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**The Role of Renin in Hypertension:
An Old Dog with New Bite**

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The Role of Renin in Hypertension: An Old Dog with New Bite

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Foreword:

Tigerstedt and Bergman discovered in 1898 the pressure-raising substance from saline rabbit kidney extracts and called the extract renin, however other scientists could not confirm their findings and in 1934, Harry Goldblatt published his results obtained in dog experiments where he clamped one or both renal arteries with a silver clamp. Numerous attempts showed no increases in plasma renin levels in patients with essential hypertension or that renin had any significant physiologic action of its own in humans. Braun-Menendez discovered that renin acted enzymatically on angiotensinogen (plasma protein) to form angiotensin I (inactive) and is further hydrolyzed by converting enzyme to form angiotensin II (vasoconstrictor), which increases the blood pressure when it is low. This is the old dog and because renin is not even mentioned in the JNC-VII (US) and the ESH (European) guidelines and when one do a renin profiling on patients/participants and apply the Laragh method to individualize the type of hypertension (volume or renin), it is evident that renin plays a large role in the maintenance of normal blood pressure and hypertension. In South African blacks whose hypertension is not under control, this will have a large impact on individualizing specific pathology and treatment and this will give the old dog new bite.

The Role of Renin in Hypertension: An Old Dog with New Bite

1 Background and Introduction

Hypertension is one of the major risk factors for cardiovascular diseases like coronary heart disease, myocardial infarction, cerebrovascular accidents, chronic renal failure and congestive heart failure in the United States and westernized world and because South Africa is in the midst of health transition, we are not spared from the higher risk. The health transition is characterised by the occurrence of epidemic infectious diseases and a rise in the prevalence of non-communicable diseases like hypertension [1-5]. Nearly 72 million Americans have hypertension and one out of three adults has hypertension [4].

1.1 Hypertension

a Patient with a systolic and diastolic blood pressure of $\geq 140/90$ mmHg or ambulatory daytime/nighttime value of 130-135/85 and $\geq 120/70$ mmHg is regarded as hypertensive [6], this cutoff value is arbitrary and this only simplifies diagnostic and treatment approaches in daily practice. Historically more emphasis was placed on diastolic blood pressure than on systolic blood pressure as predictor of morbidity and mortality. However observational studies revealed that cardiovascular morbidity and mortality showed a continuous relationship with systolic and diastolic blood pressure [6].

1.2 Types of hypertension

Primary (essential) hypertension is hypertension where about 90-95% of all people have hypertension with unknown origin and this is in contrast to those forms of hypertension that are secondary to known causes, such as renal artery stenosis [7]. There are also other types of hypertension like "One-Kidney" and "Two-Kidney" Goldblatt hypertension, hypertension caused by diseased kidneys that secrete renin chronically, hypertension in preeclampsia and neurogenic hypertension [7].

1.3 The syndrome of hypertension

Hypertension is part of a heterogeneous condition that is best described as a hypertension syndrome with genetic, acquired structural and metabolic disorders like: dislipidemia, diabetes mellitus including insulin resistance and impaired glucose tolerance, central obesity, endocrine and neurohumoral changes including the sympathetic nervous system, and the renin-angiotensin-aldosterone system, renal function abnormalities, abnormalities of vascular and cardiac smooth muscle structure and function such as arterial compliance abnormalities like the loss of elasticity, diastolic dysfunction and left ventricular hypertrophy, membranopathy like abnormal cation transport, coagulatory disorders, endothelial dysfunction, vascular inflammation, aging and accelerated atherogenesis [1]. Over 70% of patients with genetic hypertension have one or more of the coexisting metabolic or functional disorders that increase the risk of vascular damage, atherosclerosis and target organ damage [1].

1.4 Hypertension in black Africans

In black communities living in Africa under conditions of change described by Donnison in 1929 [3], blood pressure is independent of age. He also reported that during a two year period that 1800 patients hospitalized in the South of Kenya no case of raised blood pressure was reported and no diagnosis of atherosclerosis or chronic interstitial nephritis were made [3]. With the latest surveys it is shown that in patients older than 65 years of age, the prevalence is ≈30% to 40% in rural West Africa, ≈50% in semi-urban West Africa and 50%-60% in a mixed South African population [3]. A study sample (1996-1998) [5, 8] obtained in the North West Province of South Africa (Table 1), consisted mainly of Setswana speaking subjects (73.3%), the rest of the sample consisted of Sotho (11%), Xhosa (10%), Zulu and Shangaan (5.7%) and the results show 22.8% of the subjects of the total sample had systolic and 20.7% diastolic blood pressures above 140/90 mmHg on the day of the study.

Table 1. The rate of hypertension expressed as a percentage of participants (n=1783) who have SBP and DBP greater than 140/90 mmHg in the different strata [5] of urbanization (stratum 1, deep rural to stratum 3, 4 and 5, urbanized)

Gender	Variable	Stratum*1	Stratum 2	Stratum 3	Stratum 4	Stratum 5	Total
Men	n	198	114	132	232	84	760
	SBP	19.2	13.2	34.8	23.3	17.9	22.1
	DBP	14.6	13.2	22.7	19.0	22.6	18.0
Women	n	299	149	175	294	106	1023
	SBP	22.1	28.2	31.4	31.3	10.4	26.0
	DBP	21.4	21.5	26.9	25.9	13.2	22.8
Total	SBP	20.9	21.7	32.9	27.8	13.7	22.8
	DBP	18.7	17.9	25.1	22.8	17.4	20.7

* Strata: stratum 1 = deep rural, stratum 2 = farm-workers, stratum 3 = living in informal settlements, stratum 4 = living in established middle-class townships, stratum 5 = living in upper-class urban areas.

Men and women from stratum 1 to 4 (that is rural to urbanized) show increases in the incidence of high blood pressure. The rate of mild hypertension in stratum 3 was 32.9% for systolic and 25.1% for diastolic pressure respectively [5]. In a recent study from our research group **Hypertension in Africa Research Team** (HART), namely the **SABPA** (**S**ympathetic activity and **A**mbulatory **B**lood **P**ressure in **A**fricans) study (2008-2009), the incidence of hypertension in black men were 78% and in the women 57% [unpublished results].

This raises the question now, about the causes of this change in the prevalence of hypertension from a relative rarity in the 1970's [3] to a major health problem in sub-Saharan Africa. The

African Union has called hypertension one of the continent's greatest health challenges after AIDS [3].

This motivated us and was the driving force behind our endeavor to research the risk factors for hypertension in the black population of the North West Province of South Africa.

1.5 Risk factors of hypertension in Africans

One can speculate now over the risk factors for hypertension and it seems that urbanization [3, 4] and lifestyle (smoking, alcohol intake, psychosocial stress and diet) are the major risk factors in black Africans. People in South Africa especially the Africans are subjected to massive urbanization since the early 1990's. They migrate from the traditional rural settings where they live under the auspices of a tribe and tribal captain to the peri-urban informal settlements near the larger cities and towns in South Africa in order to seek other opportunities to supply in their daily subsistence. Since 1970 to 1994, the world rates of urbanization increased from 36.6% to 44.8% and it is expected to increase further to 61.1% in the year 2025 [9, 10]. The same trends are found in other developing countries and increased from an urbanization rate of 12.6% in 1970 to 21.9% in 1994 [10]. It is not only the migration of individuals from rural to urban areas that take place, but the rural areas themselves are being transformed [10], for example in the rural areas of the North West Province of South Africa the Coca-Cola sign is seen everywhere, they sell liquor from a liquor shop and cell phone reception towers are seen in the rural areas. Most households have a television and this will influence their subsistence. However there are still differences in lifestyle that exists between urbanized and rural people, like the rural people are still under the auspices of a tribal captain and they have support from their family members and friends. The urbanized lifestyle has an impact on the health of the urbanized people and adds to the chronic diseases of lifestyle risk factors typical of the western lifestyle they have to adopt.

In a sub study of the THUSA (Transition and Health during Urbanization of South Africans) study it was shown that men older than 45 years of age were at higher risk of developing cardiovascular disease [11] and with this study we quantified the influence of urbanization on cardiovascular health as a risk factor for hypertension and cardiovascular disease. The risk factors in black South Africans in the North West Province of South Africa were researched by our research group namely HART and by colleagues of other research units at the NWU by the

THUSA study, THUSA BANA (Transition and Health during Urbanization of South Africans; BANA is the Setswana word for children) study, POWIRS (Profiles of Obese Women with the Insulin Resistance Syndrome) study, the SAfrEIC (South African study regarding the influence of Sex, Age, and Ethnicity on Insulin sensitivity and Cardiovascular function) and the SABPA study [11,12,13, 14, 15, 8, 16].

2 Motivation and focus

Although antihypertensive drugs per se are effective, there are concerns why there is poor high blood pressure control, at least in developing countries like South Africa. The poor compliance to treatment as found in a study amongst Afrikaans (71.6%) and Sotho speaking (31.9%) participants in the Vaal Triangle [17] is probably one reason, because of the side effects of the drugs. By example in a developing country like Mozambique, the prevalence of hypertension was 33.1%, the prevalence of treatment among all of the hypertensives was 11.2% and the prevalence of control among all hypertensives was 4.8% [18]. In a developed country like the UK, only 11% of patients blood pressure are under control [19]. It seems that high blood pressure or hypertension is not under control and this may aggravate cardiovascular complications such as higher incidence of stroke, end-stage renal disease and heart failure. In the further sections of this article the focus will be placed on: (a) the role of the renin-angiotensin system in the control of blood pressure and volume, (b) by making use of the Laragh Method/equation to determine the role of the volume in hypertension, (c) low-renin hypertension in blacks and the influence on cardiovascular function will also be discussed and the consequences thereof.

3 The renin-angiotensin system in normal blood pressure control

There are two basic variables namely volume and pressure in the human body that must be controlled. If there is enough volume, but no pressure and vice versa, perfusion of the peripheral tissue could not take place completely. It is no wonder that there are eight control mechanisms operating to control blood pressure [7]. Except for the volume control function of the kidneys, they also have a powerful mechanism for controlling pressure namely the renin-angiotensin

system (see figure 1). Renin (enzyme) is synthesized and stored in its inactive form (prorenin) in the Juxta glomerular (JG) cells of the kidneys. When blood pressure falls prorenin is split and renin released. Renin enters the circulation from the JG cells in the kidneys and acts enzymatically on angiotensinogen (plasma protein) to release angiotensin I [7, 20, 21]. The renin persists for 30 minutes to an hour and continues to cause formation of more angiotensin I. From angiotensin I, angiotensin II is formed and this formation takes place entirely in the lungs as the blood flows through the small vessels of the lung by an enzyme namely converting enzyme (ACE). Angiotensin II is a potent vasoconstrictor and it will therefore increase arterial pressure via arteriolar constriction [7].

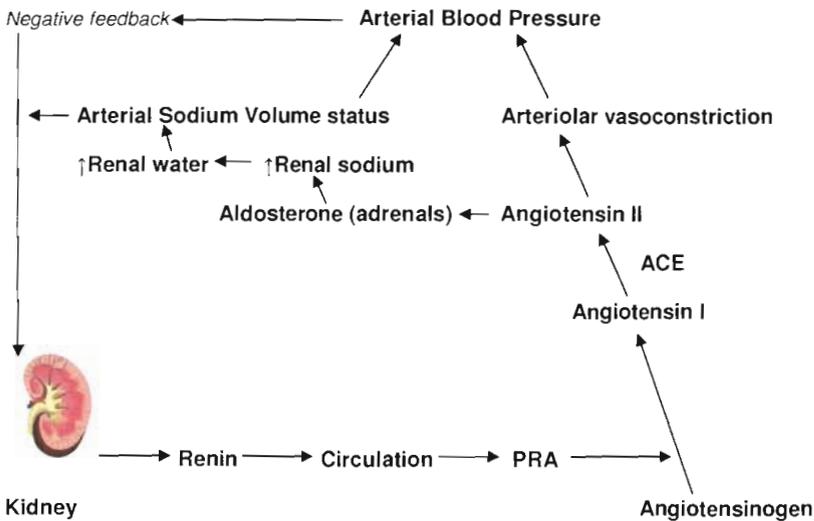


Figure 1 The renin-angiotensin system in normal blood pressure control [20, 21].

Angiotensin II also stimulates the release of aldosterone by the adrenals to increase sodium retention. The higher extracellular sodium concentration also cause an increase in water retention (dilution effect) which changes the sodium-volume status of the vascular system. Too large increase in arterial blood pressure or vascular volume will have a negative feedback influence on the kidneys to secrete less renin and increase excretion to obtain a normal blood pressure in the long term [7, 20, 21].

3.1 The development of low renin normotension

Low renin normotension (see figure 2) is a forerunner of low renin hypertension where the kidneys retain more sodium [21]. This causes an increase in arterial sodium- volume and eventually will lead to an increase in arterial blood pressure. The increase in blood pressure and volume will cause the kidney (via negative feedback) to secrete less renin and this will cause less angiotensin II which will prevent the blood pressure to increase over the long term. The lower activity of the renin-angiotensin system buffers the extracellular fluid volume effect and prevent the blood pressure from rising [21].

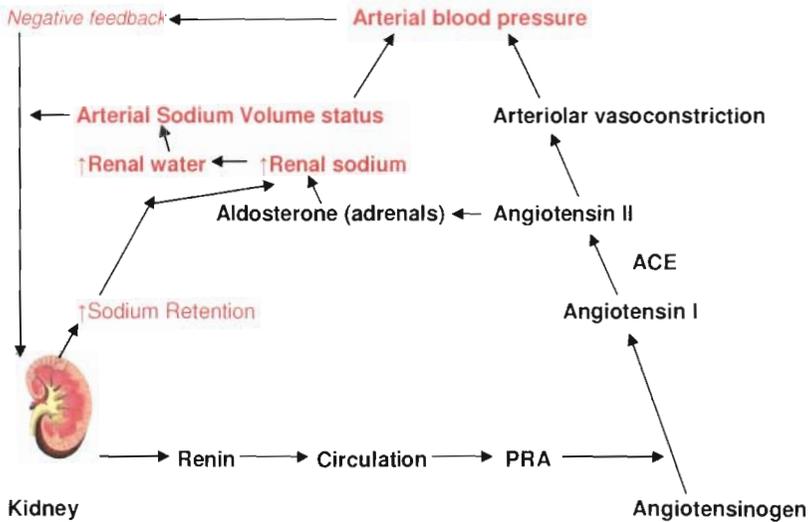


Figure 2 The renin-angiotensin system in the development of low renin normotension [20, 21].

3.2 The development of low renin hypertension

However the blood pressure does not stay normal as the sodium retention still increases (see figure 3). This higher blood pressure can exert no further influence on the kidney via negative

feedback because the renin secretion is maximally suppressed and so high blood pressure with low renin develops [21].

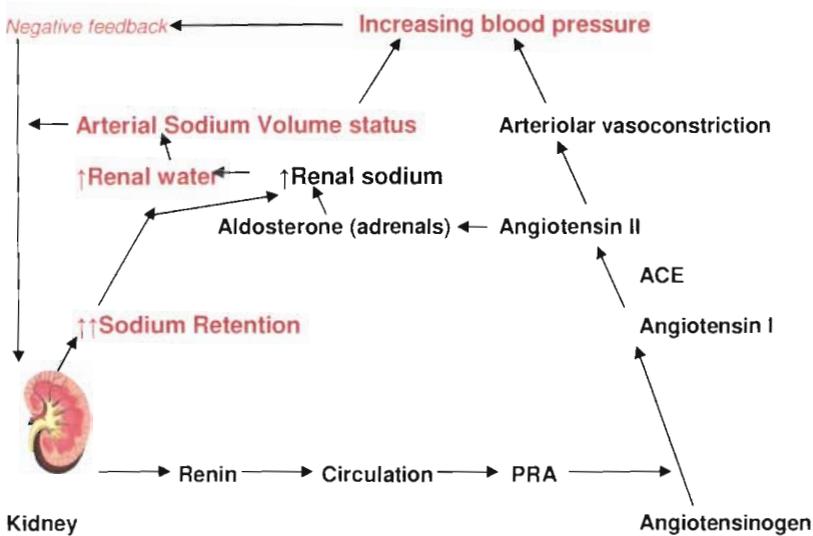


Figure 3 The renin-angiotensin system in the development of low renin hypertension [20, 21].

3.3 The development of renin dependent hypertension

The 2 million nephrons in the kidneys work together in order to maintain normal glomerular filtration rate (see figure 4) [21]. This is accomplished by each nephron to increase its renin secretion when the blood pressure falls and decrease the renin secretion when the blood pressure rises. In hypertensive patients the nephrons become ischemic and this causes the blood pressure and glomerular filtration rate to fall in the nephrons [21]. In order to correct the under perfusion the nephrons secrete more renin. As plasma angiotensin II levels rise and consequently hypertension develops, the remaining normal nephrons become over-perfused and try to compensate by turning off the renin secretion but to no prevail [21].

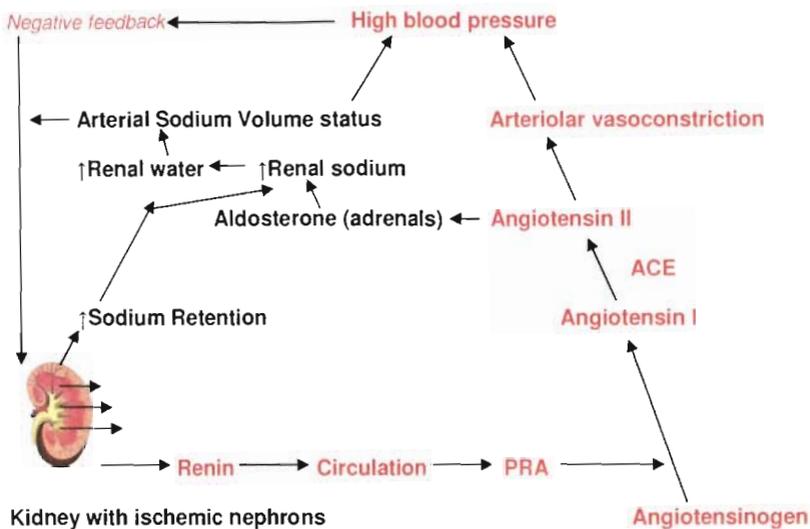


Figure 4 The renin-angiotensin system in the development of renin hypertension [20, 21].

3.4 The Laragh Method® – Two subtypes of hypertension

There are two forces namely: body salt and plasma renin that work together to determine the long-term blood pressure and tissue blood flow [21, 22]. When looking at the antihypertensive treatment one realizes that most antihypertensive drugs act either by reducing body salt or plasma renin levels [21, 22].

1. Arterial sodium-volume (V)- sodium chloride (body salt) determines the amount of water in the body and high blood pressure can develop if the kidney fail to excrete salt (see figure 3 [21]. This type of hypertension is called V hypertension because the body sodium-volume increases. It is also characterized by low renin because the kidney react

to the high arterial pressure and volume causing the high blood pressure by suppressing renin secretion [21].

2. Renin-angiotensin dependent hypertension (R) - Normally there are multiple sources of renin from the one million nephrons within each kidney and their combined secretion rate of renin leads to plasma levels of renin just enough to produce angiotensin II to constrict the arterioles and maintain normal perfusion pressure to each nephron [21]. Renin dependent (R) hypertension is related to V hypertension and R hypertension develops when circulating renin levels do not fall enough when the sodium-volume expands as described in (1) above [21]. Renin dependent hypertension develops when a few nephrons become ischemic and then try to correct their under perfusion by increasing their secretion of renin. As the angiotensin II levels rise and hypertension develops the remaining normal nephrons become over-perfused and try to compensate by turning off their renin secretion, but to no avail. The plasma renin levels become too high for the body sodium-volume content and the arterial blood pressure rises. Patients with R hypertension have medium to high plasma renin levels [21]. R hypertension develops when renin secretion cannot be suppressed to a rate that is appropriate for the current level of arterial sodium-volume [21]. Normal blood pressure is maintained by the relationship between arterial sodium-volume (V) and plasma renin (R).

3.4.1 The Laragh equation

By making use of Poiseuille's Law ($BP=CO \times TPR$), where BP is the blood pressure (i.e., the "force" generated by the heart), CO is the volume delivery of the heart and TPR is the total peripheral resistance of the arterioles. One of these two cardiovascular determinants (either volume or vasoconstriction) must change for blood pressure to change because the body salt (sodium chloride) content determines the arterial blood volume (V) and the plasma renin levels determine the size of the arterial space (R) via angiotensin II [21, 22]. If one substitutes CO by V and TPR by R, the blood pressure equation then becomes:

$BP=V \times R$ and $V=BP/R$. BP can be measured, plasma renin levels can be determined (lately with very sensitive test kits) and from this formula it is now possible to determine the sodium-volume component from the BP and renin levels [21, 22]. For a given BP, the arterial sodium-volume is reciprocally related to renin levels.

3.5 The interaction of V and R

The plasma renin levels fall to protect the normal blood pressure level for any increase in body sodium-volume content and also reciprocally the plasma renin levels rise to protect blood pressure from falling too low when there is a fall in body sodium-volume. There is an inverse relationship between V and R in a vast spectrum of clinical hypertensions (see figure 5).

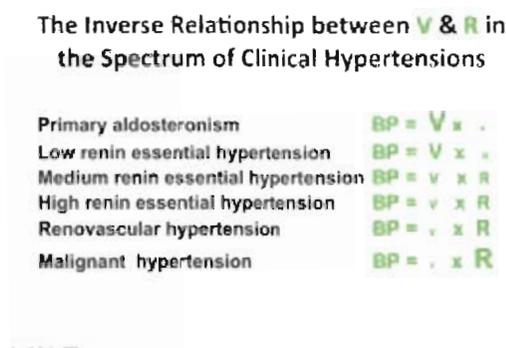


Figure 5 The inverse relationship between V and R in a spectrum of clinical hypertensions [21, 23].

For instance in patients with primary aldosteronism, the patients have a large volume component and small renin component whereas in patients with malignant hypertension, the patients have a large renin component and a small volume component [21, 23].

In patients with the R hypertension more vascular injury is encountered than in patients with volume mediated hypertension (see figure 6) [24].

The Renin-Angiotensin-Aldosterone Template for High Blood Pressure and Vascular Injury

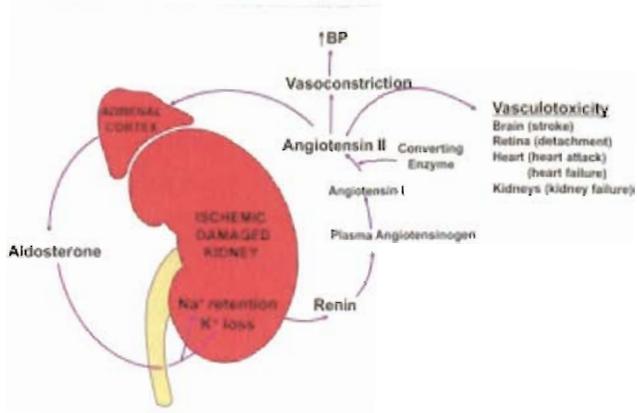


Figure 6 Vascular injury due to high plasma renin levels [21, 24].

The high renin levels in patients with the R hypertension could be toxic to the vasculature and may be one of the causes of stroke, retinal detachment, heart attack and eventually heart failure and kidney failure [21, 24]. Vascular damage can be detected with the SonoSite MicroMax apparatus (see figure 7 and 8) and a thickened intima media is indicative of vascular damage.

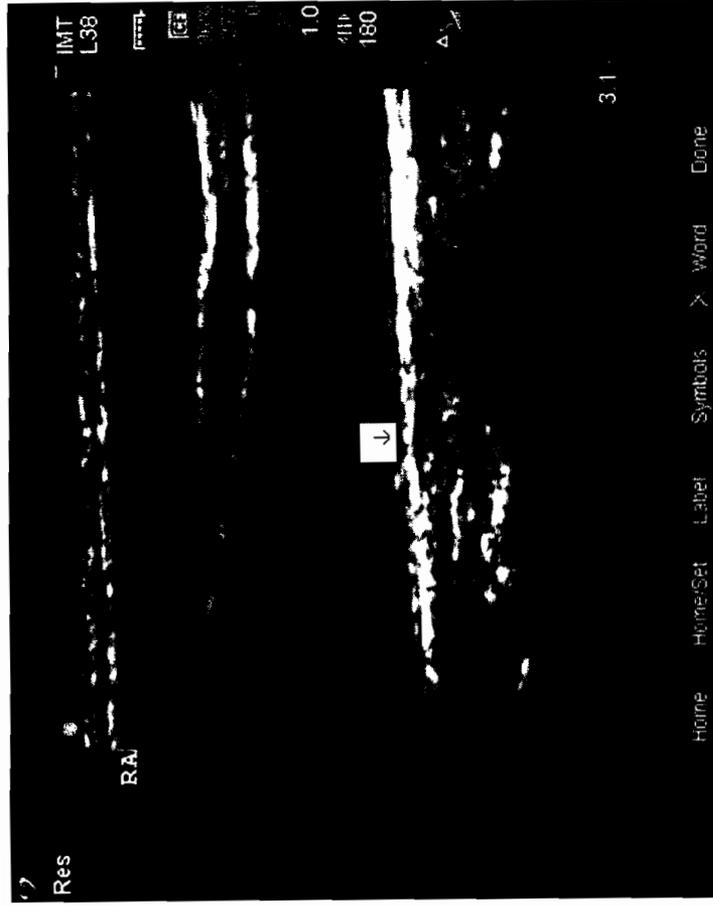


Figure 7 Normal sonar recording of the carotid artery to show the intima media.

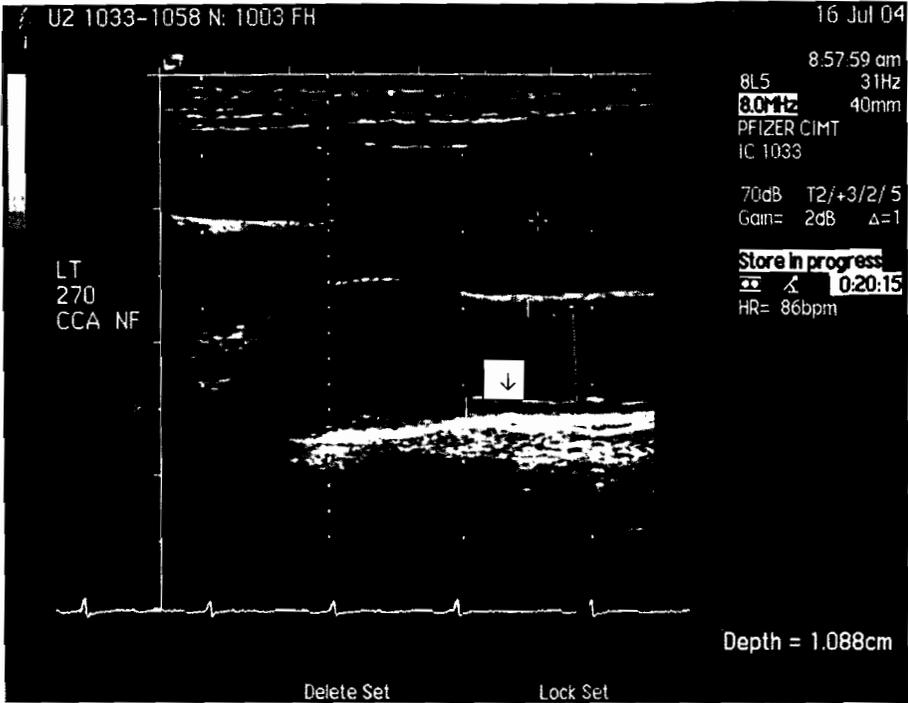


Figure 8 A sonar recording to show the thickened intima media with vascular damage.

3.6 Low renin hypertension in blacks

Opie and Seedat, 2005 [3], described that low plasma renin might be one of the causative factors of hypertension in Sub-Saharan black populations and ascribed the differences in renin levels to be environmental in origin. The trend towards low renin values is also ascribed to abnormalities such as excessive sodium renal reabsorption [3, 25, 26] and to genetic abnormalities in the renin-angiotensin system or related genes [3].

In black participants from the SABPA study (unpublished results) it is shown from figure 9 that the ambulatory systolic and diastolic blood pressure (day values) are in the hypertensive range (ESH guidelines) [6] but the blood pressure did not differ in the low - and high renin participants. The heart rate is significantly higher (82 vs. 92 beats/min) (higher sympathetic activity) in the high renin group and the sodium-potassium ratio is significantly higher in the low renin group

which is indicative of higher sodium retention in the low renin group. The volume component for the low renin participants is significantly higher (45.9 vs. 12.5) compared to the high renin participants. From figure 10 it is evident that no vascular damage (stiffness or atherosclerosis) can be encountered because the carotid intima media thickness and the pulse wave velocity are in the normal range. The albumin-creatinine ratio (1.45 vs. 3.06 mg/mmol) is significantly higher in the high renin group. Although the albumin-creatinine ratio is still within normal limits in the high renin participants it already shows albuminuria, a marker of kidney damage probably as a cause of the high renin.

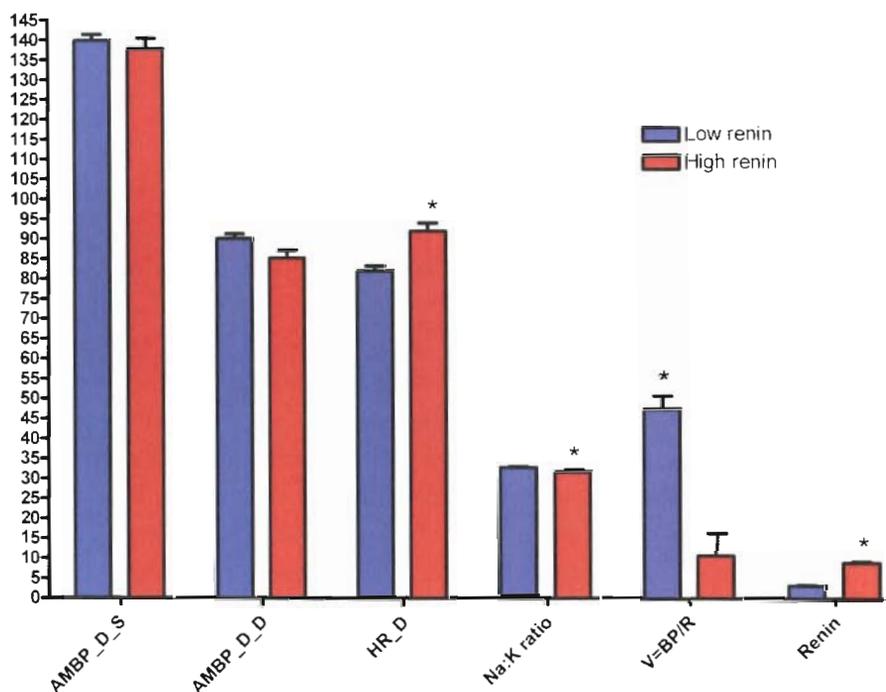


Figure 9 Cardiovascular variables in low and high renin participants. AMBP_D_S, AMBP_D_D = Systolic and diastolic ambulatory day blood pressure (mmHg), HR_D = day heart rate (beats/min), Na:K = Sodium-potassium ratio (mmol/l), V=BP/R is the volume component of the vasculature, renin (pg/ml).

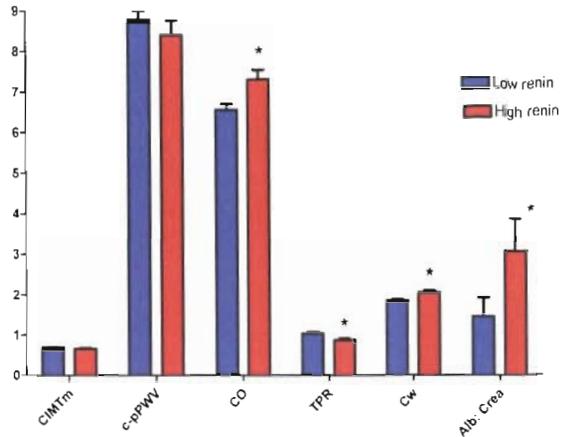


Figure 10 Cardiovascular variables in low and high renin participants. Where CIMTm = Mean carotid intima media thickness (mm), c-pPWV = carotid-pedalis pulse wave velocity (m/sec), CO = cardiac output l/min, Cw = Windkessel compliance (ml/mmHg) and TPR = total peripheral resistance (mmHg/ml/s), Alb: Crea = the albumin-creatinine ratio (mg/mmol).

After applying the Laragh equation ($V=BP/R$) [21] or the volume-vasoconstriction model to the SABPA data it is shown that 78% of the black hypertensives were in volume (V) – and 22% in renin (R) hypertension. Normally in Caucasians a third of patients with hypertension have low plasma renin levels [25]. From the literature [27] it is evident that in black children an early volume loading hypertension could be detected which may participate in hypertension in later life.

The blood pressure of most participants were also not under control despite treatment for high blood pressure because most participants received R drugs like ACE inhibitors and not V drugs (78% have V hypertension).

4 Summary and concluding remarks

Hypertension in South Africa is a widespread problem as elsewhere in sub-Saharan Africa and in our region of the North West Province, with a high incidence especially in urbanized people as an outcome of their lifestyle. It is of immense economic importance because of early mortality

and morbidity and because of the severity of its complications. In the endeavor of our research (HART) we researched the risk factors like urbanization, psychosocial stress in adults and in black children, stunting in children, the influence of obesity and adipokines on vascular function in normal - and hypertensive blacks as well as the role of the sympathetic nervous system (SABPA study) in the pathophysiology of hypertension. After application of the Laragh method on the SABPA data it is evident that the role of the old dog renin was underestimated in the pathophysiology of hypertension in blacks in South Africa. Two subtypes of hypertension namely volume hypertension and renin hypertension were encountered in the black population of the North West Province of South Africa and this may have implications in the treatment of hypertension in the future because they may react differently on different drugs. Some would react better on the volume drugs and some on the anti-renin drugs. Hypertension is not under control in our region because from the SABPA data 78% of men (mean age=43 years) and 57% of women (mean age=45 years) are hypertensive and 25% of men and 17% of women are under treatment (unpublished results). Despite treatment their BP values are still high and most participants under treatment received ACE inhibitors (anti-renin or R drug) and 78% of them have volume (V) hypertension indicating the wrong medication [25].

What I suggest as a routine regimen for the prospective Hypertension Clinic of the Faculty of Health Science of the North-West University is to do a renin profile on every patient in order to establish whether the individual patients are in volume or in renin hypertension and definitely this assessment of the role of renin in the pathophysiology of hypertension will give new bite in the endeavor to get hypertension under control in the South African population.



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