

Hypertension and renal disease: mechanisms and treatment

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INTRODUCTION

Despite the voluminous accumulation of data and the general consensus that hypertension and cardiovascular diseases are the commonest causes of death in the renal patient, it has been difficult to achieve control of blood pressure and reduce the incidence of high blood pressure related death in patients with end-stage renal disease (ESRD)^{1,2}. Although successful renal transplantation can lead to blood pressure control and restoration of haemodynamic stability, hypertension problems still abound even in this select group, as they do in patients on other renal replacement modalities such as peritoneal and haemodialysis^{3,4}.

THE HIDDEN PROBLEM

Hypertension is unlike other conditions in which detection, prevention and treatment are possible in large groups of people (such as vaccination for specific diseases) because the populace can readily understand and see the adverse effects of the disease (measles, chicken pox, smallpox) and suffer the consequences (congenital malformations and

mental retardation in German measles) in their children and relatives. Hypertension differs in that it does not show. It continues to be an elusive medical concept for lay people and for many physicians, its effects hidden until it is too late and, even at that point, not necessarily externally appreciable. Voluntary groups, such as the American Heart Association and the National Kidney Foundation, governmental agencies such as the NIH and the Centers for Disease Control (CDC) in the USA and national leagues against hypertension around the world and the International Society of Hypertension, have mounted only partially successful campaigns to alert the public to the hypertension problem. Even with the pharmaceutical industry intervention (and legislatures that have permitted it) in directly making the public aware of the public health threat that hypertension represents, it has been difficult to detect and properly control hypertension in those who suffer it.

Part of the problem may be confusion among physicians as to which drugs to use in the treatment of hypertension and the consequences of untreated or poorly treated high blood pressure. The periodic JNC hypertension reports notwithstanding, part of the confusion comes from hypertension experts, many of whom are, one way or the other, linked to the interests of the pharmaceutical emporiums. Many papers have attempted to downplay the beneficial aspects of low cost drugs, such as diuretics, and remain as testimony to attempts to enhance the use of more expensive medications whose long term effects are indistinguishable from those of the less expensive

varieties. In these controversies, contrary to what is to be expected from clinical scientists and physicians with a scientific background, people take sides as if drugs were a political party or a campaign promise, instead of a tool to improve public health.

■ PHARMACOLOGICAL AND OTHER THERAPIES

Be that as it may, dependence on the use of drugs stems from several factors. Some people do not respond well to the medication while others have their physicians change their prescription because of side effects. Yet others must depend on them because of their inability to modify their bad habits – so called “life style” – and are unable to follow good, salubrious instructions and resist self-indulgence. Obesity leading to insulin resistance and poor nutritional habits of too much dietary fat and carbohydrates, which compound the problem of insulin resistance, are clearly contributing to the world-wide increase in obesity, type two diabetes mellitus and hypertension⁵.

Many of the patients who suffer from these problems are finally received by renal replacement units as a consequence of diabetic and hypertensive renal complications. The need for a healthy relation between physician and patient is achieved only partially, which results in failure of the treatment of hypertension and control of diabetes, in great part because of poor control of extracellular volume.

■ THE PATHOPHYSIOLOGICAL PROBLEM

■ Volume regulation

Although the role of extracellular volume in the regulation of blood pressure and generation of hypertension has been inferred and accepted for a very long time, absolute proof of its role in blood pressure control comes from the discovery that a series of monogenic disturbances affecting the regulation of extracellular volume result in either low or high blood pressure. The work of Lifton and his collaborators⁶⁻⁸ has established that enhanced action of salt retaining mineralocorticoids is responsible for

volume dependent hypertension that can be treated or abolished by correcting extracellular volume. Thus, conditions such as Liddle's Syndrome (hypertension, hypokalemia and metabolic alkalosis) caused by unbridled sodium reabsorption through an open amiloride sensitive epithelial sodium channel, is curable by transplantation of kidneys not bearing the defect or controlled by amiloride. In contrast, Bartter Syndrome, wherein a defect in chloride transport in the thick ascending loop of Henle leads to hypovolaemia and hypokalemia as a result of increased sodium delivery to the sodium-potassium exchange sites in the distal tubule and collecting ducts, is characterised by low blood pressure and metabolic alkalosis, a consequence of eventual exchange of sodium for protons (H⁺), therefore, aberrant acidification of the urine despite the systemic accumulation of bicarbonate. These monogenic examples (there are others^{9,10}) of hypo or hypertension clearly establish the important role of salt retention and salt depletion in the development of hypertension and speak volumes in favour of the control of volume for the maintenance of normal blood pressure. Moreover, in the classical model of renin-angiotensin-aldosterone dependent hypertension, the two kidneys-one clip Goldblatt model, the early phase of hormonally dependent blood pressure elevation is followed by one where extracellular volume is expanded and renin falls in response to the restoration of NaCl delivery to the macula densa, its normal feedback¹¹.

Evidence for the critical role of volume in end-stage chronic renal failure can be gleaned from a series of experiments which have established without a doubt that it is possible to control and basically abrogate high blood pressure with dialysis prescriptions that concentrate on more frequent treatment schemes to reduce extracellular volume in a moderate but consistent way until a level is achieved that removes the hypertensive stimulus, reduces the number of medications needed to effect hypertension control or totally abolishes the need for pharmacological intervention^{12,13}. Long slow haemodialysis, daily dialysis for short periods of time, nocturnal haemodialysis or, more effectively, dietary salt and fluid restriction with reduction in dialysate sodium concentration, help achieve blood pressure control the best. Careful avoidance of so-called J-curve effects is mandatory. This occurs when blood pressure is reduced to levels that cannot sustain

pressure-flow relationships leading to problems of tissue perfusion, including myocardial perfusion¹⁴. Morbidity and mortality under these conditions increase with mortality from heart and cerebrovascular disease leading the pack.

■ Renin-angiotensin-aldosterone system (RAS) and the tissue effects of angiotensin II

There may be, however, a point of no return for ESRD patients whose hypertension has gone from being volume dependent to becoming hormonally mediated by endocrine, paracrine, autocrine and intracrine effects of various hormones, particularly angiotensin II (A II)¹⁵. The proven blood pressure lowering response of A I converting enzyme inhibitors and A II receptor blockers in a variety of patients, including those with ESRD, indicates the importance of the RAS in mediating at least part of the mechanisms leading to hypertension. Nevertheless, it is increasingly clear that changes in cellular function of organs, including the kidney and the vasculature function, seem to be independent of the effects of the blood pressure lowering-effects of these agents and responsible for a wide constellation of morbid events.

Through actions mediated upon binding to its AT₁ type specific receptors A II influences the regulation of salt and water balance and volume control. In addition, it exerts direct and indirect actions on peripheral resistance by influencing vascular smooth muscle tone. It accomplishes this by regulating the synthesis and secretion of vasoactive hormones such as vasopressin, norepinephrine and endothelin. On the other hand, hormonal actions *per se* and pressure elevation damage endothelial cells, leading to their permanent inability to produce vasodilatory substances such as nitric oxide. Moreover, it is clear that angiotensin II continues to exert noxious actions on organs and their blood vessels, particularly the microvasculature, by leading to smooth muscle hypertrophy and fibrosis.

A II induces a variety of genes and excessive production of the proteins for which they encode. Excess extracellular matrix deposition is stimulated by the induction of the TGF β gene and its proteins^{16,17}. Actions of angiotensin II are also key in the reduction of the breakdown of extracellular matrix through the actions

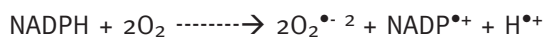
of plasminogen activator inhibitor 1 (PAI-1) that also prevents the transformation of tissue metalloproteinases, which are potent ECM degradation enzymes from latent to active forms by blocking plasminogen in plasma¹⁸. Although these alterations have possibly their greatest effects on renal interstitial tissue, most other organs studied, e.g. the liver, also undergo the castigating effects of collagen deposition leading to A II-induced fibrosis. Furthermore, it is apparent that the octopeptide induces PAI-1 gene expression in rat aortic smooth muscle cells specifically through the AT₁ receptor since the specific inhibitor candesartan blocks the response¹⁹. Candesartan also blocks the induction of PAI-1 mRNA by A II in neonatal rat cardiomyocytes, and in aortic and cardiac tissue of rats infused for three hours with A II. Of considerable interest in relation to continued damage to vascular structures and target organs in hypertensive animals is the fact that spontaneously hypertensive rats as compared to normotensive Wistar-Kyoto exhibit dramatically increased PAI-1mRNA expression in the aorta and the heart that can be sharply reduced by candesartan treatment. By contrast, the drug did not alter PAI-1 mRNA expression in WKY rats. The role of PAI-1 induction in the fibrosis is critical and it has been shown that subpressor doses on A II do not induce the parenchymal fibrosis in PAI-1 knockout mice observed in wild type mice.

PAI-1 is an important regulator of tissue metalloproteinases (MMP), a series of metzincin proteases whose primary actions are ECM degradation and remodelling. Secreted as latent, inactive zymogens by various stromal and epithelial cells (mesenchymal, T-cells, monocytes, macrophages, neutrophils, keratinocytes and tumor cells), when activated in the pericellular and extracellular space they breakdown matrix and allow cells to move onto the created spaces. In this proteolytic process, specific ECM protein fragments are created that results in altered activities of signalling molecules and regulates tissue architecture. Although MMP are responsible for normal tissue turnover, particularly in kidney, they can be activated by PAI-1, a response that can lead to excessive breakdown of ECM with the attendant migration of inflammatory cells into interstitial spaces and its consequences. Contrariwise, stimulation of tissue inhibitors of metalloproteinases (TIMPs) counteracts the ECM deposition regulation by MMPs and the result is exaggerated lay down of matrix and collagen, leading to fibrosis. All interstitial spaces can be affected by this

sequence of events, with blood vessels suffering wall thickening and loss of elasticity leading to new or worsening organ dysfunction.

■ Oxidative damage

Abnormal regulation of extracellular matrix is not the only mechanism by which angiotensin II can damage blood vessels and tissues²⁰. Widely accepted evidence exists for the oxidative powers of angiotensin II which are mediated through reactive oxygen species (ROS) that interact with NADH/NAD(P)H oxidase generating superoxide anion by the reaction:



Superoxide reacts with nitric oxide (NO) to produce peroxynitrate, a compound that has enormous capacity to oxidize and damage tissues such as the endothelium²¹. Damage to endothelial cells by ROS leads to reduced production of the vasodilator NO and enhanced secretion of other vasoconstrictors such as endothelin, the combined effect of which results in fibrosis from the deposition of excess matrix and inflammation²².

The combination of excess extracellular volume, increased vessel thickness and enhanced secretion and response to vasoconstrictor agents together with the lack of vasodilator effectors as a consequence of A II actions leads to enhanced preload and afterload, thus setting the stage for coronary heart disease and cardiac failure. This is exacerbated in the presence of renal disease, a condition characterised by curtailed and erratic extracellular volume control. It is clear that the chronic renal patient is exposed to not only excess extracellular volume but also to the effects of angiotensin II on blood vessel walls, the heart, the brain, and on what may be left of renal mass.

It would stand to reason that careful follow-up by a nephrologist watchful of control of blood volume and knowledgeable of the effects of angiotensin II in chronic renal disease is the key to improving prognosis and outcomes. Improving chances of survival require appropriate treatment by keeping the patient as close to normal to improve his/her chances of survival and increase the possibilities of successful kidney transplantation.

■ THE TREATMENT PROBLEM

■ Mortality

In a recent study²³ of subjects with chronic renal failure who had started dialysis, cardiovascular causes accounted for the largest percentage of deaths during the first year, but the rate of cardiovascular-related deaths was considerably higher in the first 120 days. Patients who were older or Caucasian, patients with low serum albumin levels at baseline, a catheter access in place at first dialysis, HIV/AIDS, a history of congestive heart failure (CHF), cancer, lung disease, neurologic disease or a psychiatric disorder, or patients who did not visit a nephrologist at least 1 month before initiating HD were at significantly elevated risk for mortality within 120 days of initiating HD. In the subsequent 121 to 365 days, older age, Caucasian race, history of lung disease or a psychiatric disorder and HIV/AIDS remained strongly predictive of mortality. Of the predictors examined, only pre-ESRD nephrology care, HIV/AIDS status, diabetes status, and calcium levels <8.4 g/dl were found to have a statistically different impact on the risk for mortality during the first year of follow-up. Clearly, since diabetes and hypertension account for a large percent of patients on dialysis it is critical to carefully treat and follow these conditions early on before the patient's renal function begins to deteriorate.

■ Peritoneal Dialysis

Long-term renal replacement treatment using peritoneal dialysis has been difficult and fraught with logistical and medical complications. Blood pressure control for patients treated with this therapeutic modality has not been an exception. Multiple linear regression analysis using data from over 200 patients²⁴ on peritoneal dialysis (PD) revealed that while age, duration of hypertension prior to dialysis, and declining residual renal function, expressed as both average of urea and creatinine clearance and residual urine output were independently associated with poor BP control, surprisingly, diabetes was not related to hypertension in this study. It is of interest that neither peripheral oedema nor the dose of erythropoietin was associated with hypertension control. Although initiation of PD resulted in early improvement of hypertension in ESRD, BP control

thereafter deteriorated steadily with time. This was associated with age, duration of hypertension, and declining residual renal function. This suggests that hypertension in ESRD patients is a progressive disease primarily related to falling glomerular filtration rate, the preservation of which might improve BP control and possibly modify cardiovascular risk. Despite the improved mortality frequently shown as a result of anti angiotensin II pharmacological agents (ACE inhibitors and angiotensin II type 1 receptor blockers) the effects of these drugs are independent of changes in blood pressure.

■ Haemodialysis

Conventional haemodialysis (CHD) performed three times a week (3.5-4 hrs per session) is the most accessible and widely used renal replacement therapy in the world. It is evident that this does not even come close to resembling the normal action of the kidneys and that the physiological effects of this therapy fall far short of what endogenous renal function above a glomerular filtration rate one quarter of normal can accomplish. As a consequence, a variant of daily haemodialysis, so-called short daily haemodialysis (SDHD), performed five to seven times per week for 1.5-3 hrs per session, has been used by many for better blood pressure control and quality of life for the kidney patient. An analysis using stringent criteria to choose published papers on the subject and perform a careful analysis of the subject was conducted by Puñal *et al*²⁵. Although there were no randomised controlled trials, SDHD seems to be more effective than conventional dialysis. Patients on daily haemodialysis presented less vascular access problems, better control of hypertension, a reduction in the antihypertensive treatment, better quality of life, lower incidence of ventricular hypertrophy, lower consumption of rHuEPO due to the better control of anaemia and a reduction in the use of phosphate binders as a consequence of the better control of plasmatic phosphorous.

SDHD might improve clinical effectiveness, mainly through a better control of arterial tension and, therefore, a lower consumption of antihypertensive drugs, and a better quality of life than CHD. Nevertheless, earlier analyses of published data by Suri *et al*.²⁶ also detected a tendency for better blood

pressure control, but were unable to reach firm conclusions because of poor design, uncontrolled and non-randomised populations. A prospective, randomised, uniform criteria study is required to reach a firm conclusion on the effectiveness of daily dialysis and its effects on blood pressure and quality of life.

■ Anti-angiotensin II medication

It has been shown in animals that treatment with the ACE inhibitor captopril prevents or reduces L-NAME-induced increase of blood pressure and heart hypertrophy^{27,28}.

Animals receiving simultaneously L-NAME and ramipril were also protected against development of hypertension and myocardial hypertrophy as well as against the deterioration of glomerular filtration rate and renal plasma flow²⁹. Enalapril also inhibited development of both arterial hypertension and left ventricular hypertrophy in NO-deficient hypertension. On the other hand, it failed to prevent ischaemic myocardial lesions, suggesting that the renin-angiotensin system (RAS) plays a major role in the development of hypertension and cardiac hypertrophy, but its participation in ischaemia induced-myocardial alterations is less probable in NO deficient hypertension³⁰.

The Ang II type 1 receptor blocker, losartan, also prevented the development of L-NAME-induced hypertension and impairment of vascular relaxation to nitroprusside, isoprenaline, and cromakalim, vasodilators acting via the formation of NO, activation of betareceptors and opening of K⁺ channels, respectively. Thus, losartan was able to improve both endothelium-dependent and -independent vascular relaxation. Hyperpolarisation of smooth muscle cells, increased sensitivity to NO and decreased oxidative stress in the vascular wall might play a part in the protective effect of losartan^{31,32}.

A pooled analysis of all causes of chronic kidney disease patients treated with either ACE inhibitors or angiotensin II blockers revealed a reduction in the risk for myocardial infarction, heart failure, and total CV outcomes when RAS blockade was compared with placebo³³. RAS blockade decreased the risk for CV outcomes and heart failure when compared with control therapy in patients with

proteinuria. There were also benefits with RAS blockade in reducing the risk of CV outcomes and heart failure in patients with diabetic nephropathy when compared with placebo. Although it is clearly more complicated and difficult to analyse results in humans than in controlled animal studies, it is apparent that blockade of the rennin angiotensin system helps reduce cardiovascular complications in renal patients before or after entering CHD.

A prospective study of frequent dialysis with adequate control of blood pressure (and the possible avoidance of hypotensive episodes) and anti-angiotensin therapy might settle this issue once and for all. It might be at least as meaningful as the Modification of Diet in Renal Disease Study and certainly more practical and cost effective.

■ AWARENESS AND TREATMENT OF HYPERTENSION

Clearly, it is axiomatic that prevention and control of hypertension (and diabetes and renal disease) is the key to success. It is still frightening that a recent³⁴ cross-sectional analysis of data of participants with chronic kidney disease from the Kidney Early Evaluation Program revealed dismal statistics related to hypertension and, thus, kidney disease treatment. The Kidney Early Evaluation Program is a US national-based health screening program for individuals at high risk of kidney disease conducted in 49 states and the District of Columbia. Of 55,220 adults with kidney disease, 10,813 completed information for demographic and medical characteristics used in the analysis. Hypertension prevalence, awareness, and treatment proportions in the screened cohort were high (86.2%, 80.2%, and 70.0%, respectively), but blood pressure control rates were low (13.2%). These proportions increased with the advancing stage of kidney disease. Elevated systolic blood pressure accounted for the majority of inadequate control. Male gender, non-Hispanic black race, and body mass index of 30 kg/m² or more were inversely related with blood pressure control. Those with stage 3 kidney disease were more likely to have blood pressure at goal than those with stage 1 kidney disease.

Despite increased awareness, control rates of hypertension in these participants are poor. This poor control rate centres on elevated systolic pressure in people who are obese, non-Hispanic black, or male. These data suggest that those who are aware of their kidney disease are more likely to achieve blood pressure control. A better practical approach to achieve better results than those we observe presently remains to be seen.

Conflict of interest statement. None declared.

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