EDITORIAL

ESSENTIAL HYPERTENSION: A RENAL PERSPECTIVE

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As early as 1836, Richard Bright had observed that "the kidney is the chief promoter of the other derangements.... including..... hypertrophy of the heart." At that time blood pressure (BP) was not measured and even though we know that many of Bright's patients had chronic glomerulonephritis (GN) the concept that kidney disease had systemic consequences involving the cardiovascular system was expressed more than 150 years ago[1].

In the United States of America (USA), 22.1 patients per million population[2] have end stage renal failure (ESRF) with hypertension (HPT) listed as a primary cause; in Australia it is 3.6 patients per million population[3] and in Singapore, 1.8 patients per million population[4]. Traditionally it is taught that Benign Essential HPT does not give rise to renal failure, unless it undergoes an accelerated phase and behaves like malignant HPT. In Singapore, 13.6% of the population of 3 million (408,000 people) have essential HPT, and yet only 5.4 patients have malignant HPT, in contrast to the USA where the rate of HPT causing ESRF is 12 fold higher than in Singapore and 6 fold higher than in Australia.

Hypertension (Hypertensive nephrosclerosis) accounts for 24% of ESRF in USA[2], 9% in Australia[3] and about 5% in Singapore[4]. In fact, HPT nephrosclerosis causes 40% of ESRF in African-Americans and 25% of ESRF in the US white (the latter mainly in patients more than 65 years old). The black:white ratio is 20:1 for the group from 25 to 45 years of age. It is possible that among the patients with HPT nephrosclerosis in the USA, that some could be due to glomerulonephritis, because some of these patients do not truly have HPT as the primary cause, some had renal artery stenosis and others had microscopic haematuria presumably due to glomerulonephritis[3]. The low renal biopsy rates in the USA also makes accurate diagnosis and disease categorization in the USA more difficult. But even allowing for these factors, patients in the United States still have higher risks of developing ESRF due to primary HPT.

There is now evidence that essential hypertension results from an inherited renal tendency towards excessive vasoconstriction or an inability to appropriately increase renal blood flow. Studies of African-Americans show that their hypertension is seen at an earlier age, increases more quickly with time, has a higher prevalence, is more severe and is associated with more adverse cardiovascular and renal effects; excluding primary atherosclerotic disease[3].

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Whilst everyone is agreed that renal hypertension whether resulting from GN or other forms of diseases involving the kidneys like diabetes mellitus (DM), systemic lupus erythematosus (SLE), chronic pyelonephritis, renal stones or renal artery stenosis is a renal disease, many would disagree that primary hypertension (HPT), whether benign essential or malignant HPT is a renal disease. But there is now a school of thought which believes that for every condition where the patient has hypertension, there has to be a primary renal basis and this includes primary or essential HPT. In other words, the origin of HPT springs from within the kidney. This is the Guytonion Nephrocentric Approach[5].

Luke[6] in a recent review accrued evidence to support the theory that Essential Hypertension is a renal disease. Such evidence can be obtained from five areas :

I. Transplantation of HPT or normotension with the kidney.
II. Pre hypertensive evidence of abnormal renal vascular response.
III. Epidemiological association of a high intake of sodium chloride with HPT.
IV. Cyclosporine-induced HPT as a model for essential HPT.
V. Lack of prevention to date of end stage renal disease (ESRD) due to hypertensive nephrosclerosis despite widespread availability of anti-hypertensive therapy.

I. Transplantation of a normotensive kidney "cures" Essential HPT.

In a study from Alabama[7], six patients, all African-Americans, all nephrectomised and had diagnosis of essential hypertension from clinical history and careful study of the removed kidneys, were selected. HPT was in "remission" at mean time of 5 years after transplant in all 6 patients. They also had documentation of regression in left ventricular hypertrophy and hypertensive retinal changes.

This observation suggests that HPT associated with hypertensive nephrosclerosis, like primary renal disease, remits after successful transplantation of an allograft in the absence of allograft chronic rejection, transplant renal artery stenosis or native kidney hypertension. Normotension continues for a long time after transplantation in these patients, provided renal function is maintained. These patients whose HPT and hypertensive disease remitted after successful renal transplant also demonstrated normal renal handling of sodium and normal changes in plasma renin activity (PRA) in response to normal, low and high salt intake.

It is postulated that Essential HPT begins with a functional defect in sodium chloride (NaCl) excretion that is associated with renal vasoconstriction. Renal vasoconstrictors such as angiotensin II (ATII) and endothelin also appear to cause both heightened responses to agonists and eventually nephrosclerosis.

II. Pre hypertensive evidence of abnormal renal vascular response.

Studies of normotensive relatives of patients with Essential HPT have shown increased renal vasoconstriction in response to mental stress and postural changes[8]. Interactions between stress, renal blood flow (RBF) and NaCl retention have also been seen. A European study of normotensive children of parents, both of whom had well established Essential HPT, in comparison with children with matched normotensive parents showed decreased RBF in children of hypertensive parents[9].

III. The role of sodium chloride intake.

The enhanced ability to conserve salt by renal mechanisms in a high temperature and very low salt environment (about 9 mEq/day of sodium) was a Darwinian advantage for the African ancestor but it need not necessarily be a good thing in our modern context.

Enhanced renal salt conservation on a low salt intake might well be associated with decreased ability to excrete a salt load. In African-Americans, a salt load is less efficiently excreted than in Caucasians as a group. Subtle salt retention on a high salt intake would lead initially to HPT with a high extracellular fluid (ECF) volume, high cardiac output and normal peripheral resistance.

Only 50% of all patients with Essential HPT show a reduction in BP on a lowered NaCl intake even though group means fell significantly. This may be related to the state of HPT (those patients with irreversible vascular changes are less likely to respond) or to different pathophysiological mechanisms for HPT including the renin-angiotensin system.

IV. Cyclosporine-induced hypertension as a model for Essential Hypertension

Cyclosporine A (CyA) in small doses reproducibly causes renal vasoconstriction after every oral administration of the drug. The glomerular filtration rate (GFR) is well maintained in the initial reversible stage of vasoconstriction but nephrosclerosis eventually occurs with a fall in GFR because of irreversible glomerular sclerosis.

In the USA, the Medicare programme initially did not pay for CyA after renal transplant. Fourteen patients had excellent renal function at approximately 10 months after transplant and had to discontinue therapy for financial reasons[10]. Renal blood flow rose and BP fell as patients were switched from CyA to azathioprine over a few weeks. HPT associated with CyA is renin dependent because BP did not fall when patients were on a low salt diet.

Renal conservation of sodium in CyA treated patients is enhanced and excretion of a salt load diminished. This is associated with predominantly afferent arteriolar vasospastic effect. Initially this is reversible, but later, over years, it becomes irreversible and associated with nephrosclerosis. There is benefit from the use of calcium channel blockers as compared with converting enzyme inhibitors in maintaining GFR, because CyA induces synthesis of endothelin by cultured human endothelial cells and calcium channel blockers can inhibit this effect. CyA binds to at least two cytosolic proteins and increases cytosolic calcium concentration.

CyA is therefore a new and iatrogenic form of HPT. It is very much like Essential HPT and can be said to be a "compressed-in-time model of Essential HPT". In both Essential HPT and CyA HPT, renal vasoconstriction precedes HPT and nephrosclerosis. There is a 10% prevalence of ESRD at 10 years after cardiac transplantation on CyA treatment. CyA offers a compressed-in-time model for Essential HPT.

V. Lack of prevention of ESRD due to Primary Hypertension.

Several retrospective studies have shown no evidence of renal protection by apparently effective anti-HPT therapy especially in African-Americans[11]. Walker and co-workers[12] demonstrated protection of renal function in white but not in black subjects. These study showed that even "moderate" primary Essential HPT can lead to ESRD especially in Blacks. Why is it that there is no protection for Blacks? There are two reasons for this. Firstly, it has been found that Blacks have inadequate potassium intake in their diet, permitting arteriolar and intimal and medial wall thickening. Secondly, Blacks have an impaired ability to excrete a sodium load. This is due to a genetic defect[6, 13].

Hypertension in Renal Parenchymal Diseases

1. Glomerulonephritis

The most common cause of renal failure worldwide is glomerulonephritis. HPT occurs in about 50% of these patients. The frequency of HPT ranges from 34% for those with normal serum creatinine to 80% for those with elevation of serum creatinine[12]. In glomerulonephritis, salt and water retention leads to increased plasma and extracellular fluid volume with increased cardiac output and increased peripheral resistance. In IgA nephritis, the commonest form of glomerulonephritis in Singapore, HPT occurs in 23% of patients[14].

2. Diabetic nephropathy

This is a common cause of ESRD throughout the world. In the USA it is the commonest cause of ESRD and in Singapore, the second commonest cause of ESRD[4]. HPT occurs in 30% to 80% of patients. Insulin resistance may mediate HPT in the hypertensive diabetic. Increased intracellular calcium availability is another cause for HPT.

3. Adult polycystic kidney disease

This autosomal dominant renal disorder is associated with HPT in 50% to 75% of patients. Increased sodium retention and elevated plasma renin assay cause HPT. HPT may also be attributed to increased production of renin by renal cysts directly or because of the ischaemia they produce.

4. Reflux nephropathy

HPT occurs in 30% to 70% of adults with reflux nephropathy. This is mediated through the renin angiotensin system. Such patients have high plasma renin assay.

5. Analgesic nephropathy

This condition is characterised by renal papillary necrosis and renal failure following heavy ingestion of analgesics. It is more common in Australia, comprising 14% of ESRD but is uncommon in Singapore. HPT occurs in 75% of patients and contributes to their high cardiac and vascular complications. The renal salt wasting in these patients causes intravascular depletion and stimulates the renin angiotensin system causing HPT. The high incidence of generalised atheroma also causes renal artery stenosis leading to HPT.

Conclusion

The renal origin of essential hypertension as discussed in this review paper, mainly the hypothesis of Luke[6], is only one of several hypotheses for the aetiology of essential hypertension and none is currently exclusive or conclusively proven. Essential hypertension is probably determined by multiple genetic factors. Race has an important impact. Many interrelated mechanisms contribute to control of blood pressure. The relative importance of salt intake, sympathetic nervous system, renin-angiotensin system, vascular reactivity, neurogenic factors, renal factors as well as environmental factors like stress, physical activity, diet and alcohol; all these may play a role in determining whether an individual develops essential hypertension.

Even though hypertension is a common cause of renal disease, by itself, Essential Hypertension is an uncommon cause of end stage renal failure, except in the African-American. However, the presence of HPT confers a worse prognosis in patients with parenchymal renal diseases by contributing to the progression of the disease.

Appropriate treatment of HPT retards the progression of chronic renal failure. It must be appreciated that uncontrolled hypertension, whether in patients with benign essential hypertension or secondary hypertension from whatever cause, can lead to accelerated hypertension which behaves like malignant hypertension and can lead to kidney failure.

References

1. Bright R. Tabular review of morbid appearance in 100 cases connected with albuminous urine. Guy's Hosp Review 1836; 1:380-410.
2. Whelton PK, Klag MJ. Hypertension as a risk factor for renal disease. Hypertension 1989; 13 (Supple 1): 19 - 27.
3. Disney AP. Australia and New Zealand Dialysis and Transplant Registry, 16th Report, 1993, Issue No. 727-3738, Woodville: Queen Elizabeth Hospital. 1993
4. Woo KT. Renal replacement therapy in Singapore in dialysis therapy in the 1990s. In Contribo Nephrol 1990; 82: 6-14.
5. Guyton AD, Manning RD Jr, Hall JE, Norman R, Young DB, Pan YJ. The pathogenic role of the kidney. Cardiovas Pharmacol 1984; 6: 5151-61.
6. Luke RG. Essential hypertension: A renal disease? Hypertension 1993; 21:380-90.
7. Curtis JJ, Luke RG, Dunstan HP. Remission of essential hypertension after renal transplant. N Engl J Med 1983; 309: 1009-15.
8. Hollenburg NK. The kidney in the pathogenesis of hypertension: a prologue. Am J Kidney Dis 1985; 5:A2-A4.
9. Van Hooft IM, Grabbee DE, Derkx FHM, de Leeuw PW, Schalekamp MADG, Hofman A. Renal hemodynamics and the renin-angiotensin-aldosterine system in normotensive subjects with hypertensive and normotensive parents. N Engl J Med 1991; 324: 1305-11.
10. Curtis JJ, Luke RG, Dubovsky E, Whelchel JD, Diethelm AG, Jones P. Cyclosporine in therapeutic doses increases renal allograft vascular resistance. Lancet 1986; 2. 477-9.
11. Rostand SG, Brown G, Kirk KA, Rutsky EA, Dustin HP. Renal insufficiency in treated essential hypertension. N Engl J Med 1989; 320: 684-8.
12. Walker WG, Neaton JD, Cutler JA, Neuwirth R, Cohen JD. Changes in serum creatinine in hypertensives participates in the Multiple Risk Factor Intervention Trial (MRFIT): Evidence that lowering blood pressure protects renal function in mild to moderate hypertension. JAMA 1992; 268: 3085-91.
13. Brown MA, Whitworth JA. Hypertension in human renal disease. Hypertension 1992; 10: 701-12.
14. Woo KT, Wong KS, Lau YK, Chiang GSC, Lim CH. Hypertension in IgA nephropathy. Ann Acad Med Singapore 1988; 17: 583-8.