The Libyan International Medical University

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CORRELATION BETWEEN RENIN ANGIOTENSIN ALDOSTERON SYSTEM AND CARDIO VSASCULAR DISEASES

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Abstract:

Hypohydration, defined as a state of low body water, increases thirst sensations , (1) then force renin–angiotensin–aldosterone system (RAAS) which is a complex system that plays an important role in maintaining haemodynamic stability in the human body through regulation of arterial blood pressure, water and electrolyte balance. (3) RAAS has been implicated with the pathophysiology of various cardiovascular disorders including hypertension, acute myocardial infarction (AMI), congestive heart failure (CHF) reduced ejection fraction (REF) and stroke. Here, we review the role of active renin, a crucial, upstream enzymatic regulator of the RAAS, as a prognostic and diagnostic plasma biomarker of heart failure with reduced ejection fraction (HFrEF) progression , Clinical and experimental studies indicate that plasma renin activity is elevated with HFrEF . Modulation of renin activity in experimental HF significantly reduces edema formation and the progression of systolic dysfunction and improves survival. Thus, specific assessment and targeting of elevated renin activity may enhance diagnostic and therapeutic precision to improve outcomes in appropriate patients with HFrEF. (2)

INTRODUCTION:

heart failure (HF) with reduced ejection fraction (rEF) affects millions and is the most common reason for heart transplantation , which it happens when the left side of the heart doesn't pump blood out to the body as well as normal.

It's sometimes called systolic heart failure. This is because of the left ventricle doesn't squeeze forcefully enough during systole, which is the phase of the heartbeat when your heart pumps blood. The types of heart failure are based on a measurement called the ejection fraction. The ejection fraction measures how much blood inside the ventricle is pumped out with each contraction. The left ventricle squeezes and pumps some (but not all) of the blood in the ventricle out to your body. A normal ejection fraction is more than 55%. This means that 55% of the total blood in the left ventricle is pumped out with each heartbeat.

Heart failure with reduced ejection fraction happens when the muscle of the left ventricle is not pumping as well as normal. The ejection fraction is 40% or less.The amount of blood being pumped out of the heart is less than the body needs. A reduced ejection fraction can happen because the left ventricle is enlarged and cannot pump normally. Examples of ejection fractions of a healthy heart and a heart with reduced ejection fraction: A healthy heart with a total blood volume of 100 mL that pumps 60 mL has an ejection fraction of 60%.A heart with an enlarged left ventricle that has a total blood volume of 140 mL and pumps 60 mL has an ejection fraction of 43%. (4)

There are many different problems that can cause heart failure with reduced ejection fraction and the most common problem or cause are High blood pressure when it pumps against your high blood pressure, your heart has to increase the pressure inside your left ventricle when it pumps. After years of working harder to pump blood, your ventricle may begin to weaken. When this happens, the pressure inside the weakened left ventricle will cause the ventricle to expand, stretching out the heart muscle. This damaging process is called dilation, and it impairs your heart's ability to squeeze forcefully. The result is heart failure.And Coronary artery disease causes gradual heart damage over time. Also ischemia is the medical term for what happens when your heart muscle doesn't get enough oxygen. Ischemia may happen only once in a while, such as when you are exercising and your heart muscle needs more oxygen than it normally does. Ischemia can also be ongoing (chronic) if your coronary arteries are so narrowed that they limit blood flow to your heart all the time. This chronic lack of

oxygen can gradually damage portions of your heart muscle. Your heart can slowly lose its ability to pump blood to your body.Both of High blood pressure and Coronary artery disease with ischemia are include in the pathophysiology of (RAAS) (5)

The renin–angiotensin–aldosterone system (RAAS) is a complex system that plays an important role in maintaining haemodynamic stability in the human body through regulation of arterial blood pressure, water and electrolyte balance. The classical RAAS hormonal cascade begins with production of renin which is released by Juxtaglomerular (JG) cells associated with the afferent arteriole entering the renal glomerulus are the primary site of renin storage and release. A reduction in afferent arteriole pressure causes the release of renin from the JG cells, whereas increased pressure inhibits renin release .Once renin secreted it enter directly into circulation then carries out the conversion of angiotensinogen, released by the liver, to angiotensin I, Angiotensin I is subsequently converted to angiotensin II by the angiotensin-converting enzyme (ACE) found on the surface of vascular endothelial cells, predominantly those of the lungs. Angiotensin II is a potent vasoconstrictive peptide that causes blood vessels to narrow, resulting in increased blood pressure. Angiotensin II also stimulates the secretion of the hormone aldosterone from the adrenal cortex . Aldosterone causes the renal tubules to increase the reabsorption of sodium and water into the blood, sodium and water retention, increased arterial blood pressure and increased myocardial contractility, which in combination increase the effective circulating volume. An increase in perfusion of the juxtaglomerular apparatus inhibits the release of renin through a negative feedback mechanism. while at the same time causing the excretion of potassium to maintain electrolyte balance. (6)

Angiotensin II, the major effector peptide of the renin-angiotensin-aldosterone system (RAAS), plays a significant role in the advent and perpetuation of these inflammatory diseases, most notably in atherogenesis. Consequently, suppression of the influence of angiotensin II by angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers may reduce or potentially reverse atherosclerosis and other inflammation-associated CVDs.Clinically, RAAS suppression reduces common carotid and femoral artery intima-media thickness, thus indicating moderation of the vascular disease process. These clinical benefits likely involve restraint of the deleterious effects of angiotensin II in addition to, or independent of, lowering blood pressure.

Aim of study : the aim of study is to detect the correlation between the RAAS and the cardiovascular diseases , also to lower the risk of cardiovascular disease by taking drugs such as :ACEI , AT1 blockers, aliskiren

:Material and method

Ang I Generation Assay: Traditionally in clinical studies, renin enzymatic activity, abbreviated as PRA, is assayed by a 2step process measuring the potential of a patient's plasma sample to convert exogenous angiotensinogen (substrate) to Ang I (product) during in vitro incubation, followed by measurement by radioimmunoassay (RIA) or enzyme-linked immunosorbent assay (ELISA) of the generated Ang I. However, the Ang I generation step is time-consuming and time-sensitive. Depending on active renin levels in plasma, this step might take from 3 to 18 h . Moreover, PRA measurements could be altered by the amount of endogenous angiotensinogen level in plasma.

Prognostic Value of Plasma Renin Activity in HFrEF : Over the past decade, the prognostic value of PRA in HF has been extensively evaluated and reported. PRA was reported to be an independent prognostic marker in prospectively enrolled patients with HFrEF , irrespective of medical treatment, Elevated PRA levels demonstrated increased risk for congestive HF and a trend toward higher mortality among patients with systolic blood pressure (SBP)≥140 mmHg, the result from Val-HeFT trials report that PRA remains a prognostic marker even in the presence of ACE inhibitors, which are known to increase PRA levels . (2)

Results:

Over the past decade, the prognostic value of PRA in HF has been extensively evaluated and orted. PRA was reported to be an independent prognostic marker in re .prospectively enrolled patients with HFrEF

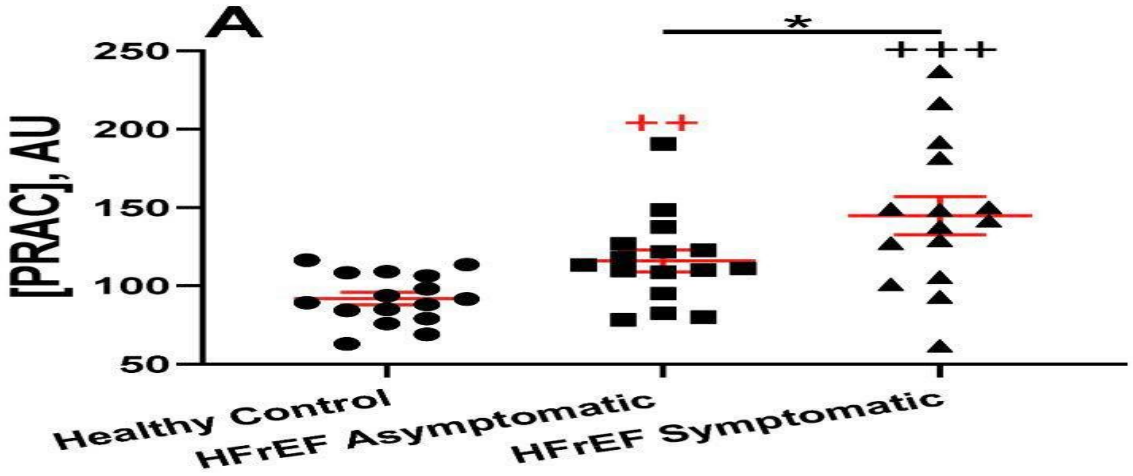

Figure 1 : show Plasma samples of healthy control patients (normal ejection fraction, EF) and patients with reduced (rEF) with and without symptomatic HFrEF. This figure show that the increase of concentration of PRAC will strongly increase the HFREF. (2)

:Discussion

Increased plasma renin activity enhances aldosterone production. The degrees of increase in plasma renin concentrations and plasma aldosterone levels correlate with prognosis in patient with HF , Aldosterone has adverse effects on the cardiovascular system, including prevention of myocardial neuronal reuptake of norepinephrine (thereby enhancing sympathetic drive) and potentiation of fluid overload and electrolyte imbalance. aldosterone play a vital pathophysiological role in the common cardiovascular disease, including hypertension, atherosclerosis, heart failure, myocardial infarction and cardiac hypertrophy. The pathophysiology of these various syndromes is similar, starting by prior microvascular injury that leads to subsequent myocardium ischemia, Aldosterone is more than 30 times as potent as desoxycorticosterone in reducing sodium excretion, and has a comparable effect in increasing the output of potassium. In excess, aldosterone has some properties of the glucocorticoids, such as corticosterone or hydrocortisone. These data indicate that there is a close correlation between aldosterone output and electrolyte balance in man. It is evident that the effect of aldosterone may vary somewhat under various conditions of renal function, electrolyte load and capillary equilibrium. Systemic RAAS activation occurs with increased plasma renin activity, which initiates the activation of the primary targets for clinical intervention: angiotensin II (Ang II) and aldosterone .

Pharmacological blockade of RAAS has proven to be the mainstream/standard treatment approach for symptomatic HFrEF patients . Standard medical therapies include RAAS blockers: angiotensin converting enzyme (ACE) inhibitors (ACE-I), which block the enzymatic conversion of Angiotensin I (Ang I) to Ang II; Ang II receptor blockers (ARB), which block the binding of Ang II to the Ang II type I receptor (AT1); mineralocorticoid receptor antagonists (MRA), which block effects of aldosterone ;and angiotensin receptor/neprilysin(NEP) inhibitors (ARNi). Although clinical trials have failed to demonstrate the value of renin activity inhibition for improving outcomes for patients with HF on concurrent RAAS blockers. Complicating the issue is the heterogeneity of patient plasma renin activity levels and their individualized responses to plasma rennin activity levels on the back ground of RAAS blockers or HF progression itself. (2)

Conclusions:

The potential value of renin activity as a diagnostic and/or prognostic biomarker of HFrEF clinically advancement has slowed with the termination of the aliskiren HF trials due to side effects and poor outcomes . In addition, the dose-related effects of aliskiren in HF studies have not been well-established. Currently, there are new DRIs (direct renin inhibitors) and (P)RR inhibitors under development, which suggest that the cardiovascular field is not prepared to give up on the promising pharmacologic potential of renin activity as a bio-target to delay HF progression . (2)

:References

Watso, J. and Farquhar, W. (2019). Hydration Status and Cardiovascular Function. *Nutrients*, 11(8), p.1866. (1)

Sullivan, R., Mehta, R., Tripathi, R., Reed, G. and Gladysheva, I. (2019). Renin Activity in Heart Failure with Reduced Systolic Function—New Insights. *International Journal of Molecular Sciences*, 20(13), p.3182. (2)

CROOK. (2012). *Clinical Biochemistry and Metabolic Medicine*. London: Taylor & Francis Ltd. (3)

(4) (Mayo Clinic, 2020)

(5) (Dynamed.com, 2020)

Harper, H., Rodwell, V., Rivera Muñoz, B., Murray, R., Bender, D., Botham, K., Kennelly, P. and Weil, P. (2016). *Harper*. México, D.F.: McGraw-Hill Interamericana. (6)