Pathophysiology of Hypertensive Renal Damage
Implications for Therapy

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Abstract—Unlike the majority of patients with uncomplicated hypertension in whom minimal renal damage develops in the absence of severe blood pressure (BP) elevations, patients with diabetic and nondiabetic chronic kidney disease (CKD) exhibit an increased vulnerability to even moderate BP elevations. Investigations in experimental animal models have revealed that this enhanced susceptibility is a consequence of an impairment of the renal autoregulatory mechanisms that normally attenuate the transmission of elevated systemic pressures to the glomeruli in uncomplicated hypertension. The markedly lower BP threshold for renal damage and the steeper slope of relationship between BP and renal damage in such states necessitates that BP be lowered into the normotensive range to prevent progressive renal damage. When BP is accurately measured using radiotelemetry in animal models, the renal protection provided by renin-angiotensin system (RAS) blockade is proportional to the BP reduction with little evidence of BP-independent protection. A critical evaluation of the clinical data also suggests that the BP-independent renoprotection by RAS blockade has been overemphasized and that achieving lower BP targets is more important than the selection of antihypertensive regimens. However, achievement of such BP goals is difficult in CKD patients without aggressive diuresis, because of their proclivity for salt retention. The effectiveness of RAS blockers in lowering BP in patients who have been adequately treated with diuretics, along with their potassium-sparing and magnesium-sparing effects, provides a more compelling rationale for the use of RAS blockade in the treatment of CKD patients than any putative BP-independent renoprotective superiority. (Hypertension. 2004;44:595-601.)

Key Words: nephrosclerosis ■ autoregulation ■ telemetry ■ antihypertensive agents ■ renin-angiotensin system ■ glomerulosclerosis

The relative risk of serious renal damage in patients with uncomplicated essential hypertension is low as compared with other cardiovascular complications. Nevertheless, given the huge prevalence of hypertension in the general population, it still remains the second leading cause of end-stage renal disease (ESRD), with the risk being substantially higher in blacks. Historically, hypertension-induced renal damage in patients with uncomplicated essential hypertension has been separated into the 2 distinct clinical and histological patterns of “benign” and “malignant” nephrosclerosis. Benign nephrosclerosis is the pattern observed in the majority of patients with uncomplicated primary hypertension. The somewhat nonspecific vascular lesions of hyaline arteriosclerosis develop slowly without overt proteinuria. Although focal ischemic glomerular obscelence and nephron loss occur over time, renal function is not seriously compromised except in susceptible individuals such as blacks in whom the process tends to follow a more severe and accelerated course. By contrast, “malignant” nephrosclerosis is observed with very severe hypertension (malignant phase of essential hypertension) and has a characteristic renal phenotype of acute disruptive vascular and glomerular injury with prominent fibrinoid necrosis and thrombosis. Ischemic glomeruli are frequent because of vascular injury. Renal failure can develop rapidly in the absence of adequate therapy. Although episodes of malignant nephrosclerosis undoubtedly contribute to the development of ESRD in untreated, noncompliant, or cocaine-abusing patients, the full-blown clinical phenotype has fortunately become uncommon with the wide availability of effective antihypertensives.

A major advance over the past 2 decades has been the recognition that the spectrum of hypertension-induced renal damage extends beyond benign and malignant nephrosclerosis. There is abundant evidence that coexistent hypertension plays a predominant role in the progression of most chronic kidney diseases (CKD), including diabetic nephropathy, presently the leading cause of ESRD. These deleterious effects are observed with even mild-to-moderate blood pressure (BP) elevations in CKD patients, indicating an enhanced vulnerability to hypertensive renal damage with a lower BP threshold for damage and a steeper slope of the relationship between BP increase and renal damage (Figure 1). However, it has been difficult to quantify the contribution of hypertension to progressive renal disease because of the lack of a specific
histological phenotype. Vascular pathology, considered the hallmark of hypertensive injury, often is not prominent in this setting of CKD. Instead, an accelerated segmental or global glomerulosclerosis (GS) seems to be superimposed on the intrinsic phenotype of the underlying renal disease.5,7 Nevertheless, recent investigations in experimental animal models have increased our understanding of the mechanisms that underlie the observed differences in histological phenotypes and susceptibility to hypertensive renal damage illustrated in Figure 1.

Pathophysiology of Hypertensive Renal Damage

The direct adverse consequences of hypertension on any vascular bed are expected to be a function of the degree to which it is exposed to the increased pressures. The pathogenic determinants of hypertensive renal damage can thus be broadly separated into 3 categories: (1) the systemic BP “load”; (2) the degree to which such load is transmitted to the renal vascular bed; and (3) local tissue susceptibility to any given degree of barotrauma. It seems self-evident that because the ambient BP profile in conscious animals is characterized by spontaneous, rapid, and often large fluctuations in BP, conventional isolated BP measurements are inherently inadequate to define quantitative relationships between BP and renal damage.5–8 The availability of BP radiotelemetry by allowing chronic BP monitoring in conscious unrestrained animals has provided a major advance in hypertensive target organ damage research.5–8

BP Load and Its Transmission to the Renal Microvasculature

Normally, increases in systemic BP, episodic or sustained, are prevented from fully reaching the renal microvasculature by proportionate autoregulatory vasoconstriction of the preglomerular vasculature such that renal blood flow and glomerular hydrostatic pressures (P_{GC}) are maintained relatively constant (Figure 2; pattern A).5,9 These autoregulatory responses therefore provide the primary protection against hypertensive renal damage.5,10 As long as BP remains below a certain limit (within the autoregulatory range), only benign nephrosclerosis is observed; however, if this threshold is exceeded, acute disruptive injury (malignant nephrosclerosis) is expected to result despite intact autoregulation.5 However, once vascular injury develops, autoregulatory responses can be secondarily compromised and result in the amplification of renal damage (vide-infra).11,12 A clear illustration of such a threshold relationship between BP and malignant nephrosclerosis has recently been demonstrated using BP radiotelemetry in the stroke-prone spontaneously hypertensive rat model.13 Moreover, as would be predicted, even modest BP reductions to below this threshold were shown to prevent such damage.13 In general, chronic hypertension tends to shift both the upper and lower limits of autoregulation to the right and represents a protective adaptation.5,14 Therefore, an acute severe elevation in BP is more likely to exceed the autoregulatory threshold and cause injury than equally severe hypertension that develops more gradually.5,13

However, even in the absence of severe hypertension, renal damage can still develop if there is an enhanced transmission of elevated systemic pressures to the renal microvasculature as illustrated in Figure 2. Any significant preglomerular vasodilation, as observed after uninephrectomy or in early type 1 diabetes (before significant nephropathy), is expected to result in a greater fractional transmission of the ambient systemic pressures (Figure 2; pattern B).15 However, if such vasodilation is not accompanied by impaired renal autoregulation or severe hypertension, only a modest increase in the vulnerability to hypertensive injury is expected.15 This may account for the largely benign renal course in most uninephrectomized individuals and possibly the long delay in the development of overt diabetic nephropathy.15,16 However, if
renal autoregulation is additionally impaired, as seen after more severe (≥75%) renal mass reduction in animals or in humans with diabetic or nondiabetic CKD (Figure 2; pattern C), the susceptibility to hypertensive injury is markedly enhanced with the greatly reduced BP threshold for damage and the steeper relationship between BP and renal damage as illustrated in Figure 1. Additionally, such enhanced glomerular pressure transmission in the absence of hypertension severe enough to cause vascular injury primarily leads to accelerated GS.3,5

The clearest demonstration of this phenomenon has been provided in the most extensively investigated model of CKD, the rat 5/6 renal ablation model.4–6 Through the use of BP radiotelemetry, it has been shown that the progressive GS of the initially normal remnant glomeruli in these rats follows the quantitative relationships with BP shown in Figure 1 and predicted by Figure 2.6,17 The importance of autoregulatory capacity as a determinant of the susceptibility to hypertensive injury is further illustrated by the effects of the dihydropyridine calcium channel blockers (CCBs) in this model. Given the critical dependence of autoregulatory response on voltage-gated calcium channels, these agents, not unexpectedly, further impair the already impaired renal autoregulation in the 5/6 ablation model5,20 (Figure 2; pattern D). And predictably, CCBs also further reduce the BP threshold and increase the slope of the relationship between GS and BP (percent increase in GS/mm Hg in BP) such that greater GS is observed at any given BP elevation as compared with untreated rats, and protection is not achieved without achieving normotension.5,20 Conversely, if preglomerular vasodilatation and autoregulatory impairment are prevented in this model through the substitution of a low-protein diet, GS is also ameliorated despite continued hypertension.10,21 However, if CCBs are given to the low-protein diet-fed rats, renal autoregulation is impaired and the protection against GS is also abolished.21 Similar adverse effects of dihydropyridine CCBs, and protective effects of a low-protein diet on GS, have also been noted in the streptozotocin-induced diabetes model.4,22

Of note, differences in autoregulatory efficiency have also been postulated to account for some of the strain (genetic) differences in susceptibility to hypertensive injury.5,11,23 However, it needs to be emphasized that these adverse effects of impaired renal autoregulation on susceptibility to hypertensive renal damage are only observed in a vasodilated vascular bed. In a vasoconstricted bed, the consequences of impaired autoregulation primarily result in a diminished capacity to maintain renal blood flow and glomerular filtration rate (GFR) when systemic pressures are reduced, with an enhanced potential for ischemic tubulointerstitial injury. A similar ischemic pathogenesis may underlie the tubulointerstitial injury observed in angiotensin infusion models.12 There is evidence that glomerular hypertrophy may be an independent risk factor for GS.5,21,24 In addition to the expected increase in wall tension (Laplace Law: tension = pressure × radius), hypertrophy of glomerular capillaries may also compromise their ability to withstand mechanical stress.25,26 It has been proposed that the glomerular capillary epithelial cell (podocyte) through its interdigitating foot processes provides structural support against pressures that are substantially higher than in systemic capillaries (≈45 versus ≈20 mm Hg). The limited replication potential of this terminally differentiated cell during glomerular hypertrophy may limit its ability to maintain physical integrity and mechanical support during hypertensive stress.

However, of the local mechanisms, the BP-independent tissue damage promoting effects of angiotensin II and, more recently, aldosterone have received the greatest emphasis.4,12,24,27–29 The triggering of several downstream deleterious cellular and molecular pathways is postulated to lead to oxidative stress and the activation of growth factors and fibrogenic mediators such as transforming growth factor-β and plasminogen activator inhibitor-1. Despite the considerable evidence in vitro demonstrating these pathways, the primary evidence to support their in vivo importance is derived from the very large number of studies in animal models that have claimed to show glomeruloprotection by renin-angiotensin system (RAS) blockade and/or aldosterone antagonists over and beyond that achieved by “equivalent” BP reductions with other antihypertensive regimens.5,24,27–30 However, when BP has been measured more continuously by radiotelemetry instead of intermittently by tail-cuff, the renoprotection can be entirely accounted for by the achieved BP reductions with little evidence of additional BP-independent protection.5,31,32 This is true of both the malignant nephrosclerosis and the accelerated GS models (5/6 ablation). No evidence of a shift to a higher BP threshold for damage or a decrease in the slope of the relationship between BP and GS is seen with RAS blockade, as would be expected with significant BP-independent protection. In this context, it is relevant to note that isolated P_G measurements like isolated BP measurements may not accurately reflect chronic pressure exposure. Such limitations probably account for the lack of consistent correlations between P_G and GS,24 even in models demonstrating excellent correlation with radiotelemetrically measured systemic BP.5,6

Collectively, these data suggest that the activation of downstream molecular mediators of tissue injury may not be exclusive to angiotensin II and/or aldosterone but may represent a response to tissue stress and/or injury per se. There is evidence that pressure alone can activate many of these downstream pathways,32–35 and the histological phenotype of hypertensive renal damage exhibits little difference in models with or without overt RAS activation.3 Conversely, little evidence of the activation of these deleterious pathways or renal damage is observed in the absence of elevated pressures despite substantial angiotensin and aldosterone increases during low salt intake, congestive heart failure, or cirrhosis, or in the clipped kidney of the 2-kidney–1-clip model of Goldblatt hypertension.36 In fact, the administration of even very large amounts of exogenous aldosterone results in little

Local BP-Independent Determinants of Tissue Susceptibility

Although still poorly defined, genetic or acquired differences in intrinsic structure or function may result in differences in the severity of damage expressed at any given degree of increased pressure exposure (barotrauma).5,8,11 For instance,
target organ damage in animals maintained normotensive on a low-salt diet. Moreover, investigations into the pathogenic role of aldosterone have usually not adequately controlled for changes in potassium balance, which can independently impact renal damage.37 Thus, although it remains possible that angiotensin II and aldosterone may amplify hypertensive renal damage through BP-independent mechanisms in certain situations and/or models, definitive evidence remains to be obtained.

Unresolved Issues

Despite the progress that has been achieved, certain fundamental issues of hypertensive target organ damage remain unresolved. The term “BP load” is used generically because the relative pathogenic importance of individual BP parameters (mean, systolic, diastolic, pulse pressure, and BP variability) remains undefined.5 Although recent clinical data have indicated that systolic and possibly pulse pressures are more closely correlated with target organ damage than mean arterial or diastolic pressures,1 the pathophysiological basis of such empirical observations remains unknown. It is also possible that the relative pathogenic potential of these individual BP parameters may differ for different target organs. Moreover, the transmission of fluctuating systemic pressures to target organs in real time must also be a dynamic process with the transmission of individual BP fluctuations depending on their rate (frequency) and the kinetics of the autoregulatory responses. And fluctuations in microvascular pressures (pressure transients and/or peak pressures) may have a greater pathogenic potential than sustained steady elevations. The unusually rapid activation kinetics of the afferent arteriolar myogenic response noted recently seem to be consistent with this protective function.38 Moreover, the fact that systolic, rather than mean, BP seems to be the trigger signal for this response38 may be indicative of a greater pathogenetic potential of systolic (peak) pressures. Biophysical approaches are being developed to separate the BP energy into its component parts and to assess the potential renal microvascular transmission and pathogenic importance of these individual components of BP power (energy/unit time).5,15,38

Therapeutic Implications

The pathophysiology of hypertensive renal damage discussed suggests 3 broad targets for therapeutic interventions: (1) reduction of BP load; (2) reduction of pressure transmission to the renal microvasculature; and (3) interruption and/or modification of the local cellular/molecular pathways that mediate eventual tissue injury and fibrosis.

Reduction of BP Load

Given the substantial evidence that local hypertension (barotrauma) plays a major role in the initiation and progression of renal damage, it seems self-evident that the most effective preventive strategy would be to treat the proximate cause of such increased pressures, ie, effectively reduce the systemic arterial pressures. However, the relative success of such BP reductions in preventing renal damage will vary with the clinical context. Even modest and easily achieved BP reductions to below the autoregulatory threshold are likely to prevent malignant nephrosclerosis in patients with uncomplicated hypertension.5,13 By contrast, BP may need to be lowered well into the normotensive range in CKD patients to prevent additional GS. The more limited success against progressive renal disease as compared with malignant nephrosclerosis and hypertensive stroke is thus not unexpected.1,2

The systolic BP goal of 140 to 150 mm Hg that was considered acceptable until recently in patients with CKD, because even if achieved, it might not have been low enough to prevent continued glomerular barotrauma. The pathophysiology of hypertensive glomerular injury in these states predicts that the more advanced the CKD (the greater the vasodilation and autoregulatory impairment), the lower the achieved BP will need to be to normalize intrarenal pressures.

Moreover, even transient episodes of BP elevations are predicted to be more freely transmitted to the glomerular capillaries, suggesting the need for around-the-clock BP control.59 The recognition of the need for more aggressive BP control for such patients in the recent guidelines is consistent with these insights.1,40 Even within the CKD population, the impact of BP reductions may differ because of intrinsic differences in susceptibility because of disease cause and severity, as well as genetic and environmental factors.5,7,8,38 The steeper the slope of the relationship between BP and renal damage, the greater the impact of any given BP reduction. Thus, it is not surprising that greater benefits from aggressive BP control are seen in proteinuric than in nonproteinuric CKD patients,40 because proteinuria may reflect increased glomerular pressure transmission or may be a biologic marker of enhanced intrinsic glomerular susceptibility.

Class Differences Between Antihypertensives

As for experimental models, the relative merits of individual antihypertensive classes and the ability of RAS blockade to provide BP-independent target organ protection have been the subject of much clinical investigation and debate.1,40–44 However, the claims for the therapeutic superiority of RAS blockade have not been sustained, at least for cardiovascular disease and stroke, most recently by the very large landmark ALLHAT trial.1,41–44 Therefore, recent guidelines now stress the primary importance of BP reductions per se in preventing target organ damage.1 In fact, based on their cost and effectiveness in the ALLHAT trial, the thiazide diuretics, despite their expected stimulation of RAS, have been recommended as the initial regimen of choice for most patients with hypertension, with other classes of drugs being added for comorbid conditions.1 Patients with CKD, however, remain a notable exception, with continued emphasis on RAS blockade as the initial regimen of choice.1,40 These recommendations are based on the results of several randomized controlled clinical trials in diabetic and nondiabetic nephropathy that have shown better renoprotection with RAS blockade, with 15% to 50% relative risk (RR) reductions in renal disease endpoints (doubling of serum creatinine, ESRD) in comparison to other antihypertensive regimens.1,40,45–48 Given that the primary importance of optimal BP control is now acknowledged by even the most avid advocates of RAS blockade, and that most CKD patients usually require at least 2 agents for such BP control, the issue of BP-independent...
renoprotective superiority of RAS blockade is more of scientific than clinical practice relevance because RAS blockers are excellent antihypertensive agents when combined with diuretics in this population (vide infra).

Nevertheless, a critical analysis of the clinical trial evidence shows that the interpretations are not as definitive and the much emphasized BP-independent benefits of RAS blockade are much smaller than have been implied. A re-examination of the landmark clinical trial in type 1 diabetic nephropathy patients by the Collaborative Study Group illustrates this issue.45 A very impressive ≈50% RR reduction by RAS blockade was reported (25 renal end-points in 207 captopril-treated patients versus 43 in 202 conventionally treated controls), with almost all of the end-points and RR reductions being observed in the higher-risk patients with a serum creatinine of ≧1.5 mg/dL at entry. Although the control group had greater proteinuria at entry, and BP during the course exhibited small but statistically significant differences favoring the captopril group, these large RR reduction estimates were claimed to not be significantly altered by statistical adjustment for these differences. However, a subsequently published substudy of the 108 nephrotic patients considered to be at greatest risk in the original cohort49 casts considerable doubts on the validity of the interpretations in the parent study. Although its implications were not addressed, this substudy revealed that these high-risk nephrotic patients had been disproportionately randomized, with 42 being entered in the captopril versus 66 in the placebo group (P<0.002 by χ2). The high-risk status of these patients was confirmed by the fact that remission in proteinuria was only achieved in 8 patients (7 in the captopril group) who also exhibited very substantial BP reductions, in contrast to the essentially unchanged BP in the 100 nonresponders whose average serum creatinine more than doubled during the study. Of note, of the 16 black nephrotic patients, none of whom responded, 14 were assigned to the control group (P<0.03). It is likely that this flawed randomization of the 24 nephrotic patients at very high risk to the placebo group largely accounted for the difference of 18 more end-points in the control group described in the initial report.

With respect to the relative magnitude of the BP-dependent versus BP-independent effects of RAS blockade, some insights may be provided by the results of the more recent IDNT and RENAAL trials of angiotensin receptor blockers (ARBs) in type 2 diabetic nephropathy.46,47 The additional renoprotection (slower decline in GFR) provided by ARBs compared with control antihypertensive regimens was ≈1 mL/min per year (≈5 versus ≈6 mL/min per year/1.73m2). However, given the GFR decline rates of 12 mL/min per year that have been observed historically in untreated patients,16 BP reductions per se in the conventionally treated groups reduced the rate of GFR decline by 6 mL/min per year. Therefore, ≈85% of the total benefit conferred by ARBs may be attributable to their antihypertensive effects. Moreover, the BP independence of even this residual additional renoprotection by ARBs may be questioned by the fact that the achieved clinic BP in the RAS blockade-treated groups, as in other clinical trials in diabetic and nondiabetic nephropathy patients, tended to be 2 to 4 mm Hg lower than in the control groups. Although such small differences have generally been felt to be insufficient to explain the 15% to 35% RR reductions observed in these studies, recent data including that from the ALLHAT study suggest that such small but significant differences in clinic pressures may have greater impact on outcomes than generally assumed.41,43 It is possible that such differences in clinic BP reflect larger differences in ambient and/or nocturnal BP, as revealed in a HOPE substudy.50 Reductions of 3/2 mm Hg in clinic pressures in a subset of 38 ramipril-treated patients translated into a reduction of 10/4 mm Hg in an average 24-hour ambulatory BP (ABP) in the same patients because of a large decrease in nocturnal BP of 17/8 mm Hg (ramipril was dosed in the evening). Thus, as in animals, BP-independent effects of RAS blockade are difficult to demonstrate when ABP monitoring is used,5,8 suggesting a need for caution when inferring BP independence based solely on clinic pressures, which are usually not controlled for the time of day and/or relationship to drug dosing. Such effects may be particularly important in diabetic hypertensive patients, who often do not exhibit the normal nocturnal decline in BP.16 Given the experimental animal data, it is not surprising that significantly better correlations are observed between 24-hour ABP measurements than clinic pressures with markers of cardiovascular target organ damage, including proteinuria.5,8 Therefore, even though intermittent 24-hour ABP monitoring may not provide as complete an assessment of the total chronic BP burden as is possible with radiotelemetry in experimental models, its incorporation in future clinical trials, at least in subsets of patients, should be strongly considered.

Caution also needs to be exercised when drawing conclusions regarding BP-independent effects based on a comparison between antihypertensive regimens. For instance, there is evidence to suggest that β-blockers, because of their effects on heart rate and the augmentation of the pressure wave reflection, may not lower central pressures as effectively as other agents, despite similar peripheral pressure measurements.51 Similarly, the superior renal outcomes with RAS blockade as compared with CCBs as in the AASK trial,48 might in fact reflect the adverse effects of CCBs on BP transmission to the microcirculation.20,21 However, it should be acknowledged that unlike rodent models, the evidence for deleterious effects of dihydropyridine CCBs in humans for hard end-points, rather than proteinuria, is more mixed.52 This may reflect the limitation of clinic BP measurements combined with the fact that the adverse effects of CCBs on renal autoregulation and BP transmission are counteracted by the achieved BP reductions, ie, the greater the BP reduction, the less the deleterious impact. Moreover, the deleterious effects of CCBs may be significant only in the accelerated GS models in which the capillary bed is the primary site of injury and may not be relevant to more proximal vascular injury. The effectiveness of CCBs in protecting against malignant nephrosclerosis as well as cardiovascular and cerebrovascular hypertensive target organ damage is consistent with such interpretations.1,41–43

Achievement of BP Goals
Over and beyond the issues of the recognition of the need to pursue lower BP targets for CKD patients, the difficulty of achieving such BP goals has proved to be a major therapeutic
challenge, with 3 to 4 drugs often deemed necessary.40 Nevertheless, there is reason to suspect that at least some of this difficulty has stemmed from an underuse of aggressive diuretic use in these patients,53 in part because of some justifiable concerns about their adverse impact on renal function parameters.54 However, hypertension in most CKD patients is volume-dependent with relative RAS suppression and exhibits an increased BP salt sensitivity because of altered pressure natriuresis.55,56 As a consequence, BP reduction by agents other than diuretics usually tends to amplify the salt retention. Such pathophysiology explains why monotherapy in CKD patients, including that with RAS blockers, is generally ineffective. Therefore, adequate BP control in CKD patients usually cannot be achieved without effective diuresis, and some hemodynamically mediated elevations in blood urea nitrogen and creatinine levels are unavoidable and, unless severe, may need to be considered acceptable. Effective diuresis also activates the RAS and restores the antihypertensive effects of RAS blockade.57 The fact that diuretics and RAS blockers counteract each other’s side effects on potassium and magnesium balance but are synergistic for BP reductions renders their combination a logical antihypertensive regimen for these patients. In fact, a better case can be made for such use of RAS blockade in achieving BP goals than for any putative BP-independent protection. It is possible that some of the BP-independent beneficial effects of both RAS blockade and the relatively small doses of Aldactone on cardiovascular morbidity and mortality in patients with congestive heart failure58 may in part stem from minimizing the potassium and magnesium depletion in these diuretic-treated patients.

Nonantihypertensive Interventions to Reduce Hypertensive Renal Damage

As noted, it is theoretically possible to mitigate renal damage by hemodynamically reducing the intrarenal transmission of systemic pressures such as through protein restriction. However, unlike its demonstrated effectiveness in rodent models, the benefits in clinical trials have been fairly modest and only discernible in those with more advanced renal disease.59 The reasons remain unclear, but it is possible that the impact of dietary protein may only become quantitatively significant after a substantial loss of functional renal mass and autoregulatory capacity.

Theoretically, other pharmacological agents that preferentially vasoconstrict the preglomerular vasculature also have the potential to reduce the intrarenal transmission of systemic pressures such as through protein restriction. However, unlike its demonstrated effectiveness in rodent models, the benefits in clinical trials have been fairly modest and only discernible in those with more advanced renal disease.59 The reasons remain unclear, but it is possible that the impact of dietary protein may only become quantitatively significant after a substantial loss of functional renal mass and autoregulatory capacity.

Conclusions

Recent investigations have provided substantial insights into the pathogenesis of hypertensive renal damage and have indicated that the severity of such damage depends on the degree to which renal autoregulatory mechanisms fail to prevent the BP elevations from being transmitted to the renal microvasculature. An impairment of these protective mechanisms in patients with diabetics and nondiabetic CKD likely accounts for their increased susceptibility to progressive renal damage with even moderate hypertension. Moreover, such renal damage is likely to initiate a vicious cycle of hypertension that is more difficult to control, resulting in more nephron loss and further enhancement of glomerular pressure transmission. Therefore, achieving normotension in CKD patients, although difficult, remains the primary clinical strategy to interrupt this vicious cycle, as recognized in recent guidelines. Little evidence for the much emphasized BP-independent protection by RAS blockade has been found in experimental animal models, when BP load has been accurately assessed using radiotelemetry. Similarly, the clinical evidence is also less definitive than has been claimed. In any event, the controversy is of greater scientific than clinical practice import. Most CKD patients require aggressive diuresis to achieve BP control and RAS blockers are very effective antihypertensives in effectively diured CKD patients. This antihypertensive synergy combined with their counteracting effects on potassium and magnesium balance provides a compelling rationale for combined diuretic/RAS blockade use in most CKD patients. In any event, finding more effective methods to achieve the lower BP goals is likely to have a greater impact on the still-escalating incidence of ESRD than a continued focus on BP-independent mechanisms to prevent hypertensive renal damage.

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