ALDOSTERONE AND RENIN IN ESSENTIAL HYPERTENSION

THESIS

SUBMITTED IN PARTIAL FULFILLMENT

FOR (M. D.) DEGREE IN

(GENERAL MEDICINE)

By

MOHAMMED SAAD HAMID

M. Sc. General Medicine

Supervisors

PROF Dr. ABOU EL MAATI NABIH AHMID

Prof. of General Medicine

Chairman of Endocrine Unit

Faculty of Medicine

Ain Shams University

PROF Dr. MOGAZY ALI MAHGOAB

Prof. of General Medicine

Faculty of Medicine

Ain Shams University

Dr. SOHAIR MOHAMED GAMAL EL DIN

Ass. Prof, of General Medicine

Ain Shams University

Dr. MOHAMMED ALAA EL DIN HAMID

Ass. Prof. of General Medicine

Ain Shams University

FACULTY OF MEDICINE

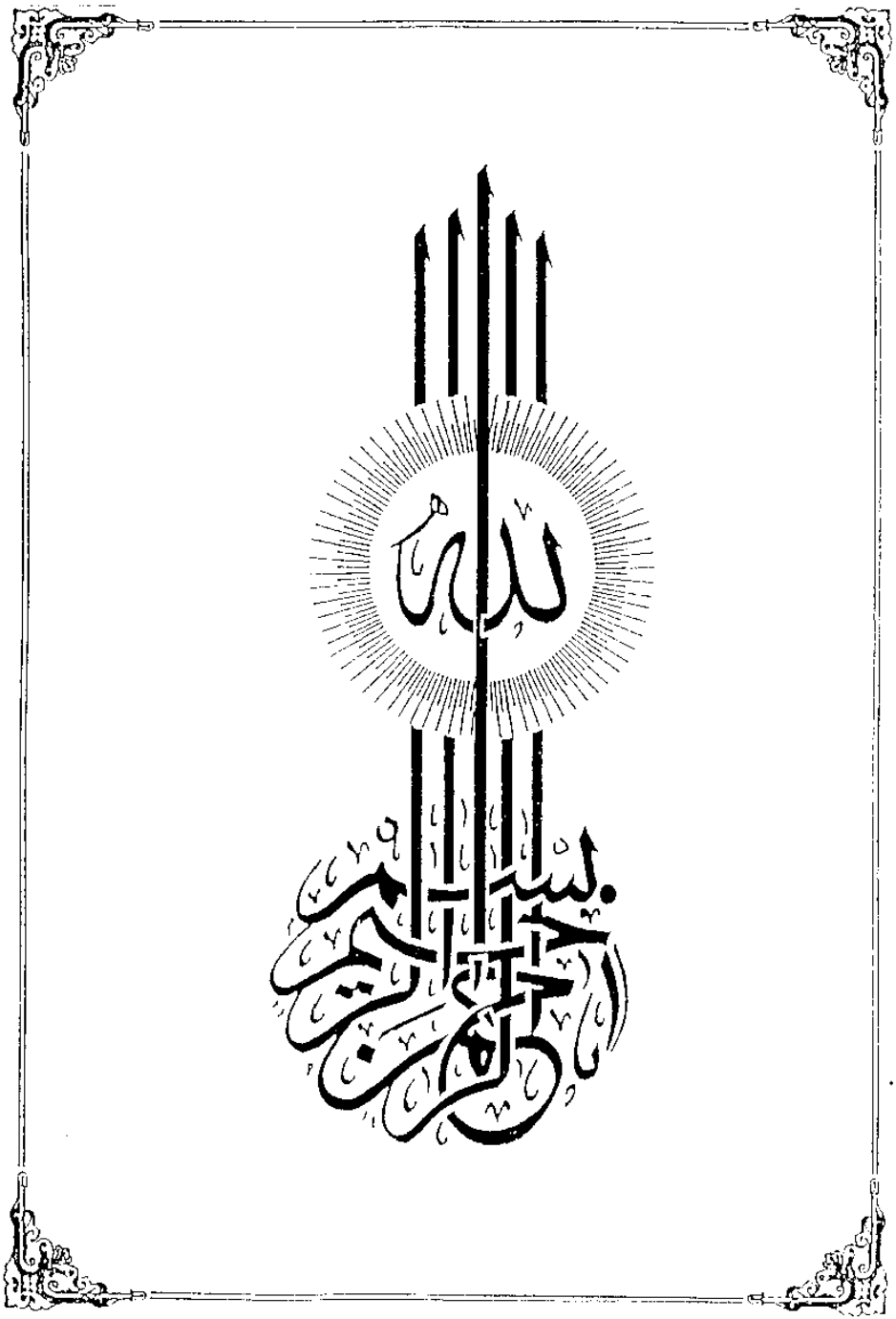
AIN SHAMS UNIVERSITY

1989

بسم الله الرحمن الرحيم

وقل رب زدني علما

صدق الله العظيم



To My future Family

C O N T E N T S

* * * * *

AGKNOWLEDGEMENT

I wish to express my deepest gratitude to Prof. Dr. ABOU EL MAATI NABIH AHMED Chairman of endocrine unit, for his sincere help, encouragement , and fruitful guidance.

I am also, deeply indebeted to Prof. Dr. MOGAZY ALI MAHGOUB , who suggested the idea of this research, for his sympathetic help and endless support.

I should mention the effort of Ass. Prof. Dr. SOHAIR GAMAL EL DIN and Ass. Prof. Dr. MOHAMED ALAA EL DIN HAMID for their kind instructions .

I should also express my deep gratitude to the laboratory chemists : Laila Aziz , Magdi Abas , together with Mrs. Nadia El Werdany.

Finally , I wish to thank Dr.Mona Mohamed El Hashemi, who carried out the statistical analysis of this study .

AIM OF THE WORK

INTRODUCTION AND AIM OF THE WORK

In the continuing effort to identify pathogenic mechanisms in patients with essential hypertension, attention has been focused on subgroups defined by characteristic features. One such feature is plasma renin activity (Dunn and Tannen 1974) which is low and unresponsive to the stimulus of sodium restriction or depletion. Patients with low renin hypertension have a renin secretion resistant to stimulatory maneuvers similar to patients with primary aldosteronism (Conn et al., 1964).

There is overwhelming evidence that sodium and fluid overload is essential for the pathogenesis of mineralocorticoid hypertension. But, obviously, the excesses of sodium and fluid which are essential for the maintenance of hypertension are much smaller than the excesses which are associated with initiation of hypertension. Several factors are implicated here, for instance, resetting of the baroreceptors, cardiac hypertrophy, functional or structural changes in the blood vessels to pressor substances, and renal changes (Brown et al.,1974).

Our aim is to clarify the role of renin and aldosterone together with the incidence of primary aldosteronism in essential hypertension of Egyptian patients.

DERANGEMENT OF RENIN ANGIOTENSIN ALDOSTERONE SYSTEM (R.A.A)

1. OEDEMA

The disease states characterized by oedema formation arises from a wide variety of underlying causes but have in common an increased tendency for the renal tubules to reabsorb excessive amounts of sodium and water from the glomerular filtrate which is regulated by a number of factors one of which is aldosterone (McDonald & Stuart., 1980).

The incresed secretion of aldosterone is more in nephrosis and cirrhosis, but is less in congestive heart failure with exception of advanced right - sided heart failure. (Laragh and Sealy., 1981).

There are also high circulating levels of angiotensin II (AII) which has a potent effect on vascular bed. Therefore the multifactorial role of renin-angiotensin system in these disorders is apparant (McDonald & Stuart., 1980).

a. CONGESTIVE HEART FAILURE (C.H.F.):

The renin-angiotensin system contributes to the elevated systemic vascular resistance that often occurs in patients with C.H.F. (Creager,etal., 1985). C.H.F. is characterized by increased peripheral vascular tone and abnormal sodium and water excretion, though what extent these changes reflect activity of renin-angiotensin-aldosterone system is unclear (Curtiss etal.,1978). The recent introduction of orally active converting enzyme inhibitors

has generated much renewed interest in the role of the R.A.A. system in C.H.F. (Ader,etal., 1980).

They may also have additional effects such as inhibition of degredation of the vasodilator peptide bradykinin (Hodsman, etal.,1982).

Increased peripheral vascular resistance commonly accompanies heart failure, and vasodilator are now well established in its treatment. Plasma renin is raised in many such patients and thus specific interference with at least one of the mechanisms leading to vasoconstriction can be achieved with converting enzyme inhibitors (Brown, etal.,1970).

The acute haemodynamic effects of captopril in heart failure comprise an increased in stroke volume, cardiac output, and stroke work index associated with a fall in systemic vascular resistance, left ventricular filling pressure, pulmonary arterial pressure, and right atrial pressure, while total pulmonary vascular resistance falls because of reduction in pulmonary capillary pressure, pulmonary arteriolar pressure is unaffected (Levine, etal., 1980 and Sharpe, et al., 1980).

The clinical effect of captopril in cardiac failure includes symptomatic improvement (Awan, et al,1981). and an increase in maximum exercise capacity (Ader,et al ., 1980).

b. HEPATIC CIRRHOSIS:

Of the known complications of hepatic cirrhosis is

the marked tendency for retaining sodium and water in the extracellular compartment. This was found to be associated with an increased activity of the R.A.A. system. The available information indicates that the increase in renin and aldosterone secretion may not be the primary cause in initiating oedema formation, but rather is the result of other primary factors which initiate the process (McDonald and Stuart., 1980).

In bilharzial liver cirrhosis, the plasma renin activity was found to be slightly decreased in non ascitic patients and increased in the ascitic one together with aldosterone. In these patients, the combination of high plasma aldosterone and high plasma renin activity indicate secondary hyper-aldosteronism in ascitic patients (Madwar,etal.,1981)

It is to be mentioned that high renin and angiotensin levels help to maintain the blood pressure, in the face of reduced effective blood volume. Therefore, the infusion of compititive inhibitor of angiotensin II (Saralasin), causes a major drop in blood pressure (Schroeder., 1976).

c. NEPHROTIC SYNDROME:

The basic pathophysiologic mechanism for the formation of oedema is simialr to that in cirrhosis, but here the cause of hypoalbuminaemia is loss of proteins (mainly albumin) in urine. The R.A.A. system is involved in a way similar to that in hepatic cirrhosis, through reduced circulating blood volume, this will stimulate renin secre-

tion through the renal nerves, baroreceptor mechanism, and possibly also the macula densa mechanism (McDonald&Stuart, 1980).

2. BARTTER'S SYNDROME:

In 1962 , Bartter and Co-workers described a syndrome characterized by hypokalaemia, hyperplasia of the juxtaglomerular apparatus, and a normal blood pressure, despite high renin and aldosterone levels. Since then many patients with some or all of these features have been reported, and many clinical and biochemical manifestations have been identified, in fact, the clinical presentation may vary from severe life threatening illness in infancy to an incidental finding with few symptoms in adult life (Simopoulos.,1979).

The pathogenesis of the condition is still uncertain, Solomon, etal (1982) suggested that the syndrome may not have a single pathogensis. It is difficult to distinguish the primary defects causing the disease from secondary metabolic consequences resulting from it.

The possibilities at the primary cause are abnormality of R.A.A. system and vascular insensitivity to angiotensin II (Bartter, etal. 1962), excess prostaglandin production might be responsible for pathogensis of the syndrome (Fichman, etal.,1979), or due to defective renal handling of electrolytes Magnesium (Solomon,etal.,1982), and potassium (Castello and Bourke.,1983).

An essential feature of the disease is normal blood pressure despite the increased production of renin and aldosterone.

Over production of vasodilators may partly explain the combination of high plasma angiotensin II concentration and normal blood pressure, and pressor hyporesponsiveness to angiotensin II and norepinephrine. Pressor hyporesponsiveness can occur in other hypokalaemic disorders and can be corrected by prostaglandin synthetase inhibitors, with only partial correction of potassium depletion or none (Hans-Georg, etal., 1980 and Fujita, etal., 1982).

Sympathetic nervous system function and the response to prostaglandin synthetase inhibition was evaluated in 7 females aged 17 to 48 years with Bartter's syndrome, all of whom showed pressor resistance to infused norepinephrine. Seven healthy subjects were also evualuated . Indomethacine administration reduced urinary secretion of epinephrine by 8%, of norepinephrine by 43%,. of metanephrine by 33%, and vanillyl mandelic acid by 20% (Hans-Georg , etal.,1980).

Peripheral sympathoadrenal activity appears to be increased in patients with Bartter's syndrome, probably as compansation for the increased vascular resistance to norepinephrine associated with hypokalaemia, and presumably mediated by an increase in circulating bradykinin and vascular vasodilator prostaglandins.

Less common finding of Bartter's syndrome include hypomagnesaemia, glucose intolerance, defect in the primary and secondary phases of platelet aggregation, but without bleeding abnormalities. Also, hypercalcaemia and hyperuricaemia have been occusionally reported (Ogihare, et al., 1982).

MANAGEMENT:

Restoration of body potassium by its feeding or by the use of aldosterone antagonist spironolactone, also, amiloride gives good results (Griffing, et al.,1982).

3. HYPORENINAEMIC HYPOALDOSTERONISM (H.H.):

The syndrome of H.H. is a disorder characterized by hyperkalaemia, hypochloraemic metabolic acidosis,mild or mederately advanced renal insufficiency and inappropriately, low levels of renin activity and aldosterone.(Sowers, et al 1985).

patients who develop this syndrome are usually in their fifth to seventh decade of life (Schambelan and Sebastian.,1979).

This syndrome has been recognized most frequently in patients with moderate renal dysfunction resulting from the diabetic nephropathy, but also, it occurs in non diabetic patients with tubulo-interstitial nephritis (Sowers, et al.,1985).

Pathogenesis of hyporeninaemia is not completely elucidated. Several mechanisms have been postulated, specially

in patients with diabetes mellitus.

Christlieb, et al., (1976), suggested that it may be due to hyalinization of the afferent arterioles destroying the renin - producing cells, physiologic suppression of renin secretion by an expanded plasma volume, autonomic neuropathy, the hyperkalaemia itself and/or a defect in the conversion of renin precursors into active renin.

Pathogenesis of hypoaldosteronism is mainly related to the decreased renin secretion, but it may be modulated by a primary abnormality of adrenal gland (Delvia, et al., 1976), Since aldosterone levels failed to rise normally following sodium restriction and postural change (Baxter, et al.,1976).

The metabolic acidosis and the hyperkalaemia are secondary to aldosterone deficiency. In diabetes mellitus; insulin defficiency tends to aggrevate the hyperkalaemia (Large, et al., 1984).

A reversible cause of hyporeninaemic hypoaldosteronism, is by indomethacin-induced prostaglandin inhibition. Renal prostaglandins appear to be cretical in modulating the response of the renin - angiotensin - aldosterone axis. The renin responses to furosemide and posture are markedly blunted by indomethacin, a prostaglandin synthetase inhibitor. Plasma and urinary aldosterone levels are reduced in parallel with renin supression (Tan,etal., 1980)

Hyporeninaemic hypoaldosteronism was detected by the furosemide stimulation test during indomethacin therapy