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Hypertension in Post-COVID Syndrome

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Background :

The COVID-19 pandemic had started as a cluster of viral pneumonia cases caused by novel Coronavirus n-SARS-CoV-2 in December 2019 in Wuhan, China. Over the past year, the virus has wreaked havoc across the globe, causing 173 million cases and 3.7 million deaths. The mortality rate in COVID-19 patients has varied between 0.5% to 9.5% across countries due to the emergence of several strains[1].

However, many patients who have recovered from the acute phase of the disease are often facing a cluster of symptoms including fever, dry cough, fatigue, anosmia, generalised body aches, angina, palpitations and headache[2]. Patients who are suffering from one or more of these symptoms even after being cured of COVID-19 are being diagnosed as Post-COVID or Long COVID Syndrome.

Hypertension has been identified as one of the major risk factors for COVID-19 patients suffering from critical illness[3], but it has not yet been associated with Post-COVID Syndrome.

Hypertension :

The European Society of Cardiology defines Hypertension as persistent elevation in systolic BP > 140mmHg and/or diastolic BP > 90mmHg[4]. Symptoms of hypertension are quite non-specific including headaches, nose bleeds, shortness of breath. Most patients are asymptomatic till they reach extremely high BP levels (Hypertensive Urgency). Long standing Hypertension has been found to be a cause of a wide range of diseases, both cardiac and non-cardiac. Cardiological risks with chronic Hypertension include Angina, Myocardial Infarction, Atrial Fibrillation and Congestive Cardiac Failure; non-Cardiological effects include Cerebrovascular Accident and Chronic Kidney Disease[5].

The physiology of blood circulation is affected by a large number of systemic and local factors. Hence, the exact cause of hypertension is not always easy to pin-point. Hypertension is grossly divided into 2 categories :

1. Essential or Primary Hypertension (~90% cases)
2. Secondary Hypertension (~10% cases)

Secondary Hypertension is caused by many organic diseases such as renovascular disease, renal failure, pheochromocytoma, and aldosteronism. Essential Hypertension is basically defined as Hypertension in the absence of these aforementioned diseases[6]. Though the exact cause behind Essential Hypertension is not definite, a large number of risk factors have been attributed to it.

Table 1 :Major Risk Factors of Essential Hypertension

Non-modifiable Risk Factors	Modifiable Risk Factors
Age	Obesity
Sex	Diet
Genetic Factors	Physical activity
Ethnicity	Environmental stress

Since a large number of factors influence the blood pressure, there are various methods of externally reducing the BP. The pharmacological agents used to lower blood pressure are termed anti-hypertensive drugs .

Table 2 : Oral Antihypertensive Drugs

Class of Drug	Mechanism of Action	Example
Diuretics	Loop Diuretic	Furosemide
	Thiazide Diuretic	Hydrochlorothiazide
	Potassium-sparing Diuretic	Amiloride
Calcium Channel Blockers	Dihydropyridine	Amlodipine
	non-Dihydropyridine	Verapamil
Beta Blockers	Non-specific β1 and β2 antagonist	Propranolol
	Selective β1 antagonist	Metoprolol
	Beta blockers with intrinsic sympathomimetic activity	Pindolol
	Combined α and β blocker	Labetalol
RAAS Inhibitors	ACE inhibitor	Ramipril
	Angiotensin Receptor Blocker	Telmisartan
	Aldosterone Receptor Antagonist	Eplerenone
Alpha Blockers	α -1 Blocker	Prazosin
Centrally Acting Drugs	α -2 Agonist	Methyldopa
Direct Vasodilators	Smooth Muscle Relaxant	Hydralazine

Physicians across the globe use one (mono therapy) or many (combination therapy) of these oral drugs for management of Hypertension in out-patient settings, while some non-enteral routes such as transdermal patch (Glyceryl trinitrate) and intravenous injections (Sodium Nitroprusside) are used in Emergency Departments or critically ill patients with excessively high BP (Hypertensive Emergency).
Out of all the oral antihypertensives listed above: Calcium Channel Blockers, Beta Blockers, Diuretics, ACE inhibitors and Angiotensin Receptor Blockers are the most commonly used class of drugs worldwide. These 5 groups of drugs in various combinations account for almost 71% of all anti-hypertensive prescriptions[7].

Renin-Angiotensin-Aldosterone System :

The Renin-Angiotensin-Aldosterone System (RAAS) is a major contributor to the physiology of blood volume and systemic vascular resistance, thus becoming a key contributor to the homeostasis of systemic blood pressure. When there is a fall in arterial blood pressure, baroreceptor reflex acts as a short-term response while the activation of RAAS is responsible for chronic alterations through a cascade of proteins and enzymes.

Within the afferent arterioles of the kidney, there are some specialised cells called Juxta-Glomerular (JG) cells, which contain Prorenin. In response to reduced blood pressure, JG cells are activated, which cleaves inactive Prorenin to Renin (active form). Once Renin is released into the blood, it acts on Angiotensinogen (secreted from liver), cleaving it to form Angiotensin I. Though Angiotensin I is inactive physiologically, it acts as a precursor to Angiotensin II. Angiotensin Converting Enzyme (ACE) is found primarily in the pulmonary and renal vascular endothelium. ACE acts as a catalyst in the conversion of Angiotensin I to Angiotensin II, which has different mechanisms of action across in different organs:

- Kidneys : In the Proximal Convoluted Tubules (PCT), Angiotensin II increases Na-H exchange. This increases sodium reabsorption, causing increased osmolarity of blood, leading to a shift of fluid into the blood and extracellular fluid (ECF).
- Adrenal Gland : Angiotensin II acts on the Zona Glomerulosa of adrenal cortex stimulating the release of Aldosterone, a steroid hormone. Aldosterone in turn stimulates insertion of luminal Na channels and basolateral Na-K ATPase proteins at the distal tubule and collecting duct of the nephron. This increases sodium reabsorption, again causing increased osmolarity and shift of fluid into blood and ECF.
- Arterioles : In the systemic arterioles, Angiotensin II acts on G protein coupled receptors, leading to a secondary messenger cascade that results in potent arteriolar vasoconstriction, causing increased peripheral resistance.
- Brain: In the brain, Angiotensin II has 3 actions-
  i. Binds to Hypothalamus to increase thirst, thus increasing water intake
  ii. Stimulates release of AntiDiuretic Hormone (ADH) or Vasopressin which inserts Aquaporin channels at the Collecting Ducts, increasing water reabsorption
  iii. Decreases sensitivity of the baroreceptor reflex, thus reducing their response to increased blood pressure.

All the above mechanisms work simultaneously to increase the systemic blood pressure[8]. However, like all other pathways, the RAAS also has a counter-regulatory mechanism to stop the uncontrolled rise in systemic blood pressure. In the arterioles, there are 3 types of receptors for Angiotensin II: Angiotensin II Type 1 Receptor (AT1R) and Angiotensin II Type 2 Receptor (AT2R). The binding of Angiotensin II with Angiotensin II Type 1 Receptor causes the aforementioned effects to increase systemic BP. However, there is a separate pathway which has anti-hypertensive effects.

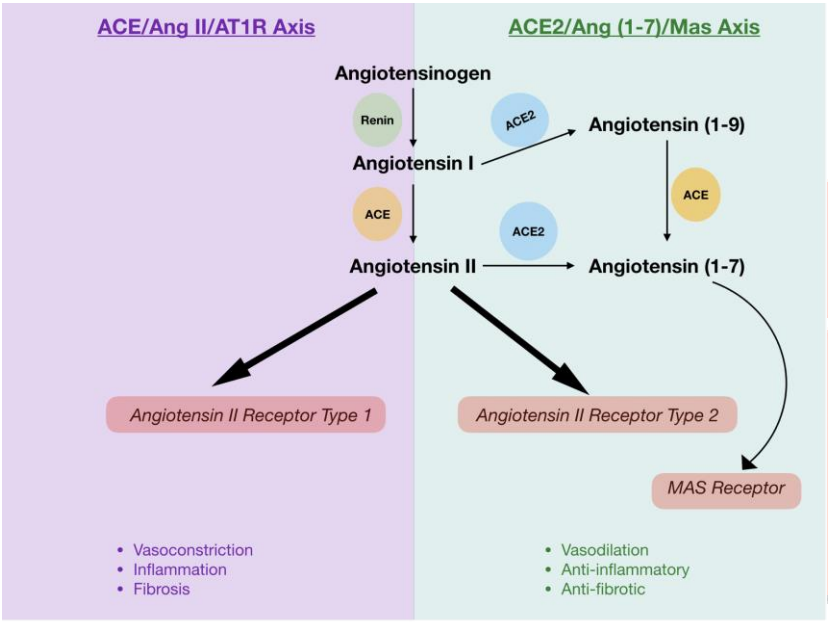


Fig 1 : Counter-regulatory effects of RAAS

While some amount of Angiotensin I is converted to Angiotensin II with the help of ACE, the remaining is cleaved to Angiotensin (1-9) with the help of Angiotensin Converting Enzyme Type 2 (ACE2). ACE then acts on Angiotensin (1-9) to form Angiotensin (1-7). Angiotensin (1-7) is also formed directly from Angiotensin II under the effects of ACE2.[9] Studies have shown the catalytic effects of ACE2 are almost 400 times on Angiotensin II than with Angiotensin I as a substrate[10]. Receptors of this counter-regulatory pathway include Angiotensin II Type 2 Receptor and Mas oncogene receptor[11]. This forms the ACE2/Ang (1-7)/Mas Axis to balance the effects of the primary ACE/Ang II/AT1R Axis.

The same substrate, Angiotensin II, produces different effects while binding to the 2 receptors. AT1R stimulates protein phosphorylation and leads to an increase in blood pressure, as already described. It also induces cell proliferation, inflammation and fibrosis. On the other hand, AT2R leads to protein dephosphorylation which causes increased production of Nitrous Oxide and Bradykinin, thus causing vasodilation. This vasodilation results in the reduction of systemic blood pressure. Again, AT2R hinders cell proliferation and induces cell differentiation, thus having anti-inflammatory and anti-fibrotic effects[12]. Colocalization and interdependence between AT2R and Mas Receptors to promote natriuresis defines the importance of Mas receptors in the ACE/Ang II/AT1R Axis[13].

ACE2 and COVID-19 :

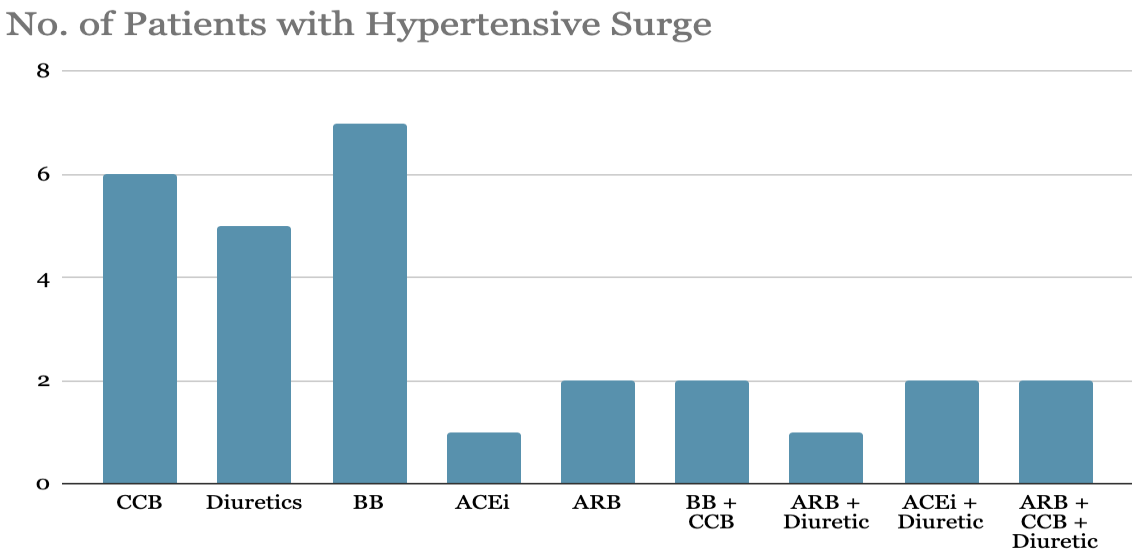
ACE2, a metallopeptidase, has been identified as the binding site for SARS Coronaviruses[14]. The viral surface spike protein mediates entry of n-SARS-CoV-2 into the cell. The spike protein binds to ACE2 through its receptor-binding domain (RBD) and is proteolytically activated by human proteases. The RBD of n-SARS-CoV-2 has a high affinity for human ACE2, thus facilitating viral entry into the human body. Cell entry of n-SARS-CoV-2 is preactivated by pro-protein convertase furin, reducing its dependence on target cell proteases for entry; this also helps in evading the host immune response[15]. Studies have shown reduced ACE2 expression and function in COVID-19 patients, linked to reduced expression of TMPRSS2 (one of the 2 proteases which cleave the ectodomain of ACE2)[16].

Hypertension in Post COVID-19 patients :

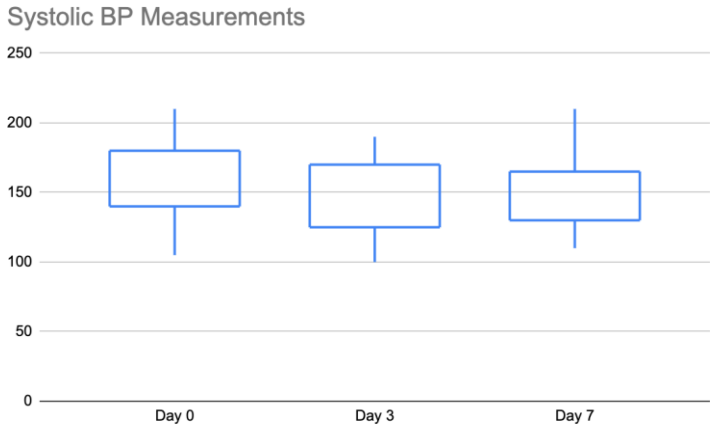
A cross-sectional observational study was conducted in India, which continued for 6 weeks from April 2021. The study included 130 patients who tested negative for COVID-19 after treatment for the same. 71 of these patients had documented hypertension before suffering from COVID-19 and were already on oral antihypertensives, BP well controlled (<130/80mmHg). Patients were selected in this study from in-patient departments, fever clinic and telemedicine consultations.

Though the Post COVID period has not been clearly defined yet, for the purposes of this study we have chosen Day 0 of Post COVID as the day of negative RT-PCR report after suffering from acute COVID-19 illness. Follow-ups were arranged on 0, 3rd and 7th day to check BP.

Out of the 71 patients who had known hypertension, 28 (39.4%) showed persistently high systemic blood pressures (Systolic BP > 140mmHg or Diastolic BP > 90mmHg). Of the remaining 59 patients who did not have Hypertension prior to COVID-19 infection, 9 patients (15.2%) had raised BP on all 3 follow-ups. Further documentation showed previously patients who were not taking any form of RAAS inhibitors were more susceptible to the Post COVID surge of systemic BP.



It is apparent from the data obtained that RAAS inhibitors play a pivotal role in prevention of Hypertensive surge during the Post COVID phase. The cause behind this may be attributed to the fact that reduction in ACE2 enzyme expression because of n-SARS-CoV-2 causes increased activation of ACE/Ang II/AT1R Axis, leading to the raised BP. No correlation was found between the rise in BP with the severity of COVID-19 infection.



This graph plots the systolic blood pressure measurements of all the 130 patients who participated in the trial. The graph shows a persistent rise in BP in the 1st week of the Post COVID phase.

Randomized control trials need to be conducted to confirm the reduced risk of Post COVID Hypertension in patients who are being administered RAAS inhibitors during the acute phase of the disease. Also, further studies need to be conducted to find out if the increased BP in previously non-Hypertensive patients is temporary or permanent.

Discussion :

Though clinicians were initially reluctant to use ACEi and ARBs in COVID-19 patients, studies have found no significant correlation between RAAS inhibitors and patient outcomes during the acute phase of the disease[17]. However, no similar study has been conducted involving the Post COVID period. An advantage of these drugs may be reduced chances of Macrophage Activation Syndrome (MAS) in Post COVID Syndrome.

The downregulation of ACE2 has been shown to cause Macrophage Activation Syndrome[18]. Angiotensin II is known to activate Signal Transducer and Activator of Transcription proteins 3 (STAT3) via AT1R. STAT3 has been identified in the binding site of TNF-α[19], the stimulation of which induces a cascade of reactions which ultimately leads to hypercytokinemia. Shifting the balance towards the ACE2/Ang (1-7)/Mas Axis with the help of RAAS inhibitor drugs can help reduce the chances of MAS in Post COVID phase, thereby leading to decreased chances of Pulmonary Fibrosis and Cardiomyopathies which account for a large number of symptoms of Post COVID Syndrome.

Apart from this, our study indicates better control of BP in patients treated with ACEi or ARBs, thus showing the benefits of adding a RAAS inhibitor in case of Post COVID Hypertension.

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