COMPLETE RAAS BLOCKADE AND ITS CLINICAL SIGNIFICANCE

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Renin Angiotensin Aldosterone System (RAAS) is an important contributor to the maintenance of blood pressure. This is again important as undue activation of this system is a major factor in determining mortality and morbidity associated with cardiovascular diseases.

The beginning of this system is with renin. It is an enzyme, chemical nature is aspartyl protease. It is produced by the juxtaglomerular apparatus consisting of -

i) Juxtaglomerular cells, ii) Macula densa & iii) Lacis cells.1

The primary stimuli for renin secretion are:

a. Decreased NaCl transport to the loop of Henle (macula densa mechanism).

b. Decreased stretch on the renal afferent arteriole (baroreceptor mechanism).

c. Sympathetic nervous system stimulation of renin secreting cells via β1 adrenoceptors.

Conditions that increase renin secretion are:1

- Na⁺ depletion
- Diuretics
- Hypotension
- Hemorrhage
- Upright posture
- Dehydration
- Cardiac failure
- Cirrhosis
- Constriction of renal arteries and aorta.

Renin secretion is inhibited by the opposite mechanisms, namely, increased delivery of NaCl to the loop of Henle, increased stretch on the renal afferent arteriole and β1 adrenoceptor blockade.

The renin substrate is angiotensinogen. It is a α2 globulin fraction synthesized in the liver. Renin converts this angiotensinogen into a decapeptide, angiotensin I.

Renin is measured by incubating the sample to be assayed and the amount of angiotensin I generated is measured. This is the plasma renin activity (PRA) of the sample.

Deficiency of angiotensinogen as well as renin may cause low PRA values. To avoid these, exogenous angiotensinogen is often added, so that plasma renin concentration (PRC) rather than PRA is measured. The normal PRA in supine subject eating a normal Na⁺ load is approximately 1ng of angiotensin I generated per ml per hour.1

Angiotensin Converting Enzyme (ACE) converts angiotensin I to the active octapeptide, angiotensin 

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II. Most of the converting enzyme in the circulation is located in the endothelial cells, primarily but not exclusively, in the pulmonary circulation. The ACE inactivates bradykinin. So, when ACE is inhibited, increased tissue bradykinin is produced, that produces cough.

The angiotensin II is a i) potent pressor substance, ii) primary trophic factor for the secretion of aldosterone by the zona glomerulosa of adrenal cortex and iii) potent stimulus for vascular smooth muscle and myocyte growth.

Aldosterone is a potent mineralocorticoid that increases the Na+ reabsorption by the epithelial Na channels (ENaC) from the renal cortical collecting ducts. Electrical neutrality is maintained by exchanging Na+ for K+ and H+ ions. So, increased aldosterone secretion may result in hypokalemia and alkalosis.

There are at least two classes of angiotensin II receptors:

1. AT1 receptors: this is a G protein coupled receptor (GPCR) having 7 transmembrane domains. Upon stimulation by angiotensin II, it increases cytosolic free Ca^{2+} level and it increases the production of caveolin 1. In humans the AT1 receptor gene is located on chromosome 3.\(^1\)
2. AT2 receptors: encoded by a gene on X chromosome.\(^1\) They are GPCR too. Upon activation it increases the production of NO and increases the intracellular cGMP.

The functions of AT1 and AT2 receptors can be summarized as given in Table 1:\(^2\)

<table>
<thead>
<tr>
<th>AT1 Receptor</th>
<th>AT2 Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasconstriction</td>
<td>Vasodilatation</td>
</tr>
<tr>
<td>Cell growth</td>
<td>Growth inhibition</td>
</tr>
<tr>
<td>Anti-apoptotic</td>
<td>Pro-apoptotic</td>
</tr>
<tr>
<td>Pro-fibrotic</td>
<td>Anti-fibrotic</td>
</tr>
<tr>
<td>Pro-thrombosis</td>
<td>Anti-thrombosis</td>
</tr>
<tr>
<td>Anti natriuresis</td>
<td>Natriuresis</td>
</tr>
<tr>
<td>Production of superoxide</td>
<td>Production of NO</td>
</tr>
</tbody>
</table>

The HARMFUL/HELPFUL table:

- HARMFUL
- HELPFUL

RAAS blockade is an invaluable component of therapeutic armamentarium in different disease conditions. Hypertension, congestive heart failure, renal diseases in both diabetic and non-diabetic is the important ones.

To understand the effects of RAAS blockade, we need to understand circulating RAAS vs. tissue RAAS first.

There exists a tissue based RAAS at various locations like blood vessels, heart and kidney. Activation of tissue RAAS accounts for the long term effects of angiotensin II. These include mainly vascular remodeling, glomerular hypertrophy, left ventricular hypertrophy and angiogenesis.

Chronic RAAS stimulation leads to tissue level growth and fibrosis due to the mitogenic effects of angiotensin II mediated by cytokines like TGF β1 (transforming growth factor β1), FGF (fibroblast growth factor) and PDGF (platelet derived growth factor) which promote extracellular matrix accumulation.

The circulatory RAAS or the acute circulatory response to RAAS activation leads to elevation in blood pressure by peripheral vasoconstriction.\(^3\)

RAAS blockade involves inhibiting the angiotensin converting enzyme (ACEI) and/or adding an angiotensin receptor blocker (ARB). Complete RAAS blockade may also incorporate a direct renin inhibitor (DRI).

Now what can be our chosen medication?

ACEI/ARB or ACEI + ARB or ACEI +ARB +DRI.

Rationale for combination ACEI and ARB therapy:\(^4\)
- More “complete” RAAS blockade.
- Increases protective properties of bradykinin.
- Averts negative consequences of “Angiotensin II escape”.
- Enhances vascular/metabolic pleotropic effects.
- Potential for additive clinical benefits.

Different trials have been conducted using either ACEI or ARB, or a combination of both drugs in different disease conditions to compare their efficacy. We can take a few examples from these trials. Interesting observations are:

1. No apparent advantage with ACEI over diuretics in old patients with hypertension (STOP).\(^5\)
2. No benefit of lisinopril over diuretics as for prevention of MI (ALLHAT).\(^6\)
3. Significant reduction of stroke risk in hypertensive patients with LVH with losartan (LIFE).\(^7\)
4. Losartan showed renoprotection in type2DM but no effects on total mortality (RENAAL).\(^8\)
5. Eplerenone showed significant risk reduction in mortality in post AMI heart failure patients (EPHESUS). 9

6. Therapeutic equivalence of ACEI and ARB for vascular events (ORTARGET) (Fig. 1). 10

7. ARB (telmisartan) no better than placebo for vascular events (TRANSCEND). 11

8. ARB (telmisartan) no better than placebo for recurrent strokes (PROFESS). 12

9. ARB (irbesartan) no better than placebo in CHF patients with preserved systolic function (i-PRESERVE). 13

Valsartan in Acute Myocardial Infarction Trial (VALIANT) (Fig. 2) 14 compared valsartan, captopril, and combination on mortality and CV (cardiovascular) death, among 14,808 patients with MI (myocardial infarction) complicated by LV (left ventricular) systolic dysfunction, HF (heart failure), or both during median follow-up of 24.7 months (Table 2).

Mortality from any cause and the combined outcome were similar comparing the 3 treatment groups.

The rate of the secondary combined CV endpoint of death from CV causes, recurrent MI, or hospitalization for HF was also similar in the 3 groups.

Thus, valsartan was as effective as captopril alone and in combination in reducing the rates of death and other adverse CV outcomes among patients at high risk for CV events after MI.

The ONTARGET investigators concluded that telmisartan was equivalent to ramipril in patients with vascular disease or high risk diabetes. The combination of the two drugs was associated with more adverse events without an increase in benefit. 10

We can observe that, rather than enhancing efficacy, combining an ACEI and ARB, in effect increases the cumulative adverse effects. The following table shows that.

A recent metaanalysis of 147 randomised controlled trials 16 showed all the classes of anti hypertensive drugs have an almost similar effect in reducing MI and stroke for a given reduction of blood pressure. Does it mean that RAAS blockade does not have much pathophysiological advantage over other drugs despite experimental evidence or currently available drugs are insufficient?

So, what will happen if we add renin inhibitors to ACEI and/or ARB?

Direct renin inhibitor (Aliskiren) targets the point of activation of RAAS i.e; it inhibits the formation of angiotensin I from angiotensinogen.

Studies 17 are available on Watanabe heritable hyperlipidaemic rabbits where they are treated with aliskiren or aliskiren and valsartan. It was shown that treatment with a direct renin inhibitor has protective effects on endothelial function and atherosclerotic changes. Furthermore cotreatment with a direct renin inhibitor and an AT II receptor blockier has additive protective effects on both. Aliskiren offers dose-dependent reductions in systolic as well as diastolic blood pressure in human studies too. 18,19 Clinical trials have compared Aliskiren with combination of Aliskiren and Valsartan and

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**Table 2 : Meta-analysis: Adverse Effects of ACE-I + ARB Rx in Symptomatic LVD**

<table>
<thead>
<tr>
<th></th>
<th>Discontinued Rx for AE</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic HF: Rx 15%; Control 11%; AMI with LVD: Rx 9.0%; Control 7.8%</td>
<td>RR 1.38 (1.22-1.55)</td>
<td>RR 1.17 (1.03-1.34)</td>
</tr>
<tr>
<td>Worsening renal function</td>
<td>RR 2.17 (1.59-2.97)</td>
<td>RR 1.61 (1.31-1.98)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>RR 4.87 (2.39-9.94)</td>
<td>RR 1.50 (1.09-2.07)</td>
</tr>
<tr>
<td>Symptomatic hypotension</td>
<td>RR 1.50 (1.09-2.07)</td>
<td>RR 1.48 (1.33-3.18)</td>
</tr>
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Complete RAAS Blockade and its Clinical Significance

have shown significantly greater reduction of blood pressure than monotherapy with either drug.\textsuperscript{20}

In 2009, the USFDA has approved the combination of Aliskiren and Valsartan at dosage of 150/160 mg and 300/320 mg for the treatment of hypertension in patients not controlled with either drug alone (Fig. 3).\textsuperscript{21}

CONCLUSION

Inappropriate activation of RAAS is a central component in the development of hypertension, cardiovascular and renal pathology in both diabetic and non-diabetic subjects. Landmark studies confirm RAAS inhibition as cornerstone of modern CV therapy as well as prevention. In general ARBs appear as effective as ACE-Is in these settings. ACE-I plus ARB might add to blood pressure reduction and heart failure benefits but surely with more adverse effects.

Targeting the renin system at its point of activation by Direct Renin Inhibitors (DRI) provide inhibition of the entire renin system. Early studies indicate DRIs are very effective in reducing blood pressure.

Overall choice of drugs stratégie depends on knowledge of the specific patients as well as population studied in clinical trials. More trials in the future can pave the way for the gold standard of therapy. We will continue to observe how renin inhibition has a place in the novel pharmacologic approach of RAAS inhibition and prevention of target organ damage.

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