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Hypertension and the Progression of Glomerulopathies

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Introduction

Hypertension is a regular accompaniment of chronic glomerular disease. If left untreated, it may contribute to the progression of glomerular injury. In diabetic nephropathy, for example, hypertension was noted to accelerate and antihypertensive therapy to lessen the rate of decline in renal function [1]. It is also well known that hypertension is more prevalent in black than in white people [2]. Recent studies have shown that black patients with glomerulonephritis and also with diabetic renal disease progressed to end-stage renal failure three to four times more often and faster than white patients with the same glomerular diseases. However, none of these diseases are known to occur more frequently among blacks thus, it is possible that blacks with primary renal diseases are more prone to develop secondary hypertension and that the latter may accelerate the renal injury.

In some populations of patients with glomerulonephritis, a relationship between control of hypertension and the rate of progression to end-stage renal failure has not been found [3-6]. In addition, there is significant variation in the rates of progression of renal failure between individuals who have similar types of renal disease and equivalent levels of hypertension. Recent animal studies have led to several explanations that may help to explain these disparate observations. Based on these investigations, we propose that hypertensive injury to diseased glomeruli is primarily dependent upon the extent to which systemic hypertension is transmitted to the glomerular capillary bed (glomerular hypertension). The variability in the relationships between these pressures may be influenced by genetic factors, effect of antihypertensive agent on glomerular hemodynamics and composition of dietary intake. The following descriptions highlight some of the experimental studies in animals.

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Systemic Hypertension vs Glomerular Hypertension

There is no perfect animal model for human essential hypertension, however there are two separate genetically inbred strains of rats with many similarities to human hypertension. Wistar Okamoto rats (SHR) develop hypertension spontaneously as they mature. Dahl salt-sensitive (DS) rats become hypertensive if they are placed on a high salt diet while their genetic counterpart Dahl salt-resistant (DR) rats do not [3, 4].

Although both the SHR and DS rats develop hypertension, their glomerular hemodynamics are different [3, 4]. Preglomerular resistance in the SHR is effectively increased and as such the intraglomerular hydraulic pressure is normal because systemic hypertension is not transmitted to the glomerulus. In fact the glomerulus is «protected». In comparison the DS rats do not have an effective increase in preglomerular resistance and increased transcapillary hydraulic pressure develops in glomeruli in association with hypertension. In this situation the glomerulus is «unprotected». Particularly important is the fact that at similar levels of systemic hypertension DS rats have significantly greater degrees of glomerular damage as well as renal functional impairment than the SHR. Moreover when the effects of an additional insult in the form of an immune complex glomerulonephritis are superimposed on the hypertensive state in these two models severe glomerular injury occurred in the DS but not the SHR [8]. When the SHR is subjected to a reduction in renal mass the remnant kidney undergoes compensatory hypertrophy. This hypertrophic response is accompanied by a reduction in preglomerular resistance. As might be expected, the uninephrectomized SHR develops significant glomerular injury when compared to the similarly hypertensive control SHR [9].

It is interesting to speculate on the role of this «protective» effect of increased preglomerular resistance in human hypertensive patients. The genetic differences in preglomerular resistance and responses to renal injury demonstrated in the previously mentioned work may be at least in part, responsible for the variability of expression of glomerular hypertensive damage in humans.

The regulation of preglomerular resistance is most certainly multifactorial and as such failure to develop preglomerular vasoconstriction may be due to many mechanisms: a) genetic factors, b) an imbalance of the renin/angiotensin and prostaglandin systems, c) a congenital or acoured decrease in the number of functioning nephrons, and d) damage to the atterent arteriole such as in diabetes mellitus or certain immune vasculitities.

Finally it should be emphasized that the intrinsic mechanism by which high glomerular pressure induces damage is not known. The intuitively simplistic mechanical effect of increased pressure may be only an initiating factor in the subsequent damage. Glomerular endothelium and mesangium appear to be particularly susceptible to the hemodynamic «stress» in the initial stages of glomerular hypertension. In the case of the mesangium, increased intraglomerular pressure may augment mesangial trapping of circulating macromolecules triggering mesangial expansion and subsequent injury [7]. This is attractive in that it gives a pausible mechanism for the additive effects of hypertension and immunological disease.

Antihypertensive Therapy

The efficacy of antihypertensive therapy in slowing the progression of renal insufficiency in patients with glomerulopathies is unknown. Favorable results have been reported by some but not by other investigators [3-6]. The reasons for the variability in the salutory effects of antihypertensive therapy may be related to the agents used. Indeed, despite similar lowering of systemic blood pressure, intraglomerular flows and pressures may vary with different antihypertensive medications. Since progression or arrest of glomerular injury may be dependent upon the reduction in intraglomerular pressures, this may explain the variable results obtained with different agents. Certain experimental observations support this hypothesis.

Hypertensive SHR and also rats made hypertensive by salt and desoxycorticosterone administration, were treated with a combination of hydralazine-reserpine-hydrochlorothiazide. Blood pressure was controlled. Glomerular pathology, however, showed either no improvement or even deterioration [10, 11, 12]. Increased intraglomerular capillary pressure was noted in both models, felt to be secondary to a disproportionate decrease in pre versus post glomerular resistances due to the predominant afferent versus efferent arteriolar dilatation induced by this drug combination. This may explain the lack of beneficial effect of this antihypertensive therapy since increased intraglomerular capillary pressure may accentuate the glomerular damage. On the other hand, glomerular injury was reduced in diabetic rats, as well as in SHR, and Munich-Wistar rats with reduced renal mass treated with enalapril, an angiotensin I converting enzyme inhibitor [12, 13, 14].

Enalapril has been shown to reduce both systemic and intraglomerular pressures [13, 14]. The latter could account for the protective effect, again underscoring the importance of intraglomerular hemodynamic changes on progressive glomerular injury.

Antihypertensive agents may differ in another aspect, that is, their effect on the plasmic flow through the glomerular mesangial channels. The glomerular mesangium comprise of mesangial cells and matrix, the latter filling the space between cells and forming channels. The mesangium is separated from the capillary lumen only by the endothelium which allows plasmic flow carrying circulating macromolecules through the mesangial channels. These macromolecules, including, immune complexes, may be trapped in the mesangium and can be potentially injurious. The frequent demonstration of immune complexes in the mesangium in human and experimental renal diseases lends support to this hypothesis [15, 16]. Diazoxiede, a potent antihypertensive and renal vasodilating agent, has been shown to increase markedly the flow of macromolecules through these channels [16]. If increase of entrapment of macromolecules follows, this may result in mesangial injury, often a fore-runner of glomerulosclerosis [16]. Other renal vasodilators theoretically can enhance glomerular damage by this mechanism.

From the foregoing discussion, it is apparent that in the future, selection of antihypertensive agents, especially in patients with pre-existing renal disease, should be guided both by their systemic antihypertensive effect as well as their action on intrarenal hemodynamics.

Dietary Factors

Many attempts have been made to modify the inexorable progression of many types of renal disease not only by controlling systemic hypertension but also by varying the quantity and composition of the diet. Studies in rats with reduced renal mass clearly shows that variation in dietary components can alter glomerular hemodynaics and induce structural abnormalities [17, 18]. High dietary protein increases glomerular hydraulic pressure by decreasing afferent arteriolar resistance while protein restriction is associated with opposite effects [19]. Coincident with the induction of high intraglomerular pressures and flow rates protein loaded rats with reduced renal mass showed progressive segmental and global glomerular sclerosis [19].

However a cause and effect relationship between high dietary protein and glomerular damage and the

possible mechanisms involved have not been completely elucidated. In addition studies in dogs with reduced renal mass fed high dietary protein have not shown glomerular injury similar to that observed in rats [20]. At this time, caution is therefore advised in drawing therapeutic conclusions from these studies because of possible species differences and the numerous potential interactions between various other nutritional components. These interactions are illustrated in the case of hypertensive nephritic Dahl-salt rats where protein restriction only partially protected the glomeruli from hypertensive damage albeit high dietary protein had additive effects on glomerular injury [21].

In man, dietary protein restriction also appeared to slow the rate of progression of renal failure in some patients with different types of renal disease. However, as noted in Dahl-S rats, this effect was less pronounced in hypertensive patients compared with their normotensive counterparts [22].

Hence, hypertension and dietary protein content do appear to be independent but complementary risk factors. Whether the beneficial or detrimental effects of dietary protein content are exclusively due to hemodynamic factors is at present unknown. Protein intake however is not the only dietary consideration to be taken into account in attempting to unravel the progressive nature of renal disease. The effect of dietary manipulation on renal failure in animals and man have also been shown to be influenced by the degree of renal failure at the time of dietary intervention, total caloric intake, and other dietary factors and also perhaps by age [22, 23].

The effects on the kidney by other dietary factors and their interaction with hypertension have been less well studied and in some cases have yielded discordant results between animal and human investigations. Total caloric restriction has been reported to decrease glomerular abnormalities in rats [17, 23] but is felt to offset any beneficial renal effects in man [24], perhaps because higher caloric intake improves nitrogen utilization when protein intake is marginal. From a clinical standpoint this is an extremely important issue since adequate nutrition must be maintained in patients. In order to maintain adequate caloric intake, protein restriction must be complemented with variation in the intake of carbohydrates and lipids.

Lakshmanan et al. have reported studies in rats which showed that dietary sucrose as compared with more complex carbohydrates was associated with more severe glomerular damage at all levels of protein intake [25]. Variation in lipid composition may also be important. Diets high in linoleic aci have been reported to offer protection from progressive glomerular damage in partially nephrectomized rats without affecting systemic blood pressure, a finding perhaps explained by hemodynamic effects from increased medullary production of prostaglandins induced by the diet [26]. How the results of these studies might relate to hypertensive renal damage and intraglomerular pressures are intriguing and require further study.

No doubt the most common dietary manipulation in studies involving hypertension and renal failure is salt. Induction or exacerbation of hypertension in experimental animals is frequently accomplished by varying dietary sodium intake. The effects of sodium loading on glomerular hemodynamics is thought to be most likely mediated by changes in systemic blood pressure. Hemodynamic effects from simultaneous variation in other dietary and other unknown factors may however make this assumption erroneous [27]. Furthermore whether there exists an independent effect by sodium on progression of renal disease, perhaps via an alteration in the vasculature itself also remains unknown. Indeed high dietary NaCl increased vascular injury in hypertensive SHR without further increasing systemic blood pressure [28].

Other electrolytes such as calcium, magnesium and potassium have all been reported to influence the levels of hypertension [29, 30], however their role in ondulating proression of renal failure in hypertensive patients and animals also remains to be determined. Experimentally, high dietary potassium in Dahl S rats has been found to have an independent protective effect on hypertensive damage to glomeruli and intrarenal vessels [29]. High dietary potassium also reduces cerebro-vascular damage in hypertensive Stroke Prone SHR [31]. Whether high dietary potassium is directly vasculo-protective or mediates its effect through changes in hemodynamics is unclear. Clearly, the inter-relationships bertween diet systemic hypertension and vasoactive agents on intraglomerular hemodynamics and renal damage are incrediously complex and will require further study.

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