomized clinical trials involving the drugs that block ACE or AII receptor or aldosterone levels. Renin inhibitors and vasopeptidase inhibitors are yet to receive the recognition in the drug armamentarium of antihypertensive therapy or CHF treatment. The RAAS blockade has a special place in the management of both HTN and CHF in the diabetics in whom the thiazides and beta-blockers are not the preferred agents.

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