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The hyperfiltration theory: A paradigm shift in nephrology

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The hyperfiltration theory: A paradigm shift in nephrology. Experimental studies incriminate glomerular hypertension in mediating progressive renal damage after any of a variety of initiating injuries. Prevention of glomerular hypertension by dietary protein restriction or antihypertensive therapy lessens progressive glomerular damage in several experimental models of chronic renal disease. Glomerular hypertension and hyperfiltration also occur in humans with diabetes mellitus, solitary or remnant kidneys, and various forms of acquired renal disease. Clinical studies indicate that dietary protein restriction and antihypertensive therapy also slow progression in many of these disorders. Large multicenter trials confirm the beneficial effects of these therapeutic maneuvers on the rate of progression of chronic renal disease.

Chronic renal insufficiency in humans usually progresses to end-stage renal failure. A decade ago, on the basis of studies in animals, Brenner and colleagues proposed that maladaptive glomerular hemodynamic changes exert a major influence on the factors that initiate and perpetuate disease progression [1, 2]. These hemodynamic changes lead to glomerular hyperfiltration, an adaptation seen in response to a reduction in functional nephron number whether induced genetically, surgically, or by acquired renal disease. The elevated single nephron glomerular filtration rate (SNGFR) common to these pathophysiologic conditions is usually caused by increases in the glomerular capillary plasma flow rate (Q_A) and mean glomerular capillary hydraulic pressure (P_{GC}), which in turn are due to adaptive reductions in preglomerular and postglomerular arteriolar resistances.

Progressive glomerular sclerosis and proteinuria eventually occur in most experimental models of renal disease characterized by glomerular hyperfiltration and hypertension. Systemic hypertension often is also present, as in extreme renal ablation [2], bilateral renal infarction [3], post-salt hypertension [3, 4], two-kidney one-clip Goldblatt hypertension [5], desoxycorticosterone (DOCA)-salt hypertension [6], and the Fawn-hooded rat [7], a strain congenitally predisposed to chronic renal failure. Systemic hypertension is not required for glomerular capillary hyperfiltration and hypertension; however, since in diabetic rats an acquired reduction in afferent arteriolar resistance (R_A) not only increases Q_A but allows a greater fraction of the systemic blood pressure to be transmitted into the glomerular capillary network, thereby raising P_{GC} despite normal renal perfusion pressure.

Prevention of glomerular hypertension leads to less glomerular injury

Amelioration of glomerular capillary hyperfiltration and hypertension by therapeutic maneuvers invariably lessens renal injury. For example, dietary protein restriction limits the adaptive increases in SNGFR and P_{GC} that occur in various models of experimental renal disease [1, 2, 6, 8–12]. Systemic blood pressure usually fails to decline with protein restriction, yet glomerular injury is consistently ameliorated compared with control animals on normal [6, 8–10] or high [6, 8, 10] protein diets, again highlighting the importance of glomerular rather than systemic hypertension in subsequent glomerular injury. Dietary protein restriction also preserves renal function and limits structural injury even when instituted in the setting of established renal injury [10], a finding of obvious relevance to the management of human renal disease.

Antihypertensive drugs also slow the progression of experimental renal disease. Here again the importance of single nephron rather than systemic hemodynamics is evident in that agents which lower systemic blood pressure without correcting glomerular hypertension do not usually ameliorate glomerular injury. Studies have also revealed that glomerular capillary hypertension, rather than hyperperfusion or hyperfiltration, is in fact the most critical determinant of glomerular injury. Anderson et al [13, 14] and Lafayette et al [15] treated partially nephrectomized rats with either the angiotensin-converting enzyme (ACE) inhibitor enalapril or with "triple therapy," a combination of reserpine, hydralazine, and hydrochlorothiazide. Both approaches ameliorated systemic hypertension, although triple therapy, having little or no beneficial effect on glomerular flows and pressures, did not protect against glomerular injury. Enalapril, on the other hand, preserved normal glomerular capillary pressure and ameliorated proteinuria and glomerulosclerosis, despite persistence of glomerular capillary hyperperfusion and hyperfiltration. An angiotensin II receptor antagonist afforded the same protective effect as enalapril [15]. Other investigators using other experimental models as well as other therapeutic maneuvers to reduce P_{GC} have obtained similar results [16–18]. Thus, when glomerular capillary hypertension is controlled, glomerular injury is prevented or greatly reduced.

Nonhemodynamic processes may also contribute to the progression of chronic renal disease. Thus, lipid-lowering agents [19], heparin [20], and dietary sodium restriction [21, 22] limit glomerular injury without controlling glomerular capillary hypertension in the uninephrectomized spontaneously hypertensive rat (SHR) and in rats with subtotal nephrectomy, presumably by limiting glomerular lipid deposition, intravascular thrombosis, compensatory growth, or capillary wall tension. Vasoactive substances themselves also may have effects on clotting and cell growth, and thus might contribute to progression through both hemodynamic and nonhemodynamic pathways.

Role of altered glomerular hemodynamics in humans

The influence of hyperfiltration, the most readily monitored surrogate of altered glomerular hemodynamics, on renal function in humans has been most thoroughly evaluated in kidney transplant donors and in patients uninephrectomized for acquired renal disease. Even after one to two decades, total GFR often averages approximately 70% of prenephrectomy values despite the 50% reduction in renal mass, indicating that the remaining kidney is indeed hyperfiltering. Most studies have shown that in association with this hyperfiltration the prevalence of hypertension in both groups tends to increase after uninephrectomy, although only in transplant donors is hypertension apt to be more prevalent than in local, control populations. Similarly, the prevalence of proteinuria tends to increase in both groups after uninephrectomy, and in one study of patients uninephrectomized for renal disease [23], proteinuria was shown to increase as a function of time after surgery as well. However, most investigators have not been able to demonstrate that blood pressure, proteinuria, or GFR correlate in any way with time since uninephrectomy, or with each other. Many conclude that because values for GFR remain relatively stable over time, hyperfiltration in these uninephrectomized adults does not adversely affect the remaining kidney. This conclusion seems premature, however, as the mean duration of follow-up in these patients is usually less than two decades [24]. Experimental data clearly show that although renal insufficiency develops very gradually in uninephrectomized animals, it eventuates much earlier than in two-kidney control subjects [25]. It is therefore crucial that renal function in these individuals be followed for several decades before conclusions regarding long-term safety are reached. Patients with unilateral renal agenesis differ from uninephrectomized adults in that they hyperfilter from birth. After approximately three decades of hyperfiltration they may develop proteinuria, sometimes but not always in association with the development of hypertension and renal insufficiency. Nevertheless, patients with this disorder who undergo biopsy for proteinuria invariably exhibit the lesions of focal and segmental glomerular sclerosis [26–29], the same lesion that develops experimentally in the setting of reduced renal mass. Interestingly, this is also true of patients uninephrectomized for unilateral disease who subsequently undergo biopsy for proteinuria [26–33]. Thus, while it is true that most people with unilateral agenesis do not develop progressive renal disease, it is reasonable to infer that at least in some, longstanding hyperfiltration may contribute to the development of renal injury.

Several reports have examined the development of renal injury in patients who have undergone a greater than 50% reduction in total renal mass [34–38]. Thirty-six of the reported patients were followed for an average of 12 years, and of these, 30% developed systemic hypertension *de novo* or required antihypertensive medications to control their blood pressure. A striking 70% of patients in whom 24-hour urinary excretion rates were measured [36–38] developed significant proteinuria. Novick et al [38] demonstrated that, just as in rats with subtotal nephrectomy, the extent of proteinuria correlated directly with the duration of follow-up and inversely with the amount of renal tissue remaining. Furthermore, in four of five patients undergoing biopsy for moderate to severe proteinuria [36, 38, 39] the pathologic lesion found was focal and segmental glomerulosclerosis. Thus, with respect to the development of hypertension, proteinuria, and glomerulosclerosis, the human model of extensive renal ablation accurately resembles its experimental counterpart. Significantly, two of the three patients followed the longest by Novick et al [38] developed end-stage renal disease requiring hemodialysis, suggesting that subtotal nephrectomy in humans may indeed lead to renal insufficiency as well. The theory that solitary kidneys given in the course of renal transplantation ultimately fail due at least in part to nonimmunologic (hemodynamic) factors has recently been postulated (see [40] for a detailed discussion of this issue).

Hyperfiltration occurs in certain pathophysiologic conditions even when renal mass is intact, as in diabetes mellitus [41, 42]. It has been shown that hyperfiltration predicts the subsequent development of nephropathy in patients with type I diabetes [43–45], independently of the degree of metabolic control.

Therapeutic options in human renal disease

Therapies shown to limit glomerular hyperfunction and to ameliorate renal injury in animals have begun to be tested in humans. Dietary protein restriction and antihypertensive drug therapy [46] have been the principal therapeutic interventions tested thus far. A recent meta-analysis of studies of low-protein diets in renal insufficiency, based only on data from prospective randomized, controlled trials in nondiabetic patients, suggests that dietary protein restriction indeed delays the onset of end-stage renal disease. Evidence also suggests that dietary protein restriction retards the progression of diabetic renal disease as well [47]. The Modification of Diet in Renal Disease Study, a large multicenter clinical trial, also demonstrates a benefit of dietary protein restriction and aggressive reduction in blood pressure on the rate of progression of chronic renal disease in humans with significant proteinuria and baseline ongoing deterioration of renal function [48]. ACE inhibitors have also been shown to offer protection in non-diabetic chronic renal failure [49].

Among diabetics, randomized multicenter clinical trials have examined the merits of ACE inhibitors in both Type I and Type II patients. Evidience in support of a strong renoprotective effect of this class of antihypertensive therapy was obtained in those with already overt nephropathy as well as in those with incipient nephropathy [50–53]. Based on these findings various professional organizations have issued formal guidelines enthusiastically supporting ACE inhibitors in diabetic subjects.

Conclusions

The history of our thinking about the inexorable progression of renal disease involves nearly a half-decade of discontinuity after the work of Addis [54]. Interest in this area was reawakened by the paper of Hostetter et al [2] and the essay by Brenner, Meyer, and Hostetter [1]. Since then, clinicians are no longer content with merely anticipating progressive loss of renal function in patients with congenital and acquired forms of chronic renal disease, but have begun instead to design, test and implement various dietary and pharmacologic interventions aimed at improved control of blood pressure (a now highly appreciated cause of accelerated progression) and particularly glomerular pressure. This paradigm shift is already deemed responsible for reducing the cumulative incidence of nephropathy in diabetic patients [55] and is anticipated to impact favorably on other forms of chronic renal disease as well.

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