Disturbances in Renal Autoregulation and the Susceptibility to Hypertension-Induced Chronic Kidney Disease

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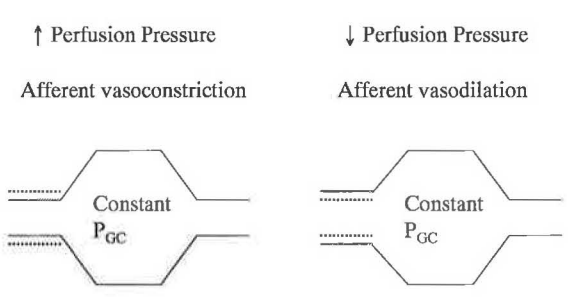
I. Introduction

The development and progression of chronic kidney disease varies considerably in patients with hypertension. Black hypertensive patients have a several fold increased risk of developing end-stage renal disease as compared to white hypertensives (1). The progression of chronic kidney disease is also more rapid in black patients (2). These differences cannot be fully explained by severity of hypertension, treatment variables, or socioeconomic factors (3). Rather, there is evidence to suggest that the kidney in blacks is intrinsically more susceptibility to the adverse effects of elevated blood pressure. This susceptibility can be demonstrated even at levels of blood pressure below the range recommended for treatment (4). Patients with diabetes mellitus and chronic kidney disease of other causes are also known to be particularly vulnerable to the damaging effects of even mild hypertension.

One mechanism to explain varying susceptibility to hypertension-induced renal injury is a disturbance in renal autoregulation. Under normal circumstances renal autoregulation allows intraglomerular pressure to be maintained relatively constant in the setting of wide variations in arterial pressure. A decrease in the efficiency of this system allows systemic pressure to be more easily transmitted into the glomerular circulation causing intraglomerular pressure to increase. Sustained elevations in intraglomerular pressure contribute importantly to renal injury. This paper will focus on the role that abnormal renal autoregulation plays in explaining the varying risk of hypertension-induced renal injury. The therapeutic implications of this abnormality will be discussed.

II. Renal Autoregulation

Renal autoregulation is accomplished by two mechanisms intrinsic to the kidney: a myogenic reflex intrinsic to the afferent arteriole and tubuloglomerular feedback (TGF). The myogenic reflex describes the ability of the afferent arteriole to either constrict or dilate in response to changes in intraluminal pressure. Constriction of this vessel in the setting of increased arterial pressure provides the most immediate response to guard against excessive rises in intraglomerular pressure. The mechanism of the myogenic response is related to distension of the vessel as intraluminal pressure rises. Vessel contraction in response to increased pressure is associated with membrane depolarization and increased calcium entry through voltage-gated L-type calcium channels (5). L-type calcium channel blockers inhibit this effect (6). The myogenic response is also present in the arcurate and interlobular arteries. The diffuse location of this response within the pre-glomerular



circulation and the rapidity with which it can be elicited (measured in seconds) provide a mechanism to buffer the glomerular capillaries from sudden changes in arterial pressure.

Tubuloglomerular feedback (TGF) is a second component of renal autoregulation that serves to reinforce the myogenic reflex by responding to changes in distal NaCl concentration. The anatomic basis for TGF lies in the juxtaposition of the macula densa cells in the distal nephron to smooth muscle cells in the afferent arteriole. The macula densa cells respond to changes in luminal NaCl concentration by way of a Na-K-2Cl co-transporter located on the apical membrane (7,8). An increase in arterial pressure causes an initial rise in intraglomerular pressure and glomerular filtration rate resulting in increased distal delivery of NaCl. The increase in NaCl concentration is sensed by the macula densa causing a vasoconstrictive signal to be sent to the afferent arteriole. As a result, intraglomerular pressure and glomerular filtration rate are returned towards normal and distal NaCl delivery falls.

In summary, changes in tone of the afferent arteriole influenced by both the myogenic reflex and TGF serve an important role in guarding against the development of glomerular hypertension in the setting of increased blood pressure. Dysfunction of one or both of these mechanisms can result in a blunted ability of the pre-glomerular circulation to constrict in response to an increase in renal perfusion pressure. As a result, even modest degrees of hypertension will be associated with exaggerated increases in glomerular capillary pressure ultimately predisposing to renal injury (Figure 1).

III. Abnormal Renal Autoregulation and Renal Injury in Animal Models of Hypertension

Differing susceptibilities to renal injury have been noted in animal models of hypertension (9-12). The spontaneously hypertensive (SH) rat develops renal injury only slowly and very late in life despite high arterial pressures that progressively worsen with age. By contrast, the fawn hooded hypertensive (FHH) rat dies of renal failure much earlier in life despite more modest degrees of hypertension. Similarly, the Brown Norway (BN) rat is also sensitive to hypertension-induced renal injury.

Transplantation studies between BN and histocompatible SH rats suggest that factors intrinsic to the kidney are responsible for differences in susceptibility to renal injury (11). In these studies uninephrectomized animals receive a second kidney from a rat of the same strain or from the other strain. The development of renal injury is then compared between the recipients native and transplanted kidney. BN and SH rat kidneys transplanted into the normotensive BN rat function normally and show no evidence of glomerulosclerosis or proteinuria. A SH rat kidney transplanted into the SH rat recipient also shows no injury. By contrast, the BN kidney transplanted into the hypertensive SH rat rapidly develops progressive proteinuria and renal injury.

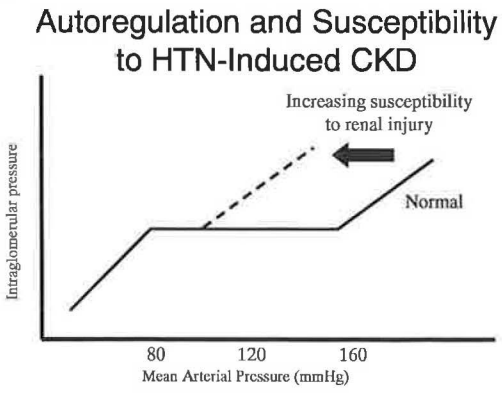
Differences in renal autoregulation may explain the differences in susceptibility of the BN and SH rat kidney to hypertension-induced renal injury. Autoregulation in the SH rat is highly efficient and remains so even in the setting of high arterial pressures (13,14). The afferent arteriole in these animals effectively buffers the intraglomerular circulation from high systemic pressures thereby rendering them more resistant to hypertension-induced glomerular injury. By contrast the autoregulatory response of the BN rat is limited and rapidly fails as systemic arterial hypertension develops (10).

Inadequate vasoconstriction by the afferent arteriole allows systemic pressure to be more easily transmitted into the glomerular circulation resulting in vascular injury.

A similar link between failure of autoregulation and susceptibility to renal injury has been noted in the FHH rat (12). This strain is characterized by the early onset of hypertension and development of proteinuria and glomerulosclerosis. Glomerular capillary pressure is increased prior to the development of renal injury and the degree of glomerular hypertension correlates closely with the level of systemic arterial pressure. These findings are consistent with a disturbance in the pre-glomerular circulation predisposing to glomerular hypertension in the setting of increased arterial pressure.

A second inbred strain from the same ancestry, (the fawn-hooded low blood pressure (FHL) rat), remains normotensive and does not develop proteinuria and glomerular disease until much later in life (12). However when hypertension is induced in these animals by treatment with nitro-L-arginine methyl ester the incidence of focal glomerulosclerosis markedly increases. In comparing these two strains, renal autoregulation is found to be impaired in the FHH rat before the development of glomerular disease. In the FHL animals autoregulation is intact at baseline but becomes impaired as hypertension develops. In both cases the development of renal injury correlates with a disturbance in renal autoregulation. Additional studies have localized this disturbance to the myogenic reflex (15,16). As compared to Sprague-Dawley and Wistar rats which are normally resistant to the development of renal disease, isolated pre-glomerular vessels taken form the FHH and FHL rats exhibit a blunted ability to vasoconstrict in response to increased perfusion pressure. In comparing the two strains of FH rats, the defect is more pronounced in the FHH animal.

In addition to genetic causes, abnormal autoregulation can be an acquired disorder. Acquired derangements can transform an animal previously resistant to one now susceptible to renal injury. In addition such derangements can accelerate the progression of already established renal disease no matter what the underlying cause. As previously mentioned, the SH rat is relatively resistant to the development of renal failure as a result of a highly efficient autoregulatory capacity. When these animals are subjected to 5/6 renal ablation, the renal autoregulatory capacity becomes markedly impaired due to dysfunction of the pre-glomerular circulation (17). The ablated animals develop severe microvascular disease due to more direct transmission of systemic pressure into the renal vasculature. In essence, what was originally benign essential hypertension is transformed into malignant nephrosclerosis. A similar association between increased susceptibility to hypertensive renal damage and impaired autoregulatory response has been demonstrated in other models of renal mass reduction (18,19).



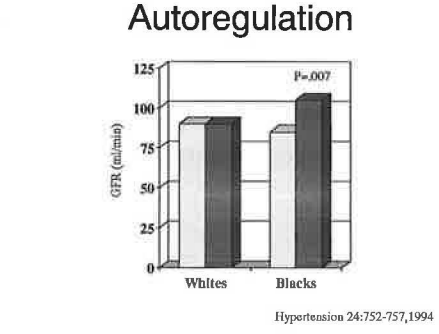
The administration of a high salt diet leads to the development of hypertension and the rapid onset of renal failure in the Dahl salt-sensitive (DS) rat (20). Renal

autoregulation is intact while on a low salt diet but becomes impaired as a consequence of the increased salt intake. In a manner similar to the ablated SH rat, this acquired derangement in renal autoregulation plays an important role in the rapid decline in renal function. By contrast, renal autoregulation is intact in the Dahl salt-resistant rat and is unaffected by increased dietary salt. Renal injury in these animals is less severe and develops much later in life.

In summary, renal autoregulation through proportionate increases in pre-glomerular resistance serves to buffer changes in intraglomerular pressure from increases in systemic arterial pressure. Decreased efficiency of this response may, in part, account for the differences in susceptibility to renal injury noted in various animal models of hypertension. A highly efficient system as in the SH rat may explain the relative resistance these animals demonstrate toward the development of hypertension-induced renal injury. By contrast, the blunted autoregulatory response noted in the BN, FH, DS rats, and models of renal ablation may explain the rapid and severe renal injury that develops in association with increases in systemic pressure.

IV. Renal Autoregulation and Susceptibility to Renal Injury in Hypertensive Patients

Differences in the efficiency of renal autoregulation may also explain the varying risk of renal disease is human hypertension. Black patients with hypertension are generally considered to be salt sensitive and are at increased risk for development of renal failure (21). In a study comparing white and black patients with essential hypertension and normal renal function, administration of a high salt diet was found to cause similar increases in blood pressure and renal blood flow (22). By contrast, the glomerular filtration rate increased significantly in the black subjects but remained unchanged in the white subjects. This increase in glomerular filtration rate in response to increased blood pressure is consistent with more direct transmission of pressure into the glomerular circulation due to a less efficient autoregulatory response. The stability in glomerular filtration rate despite a similar increase in blood pressure suggests renal autoregulation is intact in the white subjects.



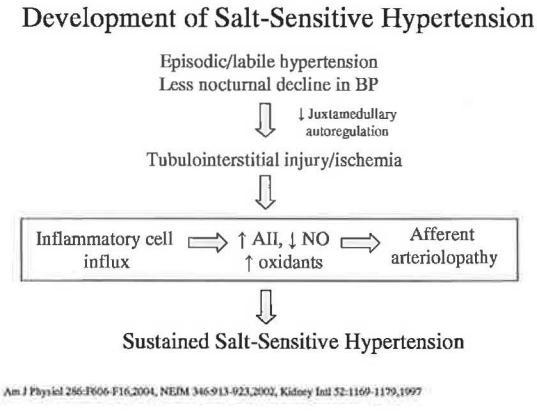
Renal hemodynamics has also been compared in black and white hypertensive subjects with normal renal function following the graded infusion of norepinephrine (23). At baseline, systolic and diastolic blood pressure, renal blood flow, and glomerular filtration rate were slightly higher in the black subjects. In response to norepinephrine-induced increased blood pressure, renal blood flow did not change in either group. By contrast, there was a significant increase in the glomerular filtration rate in the black subjects while the glomerular filtration rate remained unchanged in the white subjects. The higher baseline glomerular filtration rate that increased further in response to elevations in arterial blood pressure is consistent with less efficient autoregulation in the

black subjects. These findings would imply that the glomerular circulation is less well protected from elevations in arterial pressure potentially making the kidney in these black subjects more vulnerable to injury in the setting of hypertension.

Inefficient autoregulation could also lead to pressure-dependent glomerular injury in subjects who are considered to be normotensive but who have increased blood pressure lability. In a rat model of surgically reduced renal mass, blood pressure was radiotelemetrically monitored at 10-minute intervals for 15-16 weeks (24). Despite remaining normotensive these animals developed evidence of pressure dependent glomerular injury. While the average systolic blood pressure remained in the normotensive range there was evidence of substantial systolic blood pressure fluctuations over the course of the study with values often exceeding 150 mmHg. A strong correlation was noted between the amount of glomerulosclerosis and the percentage systolic blood pressure readings >150 mmHg. Such findings may be of particular relevance to black subjects who, as compared to whites, exhibit both greater blood pressure lability and less nocturnal decline in blood pressure (23,25-27). Transient excursions into the hypertensive range or sustained elevations of blood pressure at night could contribute to pressure mediated glomerular injury in patients considered normotensive by conventional periodic measurements. Blood pressure profiles of this kind could account for the greater prevalence of albuminuria noted in otherwise normotensive black subjects (4).

Patients with labile or episodic hypertension are at increased risk for developing sustained hypertension. Regional differences in the efficiency of renal autoregulation may be of relevance in this regard. Under normal circumstances cortical blood flow exhibits a high degree of autoregulation, while efficiency is less in the juxtamedullary region of the kidney (28,29). This difference may explain why histologic evidence of injury can first be detected in the juxtamedullary and medullary regions of the kidney in both experimental models of hypertension and human hypertension (30-32). Subtle injury in this region of the kidney can initiate a process that potentially explains the eventual transformation of episodic elevations in blood pressure to sustained hypertension that is salt sensitive in nature (30-32).

This transformation of labile or episodic hypertension into sustained salt-sensitive hypertension has been linked to an influx of inflammatory cells into the interstitium of the kidney in response to pressure-induced injury (32). These cells become the source of increased local production of angiotensin II and oxidants that in turn cause the depletion of nitric oxide. Depletion of nitric oxide has been shown in several models to be strongly associated with the development of salt sensitive hypertension. This process also contributes to the development of an arteriolopathy of the afferent arteriole that can perpetuate injury by contributing to downstream ischemia.

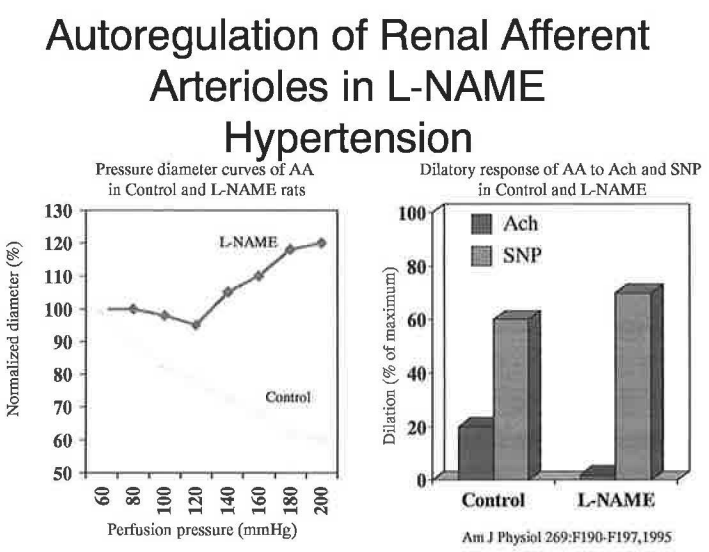


Several lines of evidence support an important role for injury induced influx of inflammatory cells in the genesis of salt sensitive hypertension (reviewed in 32). First, a mild inflammatory cells infiltrate is seen in virtually every animal mode of hypertension. Second, the degree of cellular infiltrate directly correlates with the severity of hypertension. Third, treatment strategies that result in a reduction in the renal inflammatory cell infiltrate either prevent or ameliorate the development of salt sensitive hypertension.

Once hypertension becomes sustained abnormalities in autoregulation are likely to worsen as a result of direct effects of increased blood pressure. In a model of hypertension induced by chronic infusion of angiotensin II renal injury is primarily localized to the outer medullary region of the kidney (33,34). Histologically there is progressive development of sudanophilic lesions throughout the pre-glomerular circulation to include the arcuate, interlobular, and afferent arterioles. However, impairment of afferent autoregulatory behavior can be detected prior to the development of these vascular lesions suggesting the abnormality is initially functional in nature (35). Preventing the development of hypertension by administering an AT_1 blocker, triple therapy, or servo-control mechanisms normalizes autoregulatory function suggesting the impairment in renal autoregulatory capability is a direct effect of increased blood pressure (33,35-37).

V. Endothelial Dysfunction as a Cause of Abnormal Renal Autoregulation

The pathophysiologic mechanism responsible for impaired autoregulation is not known. The myogenic response is thought to be an intrinsic property of vascular smooth muscle in the afferent arteriole in which distension due to increased intraluminal pressure results in membrane depolarization, increased calcium entry, and finally vessel contraction. However, the kidney produces a variety of locally generated substances including ATP, adenosine, angiotensin II, arachidonic acid metabolites, endothelin, and nitric oxide that can potentially influence the response of vascular smooth muscle to changes in perfusion pressure (37-40). For example, in the angiotensin infusion model of hypertension previously mentioned, administration of bosentan strikingly reduced the development of pre-glomerular vascular lesions and prevented the development of autoregulatory failure (34). These beneficial effects occurred without reducing blood pressure suggesting an important role of endothelin in mediating both the structural and functional alterations of the pre-glomerular circulation.



Nitric oxide is another substance that has been shown to modulate myogenic autoregulation in the kidney as well as other organ systems (41-45). Nitric oxide has both direct and indirect effects on potassium channels and therefore could modulate myogenic activity by affecting the membrane potential of vascular smooth muscle cells (46). In the animal model of hypertension induced by chronic administration of NG-nitro-L-arginine methyl ester (L-NAME) there is loss of myogenic autoregulation along the entire pre-glomerular vasculature in juxtamedullary nephrons (47). This effect occurs in the absence of vascular hypertrophy suggesting a functional disorder related to nitric oxide deficiency although increased blood pressure may also play a contributory role.

Since endothelium-derived substances such as endothelin and nitric oxide can influence myogenic autoregulation, endothelial dysfunction may play a contributory role in the genesis of abnormal renal autoregulation. The Wistar rat subjected to 5/6 nephrectomy is a model characterized by progressive renal damage associated with increases in glomerular pressure. However, it has been noted that there is a large degree of individual variability as to whether renal damage occurs or not. The animals that eventually develop progressive renal injury have been shown to exhibit impaired endothelium dependent vasodilation of the interlobar arteries prior to the ablative procedure (48). This vessel is part of the pre-glomerular circulation known to exhibit myogenic autoregulation. The baseline contribution of nitric oxide and vasodilatory prostaglandins to the vasodilatory response was less in these animals. The presence of endothelial dysfunction within the pre-glomerular circulation predicted the eventual development of renal injury following renal ablation in this study.

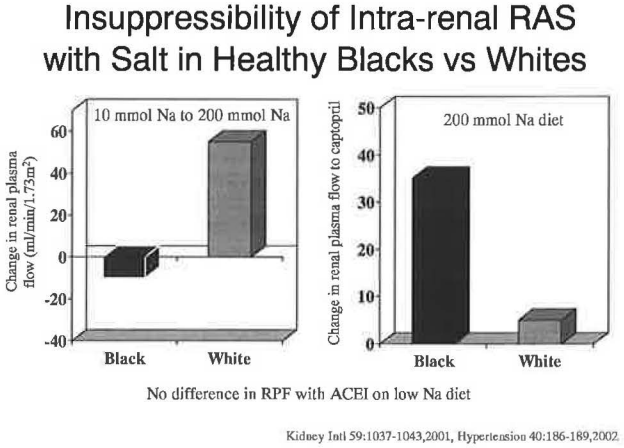
Abnormal renal autoregulation in black patients may simply be the renal manifestation of a more widespread disorder in endothelial function. Studies in healthy subjects have demonstrated decreased ischemia- and mental stress-induced endothelial dependent vasodilation in the forearm circulation in blacks as compared to whites (49-52). Similar racial differences have also been observed in hypertensive patients suggesting that endothelial dysfunction may play a more prominent role in the development of hypertension in blacks (53). In addition, endothelial dysfunction in patients with essential hypertension has been linked to the development of future cardiovascular disease events (54,55).

In this regard, endothelial dysfunction may contribute to impaired autoregulation in other vascular beds such as the cerebral circulation. In a manner similar to the glomerular circulation, cerebral autoregulation serves to limit excessive transmission of pressure into the brain (56,57). It is interesting to speculate that the disproportionate risk of stroke in black patients is the result of more direct transmission of systemic pressure into the cerebral circulation due to abnormal cerebral autoregulation (58,59).

Endothelial dysfunction in various vascular beds has been linked to deficient nitric oxide production and increased activity of angiotensin II. There is evidence of both these abnormalities in the kidney of black hypertensive patients (60). Evidence that intra-renal nitric oxide bioavailablity is reduced comes from studies in animals models in which inhibition of nitric oxide gives rise to salt sensitive hypertension mimicking that which is seen in black patients (61). In the DS rat, the development of hypertension is accompanied by a decrease in medullary blood flow both of which are prevented by the intramedullary infusion of L-arginine (61,62). Clinical studies, while indirect, are also consistent with decreased intrarenal nitric oxide bioavailability. In patients with type II

diabetes mellitus, microalbuminuria, and a normal glomerular filtration rate, there is less of an increased in glomerular filtration rate and renal plasma flow following an amino acid infusion in blacks as compared to whites. This decrease in functional reserve was associated with decreased clearance of nitrite and nitrate suggesting a deficiency of intra-renal nitric oxide production in the black subjects (63). In salt sensitive hypertensive blacks, infusion of L-arginine causes a greater fall in blood pressure and less of an increase in renal plasma flow as compared to a control group further suggesting dysregulation of nitric oxide metabolism in the kidney of black patients (64).

There is also evidence of increased intra-renal activity of the renin-angiotensin system in blacks. Angiotensin II can contribute to the accelerated degradation of nitric oxide by increasing NAD(P)H oxidase-mediated vascular superoxide production (32). In studies comparing healthy white and black subjects, renal perfusion was found to be lower in blacks as compared to whites while on a high salt diet (65,66). After receiving an angiotensin converting enzyme inhibitor this difference was no longer present. In the setting of a low salt diet no difference in renal plasma flow is seen between black and white subjects. Moreover the renal hemodynamic response to an ACE inhibitor or infusion of angiotensin II is similar under these conditions. These data are consistent with increased activity of the renin-angiotensin system in black subjects ingesting a high salt diet.



In summary, hemodynamic studies in black hypertensive patients show evidence of impaired renal autoregulatory capability. There is evidence of increased intrarenal activity of angiotensin II and decreased nitric oxide bioavailability. This imbalance between angiotensin II and nitric oxide may contribute to endothelial dysfunction within the pre-glomerular circulation similar to what has been described in other vascular beds. Endothelial dysfunction can lead to an attenuated response of the myogenic reflex and allow systemic pressure to be more easily transmitted into the glomerular circulation. Early on when hypertension is initially labile or when there is only a blunted decline in nocturnal blood pressure, injury to the kidney is concentrated in the juxtamedullary region where autoregulatory efficiency is less. Injury is this region can initiate a process that leads to the development of sustained salt sensitive hypertension. Sustained hypertension can contribute to more widespread disturbances due to direct adverse effects on myogenic autoregulation as well as exacerbate the imbalance between angiotensin II and nitric oxide. The net effect is a change in autoregulatory capability that renders the kidney more susceptible to the damaging effects of systemic hypertension.

VI. Other Conditions that Impair Renal Autoregulation

The degree to which autoregulation is impaired is likely to be variable in individual subjects thus explaining why some hypertensive black patients do not develop chronic kidney disease. While the severity of hypertension and degree to which it is controlled is important in this regard, equally as important is the presence of other factors that can further impair the autoregulatory response. The risk for developing chronic kidney disease in the setting of hypertension is likely to increase in parallel with the number of factors present reflecting the degree to which renal autoregulation is impaired. Those patients with multiple factors presumably will have the greatest impairment in renal autoregulation and will be at risk for development of chronic kidney disease even when blood pressure is only minimally elevated (Figure 2). As discussed below, various components of the metabolic syndrome have been linked to disturbances in renal autoregulation. In data from the third National Health and Nutrition Examination Survey (NHANES III) a graded relationship was found between the number of metabolic syndrome components and risk for chronic kidney disease or microalbuminuria (67)

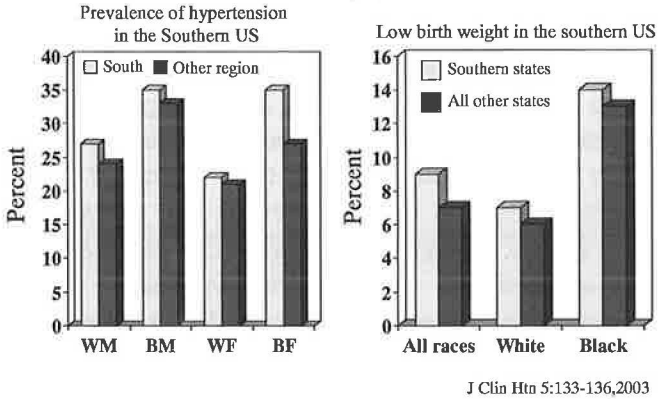
Conditions that Impair Myogenic Autoregulation

- Ethnic differences
- Low birth weight
- Aging
- Pre-existing CKD
- Diabetes mellitus
- Obesity and insulin resistance
- Hypercholesterolemia
- Hyperuricemia

A. Low Birth Weight and Intrauterine Growth Retardation

Low birth weight (LBW) and intrauterine growth retardation (IUGR) have been linked to the subsequent development of hypertension and kidney disease in adult patients (68,69). Black race and maternal hypertension are two known risk factors for LBW and IUGR. Maternal hypertension is more prevalent in black women as compared to whites making the population-attributable risk of LBW highest among babies of hypertensive black women (70). In the southern United States the low birth weight rate is nearly twice as high in blacks as compared to whites. This difference in risk for LBW is paralleled by similar racial disparities in the prevalence of hypertension and risk of end-stage renal disease (71). In the state of Mississippi alone

Low Birth Weight as a Risk Factor for Hypertension



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blacks have an estimated risk of end-stage renal disease that is five times greater than whites.

The eventual development of hypertension and kidney disease in adults born with IUGR and LBW has been attributed to a decrease in nephron number. In the course of normal renal development nearly 60% of nephrons are formed in the third trimester with further formation stopping at 36 weeks gestation. Interference with third trimester fetal growth has been shown to affect nephron development. LBW offspring in rats have nearly a 30% reduction in nephron number (70,72). A significant reduction in nephron number has also been found in human neonates (73). In addition, an inverse correlation has been noted between glomerular number and volume (74,75). In this regard, glomerular volume has been noted to be greater in renal tissue taken from black kidney donors and from autopsies performed in young healthy black subjects (76,77).

Increased glomerular volume is thought to represent compensatory hypertrophy and hyperfiltration in an attempt to sustain adequate renal function in the setting of reduced nephron number. However these changes in glomerular structure and function may leave the kidney more susceptible to hypertension induced injury through a number of mechanisms related to impaired autoregulation. In the setting of reduced renal mass there is vasodilation of both afferent and efferent arterioles. Because the afferent vessel dilates to a greater extent intraglomerular pressure is also increased. The vasodilated pre-glomerular circulation leaves the kidney more vulnerable to further increases in glomerular pressure should systemic hypertension eventually develop.

During renal development the last population of nephrons to form are those in the outermost cortex. Consequently, the reduction in nephron mass associated with LBW or IUGR would presumably be concentrated in this region leaving the number of juxtamedullary nephrons relatively normal since their development is completed much earlier. Juxtamedullary nephrons would now comprise a greater percentage of the total nephron mass. As previously mentioned, juxtamedullary nephrons are known to exhibit less efficient autoregulation as compared to superficial cortical nephrons. As a result, the adult black patient with a history of IUGR and LBW would be born with kidneys intrinsically more susceptible to hypertension-induced injury.

Endothelial dysfunction may also be responsible for abnormal renal autoregulation in patients with a history of LBW and IUGR. Endothelial dysfunction is already demonstrable in neonates with a history of low birth weight (78,79). This disturbance persists into childhood and adult life in the absence of other cardiovascular risks factors (80-82).

B. Aging

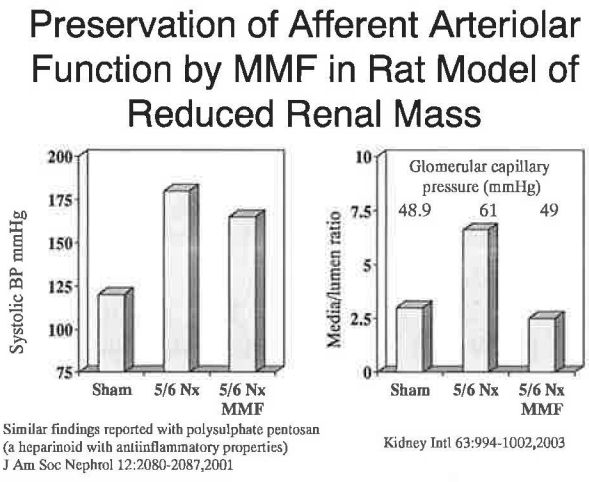
There is evidence that advancing age is associated with a loss in autoregulatory efficiency placing the elderly at increased risk for hypertension-induced renal injury. In a recent study of human kidneys taken from normotensive subjects, afferent arterioles with non-occlusive hyaline deposits were found to have nearly twice the luminal diameter as compared to vessels without such lesions (83). These dilated arterioles were more prominently associated with hypertrophied glomeruli containing larger than normal capillary lumens particularly in the hilar region reminiscent of those found in experimental models in which glomerular hypertension, hyperfiltration, and impaired autoregulatory capacity are present. While focal in nature these changes are consistent

with morphologic evidence of impaired autoregulatory capability accompanying the aging process. The smooth muscle in afferent arterioles with greater luminal diameter would face greater wall tension as predicted by the law of Laplace. As a result, myogenic contraction in response to vessel distention would likely be impaired. The net effect is less diminution of pressure transmitted between the systemic and glomerular circulation.

Advancing age is associated with progressive loss of renal mass that is primarily cortical, with relative sparing of the renal medulla (Reviewed in 84). A preferential increase in perfusion of more juxtamedullary nephrons during the aging process would be consistent with the morphologic changes discussed above since this region of the kidney is known to autoregulate less well as compared to the outer cortex. Early injury to this region of the kidney could account for the development of salt sensitive hypertension which is characteristic of elderly hypertensive patients (30). In addition, inefficient autoregulation may play an important role in the age-related increase in number of hyalinized or sclerotic glomeruli identified in histologic studies of aging kidneys, an effect likely made worse with the development of hypertension.

C. Chronic Kidney Disease

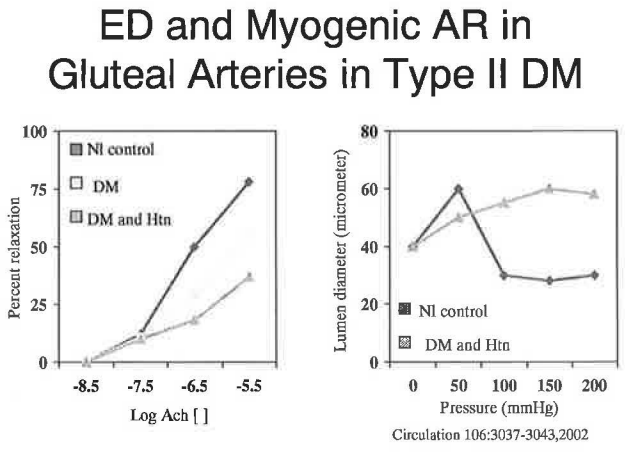
Poorly controlled blood pressure is one of the most important factors contributing to accelerated loss of renal function in patients with chronic kidney disease of any cause. Abnormal renal autoregulation plays an important role in explaining this sensitivity to hypertension. Loss of nephron mass is associated with increased intraglomerular pressure and hyperfiltration in the remaining renal tissue (85-87). The renal circulation takes on the characteristics of a pressure passive system in which increases in systemic pressure become accompanied by proportionate increases in intraglomerular pressure (88,89). This loss of renal autoregulation is analogous to that which occurs in the SH rat subjected to renal ablation.



In rats subjected to 5/6 nephrectomy, hypertension and proteinuria develop in association with increased glomerular pressure (90). These animals also develop evidence of an arteriolopathy of the afferent arteriole characterized by a significant increase in the media to lumen ratio consistent with hypertrophy of the vessel wall. Treatment with mycophenolate mofetil has been shown to attenuate these vascular changes and at the same time prevent the development of glomerular hypertension despite the persistence of systemic hypertension. This dissociation between systemic and intraglomerular pressure suggests an improvement in glomerular hemodynamics due to restoration of the functional myogenic response of the afferent arteriole.

D. Diabetes Mellitus

Diabetic patients are at increased risk for accelerated loss of renal function in the setting of hypertension. In the very earliest stages of the disease renal function is characterized by increased renal blood flow and glomerular filtration rate. This hyperdynamic circulation has been linked to impaired renal autoregulation (91). Studies in experimental models of diabetes have confirmed that renal autoregulation is impaired in the earliest stages of the disease and is an important factor contributing to these circulatory changes (92,93). The basis for impaired autoregulation in this setting has been attributed to changes in TGF signaling (94). There is evidence for a primary increase in NaCl reabsorption in the proximal nephron that has been attributed to the combined effects of increased activity and expression of the Na-glucose transporter and generalized hypertrophy of the proximal nephron. The resultant decrease in concentration of NaCl reaching the macula densa would have the effect of sending a vasodilatory signal to the afferent arteriole. The resultant increase in renal blood flow and glomerular filtration rate would serve to partially restore fluid and electrolyte delivery to the distal nephron but at the expense of hyperfiltration. In addition these changes would allow any increase in systemic blood pressure to be more easily transmitted into the glomerular capillaries predisposing to glomerular injury.



In addition to changes in TGF signaling, there is also evidence of dysfunction in the myogenic component of autoregulation. Changes in the characteristics of smooth muscle calcium and potassium channels have been described to account for afferent arteriolar vasodilation (93). Inhibition of prostaglandins synthesis has been shown to correct the myogenic response in an experimental model of diabetes (95). This observation again emphasizes that the efficiency of myogenic autoregulation can be influenced by locally produced factors, some of which may be derived from the endothelium, and is consistent with the notion that impaired renal autoregulation may be a manifestation of endothelial dysfunction within the renal circulation.

In patients with type II diabetes mellitus small arteries obtained from a gluteal biopsy demonstrate evidence of endothelial dysfunction and impaired myogenic responsiveness as compared to non-diabetic subjects (96). The presence of similar defects elsewhere in the microvasculature would predispose to enhanced transmission of systemic pressure into target organs such as the eye, brain, and kidney.

E. Hypercholesterolemia

Studies in human subjects have shown that hypercholesterolemia is associated with endothelial dysfunction in a variety of vascular beds (97). A similar disturbance in the renal circulation could impair renal autoregulation and predispose to renal injury. In

this regard diet induced hypercholesterolemia in the pig is associated with impaired renal perfusion (98). As compared to normal controls, hypercholesterolemic animals exhibit a blunted increase in renal blood flow and glomerular filtration rate in response to acetylcholine infusion. Treatment with either an endothelin receptor blocker or an angiotensin receptor blocker corrects the abnormality suggesting that endothelin and/or angiotensin II is playing a role in the genesis of cholesterol-induced endothelial dysfunction within the renal circulation (98,99). Hypercholesterolemia-induced disturbances in renal autoregulation could account for the findings of a recent prospective study linking high cholesterol levels with the development of chronic kidney disease in apparently healthy men (100).

F. Uric Acid

Hyperuricemia is commonly present in older persons with hypertension and may play a contributing role to the development of renal injury (101). In normal rats made mildly hyperuricemic, an arteriolopathy develops in the afferent arteriole (102). These animals also develop hypertension and increased glomerular pressures. The increase in glomerular capillary pressure is positively correlated with serum uric acid levels and the degree of thickening in the pre-glomerular arterioles. It was postulated that proliferation of smooth muscle cells and increased collagen content might have limited the capacity of the afferent arteriole to contract in response to a higher perfusion pressure thus rendering the animals more susceptible to hypertension–induced injury.

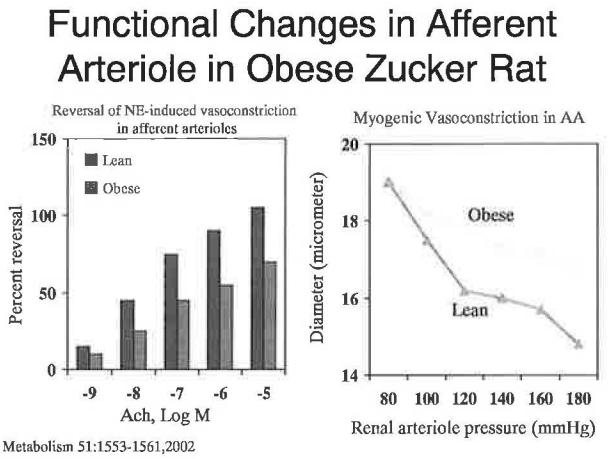
In rats subjected to 5/6 nephrectomy the induction of mild hyperuricemia worsens the degree of proteinuria and hypertension and accentuates the arteriolopathy that typically occurs in the afferent arteriole of remnant rats without hyperuricemia (103). Treatment with allopurinol to prevent hyperuricemia prevents these histologic changes and lowers intraglomerular pressure despite the persistence of systemic hypertension. Similar to what was observed in the ablated rat model treated with mycophenolate mofetil, this disassociation between systemic and intraglomerular pressure suggests the myogenic response of the afferent arteriole had been restored with correction of the hyperuricemia.

Uric acid can alter the structure and function of the afferent arteriole through a variety of mechanisms. Uric acid has been shown to induce cellular proliferation and stimulate a variety of growth factors that could potentially account for thickening of the vessel (104-107). Functional alterations can be the result of structural alterations but may also result from an inhibitory effect of uric acid on nitric oxide production. Uric acid has been shown to correlate inversely with plasma nitric oxide levels and with acetycholine-dependent vasodilation (108,109). Treatment of hyperuricemia with allopurinol improves endothelial dependent vasodilation in patients with congestive heart failure and diabetes (110-112).

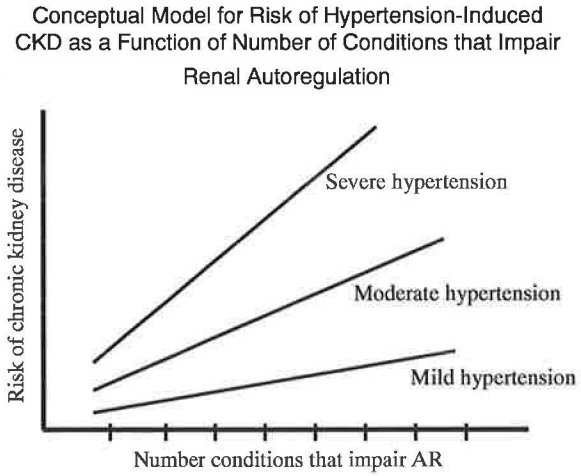
G. Obesity

Obesity is associated with impaired endothelial dependent vasodilation in the forearm and leg circulation due to impaired release of nitric oxide (113). Hemodynamic studies of the kidney in obesity suggest endothelial dysfunction is also present in the renal circulation contributing to impaired renal autoregulation (114). As compared to healthy controls, renal plasma flow and glomerular filtration rate are increased in

otherwise normal obese subjects. The increase in glomerular filtration rate is relatively greater resulting in a higher filtration fraction. An analysis of dextran sieving data suggests the increase in glomerular filtration rate is primarily accounted for by an increase in glomerular capillary pressure. Enhanced transmission of systemic pressure into the glomerular circulation through a dilated afferent arteriole can account for these findings. These hemodynamic changes along with the frequent occurrence of hypertension and diabetes may account for the greater risk of end-stage renal disease in obese subjects (115).



Studies in obese Zucker rats suggest a role for insulin resistance in the development of impaired afferent arteriolar vasomotor activity (116). These animals exhibit a blunted ability to constrict the afferent arteriole in response to increased perfusion pressure when compared to Zucker lean rats. In addition, the vasodilatory response of the vessel to acetylcholine is diminished consistent with the presence of endothelial dysfunction. These vasomotor abnormalities were improved following treatment with the insulin sensitizing agent troglitazone.



VII. Therapeutic Implications

Impaired renal autoregulation leads to the development of a higher intraglomerular pressure for any given level of systemic blood pressure. This effect can initiate or exacerbate renal injury since glomerular capillary hypertension is known to be an important hemodynamic alteration associated with the development of glomerular sclerosis and progressive kidney failure. The two most effective strategies to minimize an increase in intraglomerular pressure in patients with impaired autoregulation are

aggressive lowering of systemic blood pressure and inhibition of the renin-angiotensin system (117).

Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARB) are effective antihypertensive agents that possess the unique ability to lower intraglomerular pressure through dilation of the efferent arteriole of the glomerular circulation. Of particular importance, this reduction in intraglomerular pressure will occur even in the setting of no or only a minimal fall in systemic blood pressure. The ACEI and ARB class also interfere in other angiotensin II-mediated effects that may play a role in the progression of renal disease (118).

With respect to renal autoregulation, decreasing the formation or activity of angiotensin II can potentially have an adverse effect with regards to tone of the afferent arteriole. Angiotensin II activity has important effects in altering the sensitivity of the TGF system. A decrease in AII activity leads to decreased sensitivity of TGF such that there is less vasoconstriction of the afferent arteriole for any given amount of distal NaCl delivery (7,8). As a result, transmission of pressure into the glomerular circulation is facilitated. The attenuation in TGF response could potentially negate the beneficial effect that ACEIs have on lowering intraglomerular pressure mediated through efferent arteriolar vasodilation.

Despite this concern, studies in the FH rat have shown that prolonged administration of an ACEI actually leads to a normalization or increase in sensitivity of the TGF system (119). It is possible that the improvement in TGF sensitivity in the setting of prolonged ACEI therapy is due to a direct effect in improving endothelial function at the level of the afferent arteriole. In support of this idea is a large amount of evidence implicating excess angiotensin II and deficient nitric oxide in the genesis of endothelial dysfunction (120). Inhibiting the renin-angiotensin system with either ACEI or ARB therapy has been shown to improve endothelial function in numerous vascular beds.

Studies have also been performed examining whether inhibition of angiotensin II leads to an improvement in endothelial dysfunction in the renal vascular bed. Renal endothelial function is assayed by examining the effect of L-arginine on renal hemodynamics (121,122). The integrity of endothelial function is reflected by the degree of renal vascular relaxation presumably mediated by the endothelial conversion of L-arginine into nitric oxide. In these studies, infusion of L-arginine into hypertensive subjects is associated with a blunted renal vasodilatory response as compared to normotensive subjects. The decrease in renal vascular resistance, the increase in renal plasma flow, and the decrease in filtration fraction were significantly attenuated in the hypertensive group. In addition there was a smaller increase in urinary nitrate/nitrite excretion in the hypertensive subjects despite similar baseline values. These results were interpreted as indicating that endothelial-dependent renal vascular relaxation and production of nitric oxide are impaired in hypertensive subjects (121).

In a double blind randomized trial of hypertensive subjects, the effect of L-arginine infusion on renal hemodynamics were compared before and after twelve weeks of therapy with either the calcium channel blocker, amlodipine, versus the angiotensin converting enzyme inhibitor, imidapril (122). At the end of twelve weeks blood pressure was similarly reduced in the two treatment groups. At baseline the degree of L-arginine-induced renal-vascular relaxation was similar in the imidapril and amlodipine groups.

There was a similar increase in renal plasma flow and similar decrease in renal vascular resistance and filtration fraction. After twelve weeks of drug therapy, the vasodilating response to L-arginine was augmented in those patients treated with the angiotensin converting enzyme inhibitor, whereas L-arginine induced changes in the amlodipine group were unaltered. In addition, urinary excretion of nitrate/nitrite in the ACEI group increased at twelve weeks but remained unchanged in the amlodipine treated subjects. These findings suggest that ACEI therapy is associated with an improvement in impaired renal endothelial dysfunction due to an increase in nitric oxide bioavailability. This benefit is independent of blood pressure control.

The beneficial effects of inhibiting the activity of angiotensin II on endothelial dysfunction in the renal circulation may also extend to the cerebral circulation. In the Losartan Intervention for Endpoint reduction in hypertension (LIFE) trial administration of an angiotensin receptor blocker was found to significantly reduce the incidence of stroke as compared to a beta blocker despite the same level of blood pressure control (123). It is interesting to speculate that this benefit resulted, in part, from an improvement in endothelial dysfunction leading to restoration of normal autoregulation in the cerebral circulation (124).

A second strategy to prevent the development of glomerular hypertension is aggressive lowering of systemic blood pressure. This approach is effective since changes in intraglomerular pressure begin to parallel changes in systemic pressure when renal autoregulation is impaired. Just as an increase in systemic pressure tends to raise intraglomerular pressure, a decrease in systemic blood pressure should effectively lower intraglomerular pressure.

The necessity of lowering mean arteriole pressure in a sufficient amount to decrease intraglomerular pressure is of particular relevance to the use of calcium channel blockers. In addition to lowering mean arterial pressure, these agents have a vasodilatory effect upon the afferent arteriole. As a result, the net effect of calcium channel blocker therapy can be to increase intraglomerular pressure particularly when the reduction in systemic arterial pressure is inadequate. This effect is exacerbated when these drugs are used in the setting of an already impaired autoregulatory capacity since these agents can totally abolish the autoregulatory response (125).

Such effects may explain why amlodipine was associated with an adverse renal outcome in African American patients with early hypertensive nephrosclerosis despite causing an initial increase in glomerular filtration rate (126). While all calcium channel blockers dilate the afferent vessel the disruption in renal autoregulation is greater with dihydropyridines (127). This difference may in part explain some of the differences in renal outcome reported between the various classes of calcium channel blockers. Despite this effect, dihydropyridine calcium channel blockers are effective blood pressure lowering agents and are therefore useful in hypertensive patients with chronic renal disease. To guard against potential adverse effects on renal hemodynamics they should not be utilized in the absence of either an ACE inhibitor of an angiotensin receptor blocker in patients with established nephropathy (128).

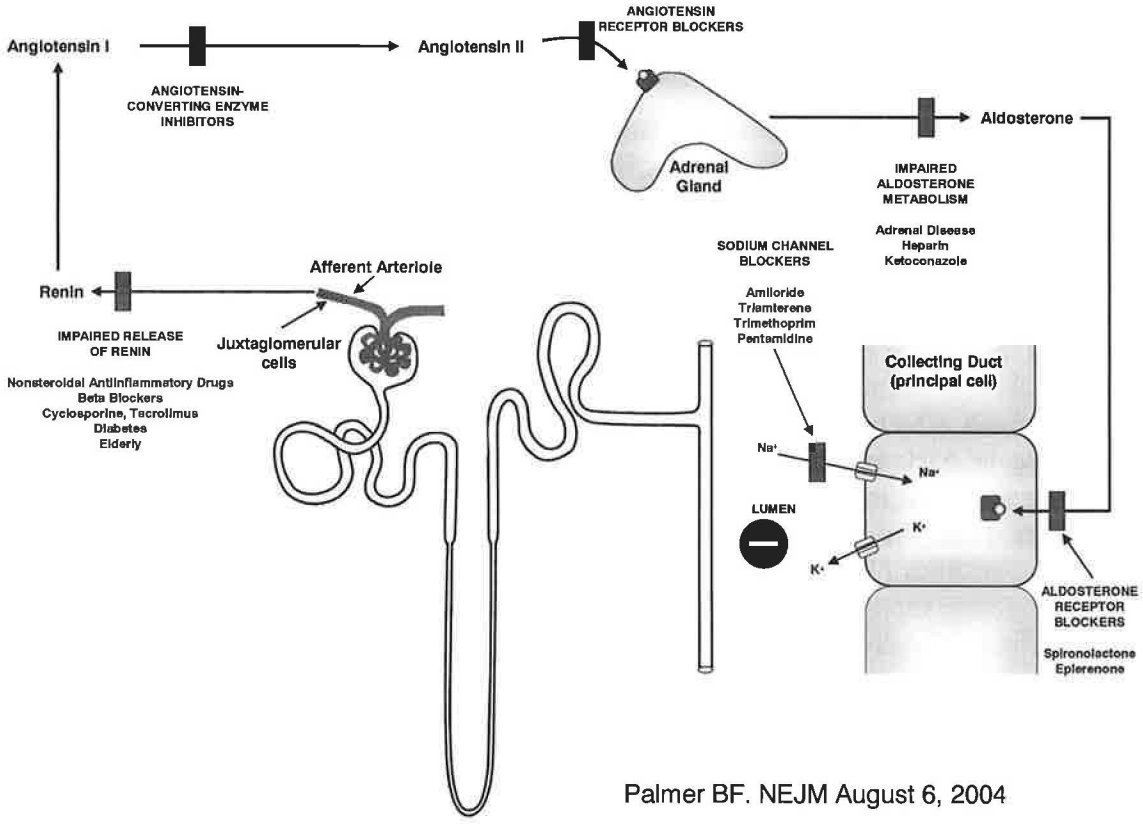
Administration of a low protein diet may also be of benefit in states of impaired renal autoregulation. A low protein diet is commonly prescribed to patients with chronic renal failure as an additional way to slow the progression of renal disease. The beneficial effects of a low protein diet have been primarily attributed to favorable effects on renal

hemodynamics and structural glomerular hypertrophy. In a recent report using a rat model of renal ablation, preservation of renal autoregulation was found to be central to the renoprotective effects of a low protein diet (129).

It is likely that other therapies that improve endothelial dysfunction in non-renal vascular beds would have similar benefits in the renal circulation and therefore could potentially improve renal autoregulation. In this regard, statins are known to have renoprotective effects as well as beneficial effects on endothelial dysfunction (97,130). It is possible that improvement in renal endothelial dysfunction may be one of the mechanisms by which these drugs benefit the kidney. Similarly, the thiazolidinediones have been shown to improve endothelial dysfunction in extrarenal vascular beds and therefore may be of benefit in patients with or who are at increased risk of renal disease (131).

VII. Hyperkalemia Complicating the use of ACE inhibitors and ARB's

Use of ACE inhibitors or ARB's in patients with chronic renal disease can be associated with hyperkalemia. As with a rise in the serum creatinine concentration, many physicians respond to even mild increases in the serum potassium by immediately discontinuing these drugs without first considering steps that might be taken to minimize this complication. In many instances physicians are reluctant to even initiate such



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therapy simply because the patient has an elevated creatinine concentration. Such an approach is strictly to the patients disadvantage since patients with more advanced renal insufficiency derive a greater amount of protection from renal disease progression with

these drugs. While close monitoring is required, several steps can be taken to minimize the likelihood of developing hyperkalemia.

One should review the patient's medication profile and wherever possible discontinue drugs that can impair renal potassium excretion. Nonsteroidal anti-inflammatory agents, either prescribed or those taken over-the-counter, are common offenders in this regard. The patients should be placed on a low potassium diet with specific counseling against the use of potassium containing salt substitutes. Diuretics are particularly effective in minimizing hyperkalemia. In patients with a serum creatinine <1.8 mg/dl, thiazide diuretics can be used but with more severe renal insufficiency loop diuretics are required. In chronic renal failure patients with metabolic acidosis (bicarbonate concentration < 20 mEq/l), administration of sodium bicarbonate should be given. Decreasing the dose of the ACE inhibitor or switching to one that is not totally dependent on renal excretion may be of help. In one study of patients with mild chronic renal failure use of an ARB was found to have less of an effect to increase serum potassium when compared to an ACE inhibitor. However, this difference was small and at present these agents should be viewed as having similar risks for developing hyperkalemia. Intermittent use of a potassium binding resin can be tried however this drug is poorly tolerated when used on a chronic basis and has been associated with gastrointestinal ulceration.

With implementation of these steps the risk of hyperkalemia severe enough to warrant discontinuation of ACE inhibitors or angiotensin receptor blockers is quite low even in patients with moderate to severe renal insufficiency. In patients with chronic renal disease the serum potassium should be checked within 1-2 weeks of starting an ACE inhibitor or an angiotensin receptor blocker. If the potassium concentration increases to a value greater than 5.6 mEq/l despite the precautions noted above then another class of antihypertensive therapy will need to be utilized.

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