Clinical Implications of Impaired Renal Autoregulation

Internal Medicine Grand Rounds
October 12, 2000

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This is to acknowledge that Biff F. Palmer, M.D. has disclosed no financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Palmer will not be discussing "off-label" uses in his presentation.

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I. Introduction

The kidney maintains renal blood flow and glomerular filtration rate (GFR) within a narrow range despite wide variations in systemic blood pressure. This process of autoregulation can be linked to two primary mechanisms that are both intrinsic to the kidney: a myogenic reflex localized to the afferent arteriole and tubuloglomerular feedback (TGF). This paper will first review the normal physiology of renal autoregulation and then discuss the clinical implications of impaired autoregulation in the setting of hypertension and chronic renal disease.

II. Myogenic Reflex

Since intraglomerular pressure is an important determinant of GFR, small changes in arterial pressure would be expected to result in large fluctuations in GFR. However, under normal circumstances renal blood flow and GFR are kept fairly constant despite changes in mean arterial pressure that vary between 80 and 170 mmHg (1). The autoregulation of GFR and renal blood flow within this range of arterial pressure is accomplished by adjustments in renal vascular resistance primarily at the afferent arteriole. An increase in arterial pressure leads to increased tone of the afferent arteriole such that transmission of the increased pressure to the glomerular capillaries is limited. Conversely, as arterial pressure falls the afferent vessel relaxes thereby allowing increased pressure to be transmitted to the glomerulus. In this manner intraglomerular pressure is kept fairly constant and GFR are maintained within a narrow range.

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 (2). L-type calcium channel blockers inhibit this myogenic reflex (3). The myogenic response is also present in the arcurate and interlobular arteries. The diffuse location of this response within the preglomerular circulation and the rapidity in which it can be elicited (measured in seconds) provide a mechanism to buffer the glomerular capillaries from sudden changes in arterial pressure.

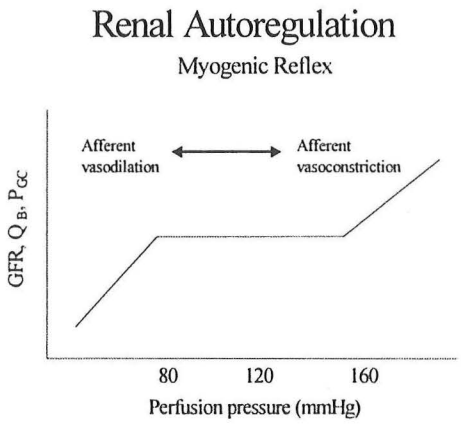

Figure 1

A fall in mean arterial pressure to values less than 80 mmHg leads to an inability to maintain renal hemodynamics (Figure 1). In this setting GFR and renal blood flow fall in parallel with the drop in systemic pressure. With extreme elevations of blood pressure there is also a loss of renal autoregulation such that high systemic pressures are directly transmitted into the glomerulus resulting in glomerular injury and rapid loss of renal function (4).

The pressure at which autoregulation fails is variable and is related to the suddenness and rapidity of rise in blood pressure. With chronic or slowly progressive hypertension there is a right ward shift in the curve relating systemic perfusion pressure and intraglomerular pressure. This resetting allows the autoregulatory response to be maintained at much higher systemic pressures. By contrast, hypertension that is sudden and rapid in onset may result in loss of renal autoregulation at pressures that are of much less in magnitude.

III. Tubuloglomerular Feedback

TGF is a second component of renal autoregulation in which the GFR is altered by changes in tubular flow rate. This mechanism provides a means for adjusting glomerular hemodynamcis in response to the metabolic demands of the tubules. The system serves to prevent extreme changes in distal sodium delivery that would otherwise impair the ability of the distal nephron to properly adjust the final composition of the urine. 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 cotransporter located on the apical membrane (5).

An increase in arterial pressure causes an initial rise in intraglomerular pressure and GFR resulting in increased distal delivery of NaCl (Figure 2). The increase in NaCl concentration is sensed by the macula densa cells causing a vasoconstrictive signal to be sent to the afferent arteriole. As a result, intraglomerular pressure and GFR are returned towards normal and distal NaCl delivery falls. Conversely a decrease in renal perfusion results in a transient decrease in GFR. The resulting fall in distal NaCl concentration results in relaxation of the afferent vessel thereby restoring intraglomerular pressure and GFR. These hemodynamic changes lead to an increase in distal NaCl delivery. The vascular response to changes in renal perfusion pressure is rapid, nonlinear, and has its greatest sensitivity in the range of ambient NaCl concentrations (6-8).

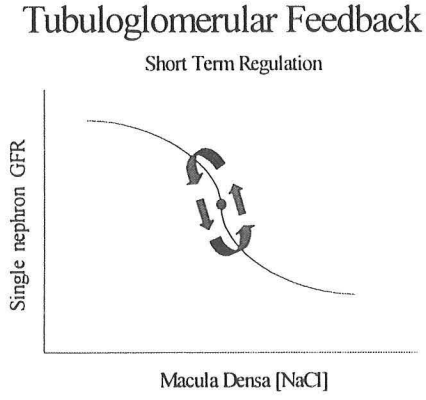

Figure 2

The ability to rapidly adjust GFR in response to changes in distal NaCl concentration provides a mechanism to prevent excessive bursts of urinary sodium excretion or retention that are not relevant to maintenance of total body salt balance. For example, it would be inappropriate to salt balance to have a burst of urinary salt excretion in response to transient episodes of increased arterial pressure brought on by daily stress or changes in posture. Similarly, salt retention elicited by a decrease in arterial pressure induced by recumbency or sleep would likewise be inappropriate. TGF provides a means to ensure relative constancy of distal NaCl delivery in the setting of random and fast changes in mean arterial pressure that are unrelated to total body salt balance.

When alterations in distal NaCl concentration become sustained as in the setting of increased or decreased total body salt content the previously described response of TGF would appear maladaptive. For example, reducing GFR in response to a sustained increase in distal NaCl concentration as with the ingestion of a high salt diet could limit salt excretion and lead to volume overload. Conversely, increasing GFR in response to a persistent decline in distal NaCl concentration as during hemorrhage could lead to salt wasting and further contribute to hemodynamic instability. Such maladaptive responses are prevented by two effects. The first effect relates to TGF-induced alterations in renin release and subsequent formation of angiotensin II. Sustained increases in NaCl concentration at the macula densa result in suppression of renin release from the juxtaglomerular cells while sustained decreases in NaCl concentration stimulate the release of renin. Subsequent alterations in the renin-angiotensin-aldosterone axis lead to adjustments in urinary sodium excretion that are appropriate to maintenance of normal extracellular fluid volume.

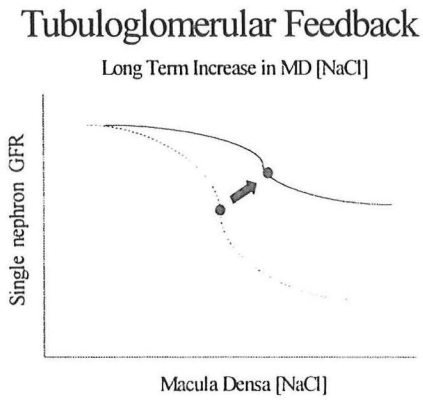

Figure 3

The second effect that prevents a maladaptive response is a change in sensitivity of the TGF mechanism. A persistent increase in distal NaCl concentration leads to decreased sensitivity of TGF such that GFR is not reduced but rather stays the same or actually slightly increases (Figure 3). In a similar manner, sustained decreases in NaCl concentration enhance the sensitivity of TGF so that GFR remains stable or slightly decreases (Figure 4). This adaptation in TGF to long term alterations in NaCl delivery ensures that adjustments in renal hemodynamics are appropriate to the maintenance of normal salt balance. It should be noted that with resetting of TGF to a new set point, the system continues to exhibit the rapid response to random oscillating alterations in NaCl concentration that are not related to salt balance.

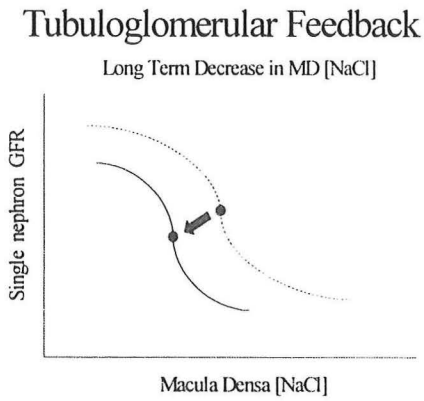

Figure 4

The phenomena of macula densa-induced alterations in renin release and TGF resetting are mechanistically coupled. Although multifactorial in origin, angiotensin II is the single most important factor in determining the sensitivity of TGF. Increased levels of angiotensin II are associated with enhanced sensitivity while decreased levels suppress the sensitivity of the system (9). In this manner, changes in the renin-angiotensin system brought on by sustained alterations in distal

NaCl concentration not only play a role in adjusting urinary salt excretion but also importantly influence the sensitivity of the TGF process. The precise mechanism by which angiotensin II can lead to resetting of TGF is not known but may involve interactions with adenosine and nitric oxide.

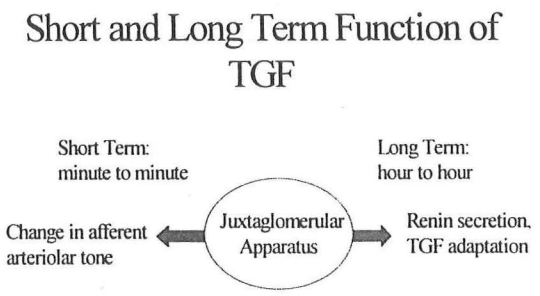

Figure 5

To summarize, the distal nephron has a limited total reabsorptive capacity but is important in defining the final qualitative characteristics of the urine. By preventing excessive swings in distal NaCl delivery, the TGF mechanism helps to ensure optimal function of the distal nephron. One component of this system is short term regulation of GFR in response to fast and random perturbations in NaCl delivery that are unrelated to total body salt balance. A second component of this system is the ability to reset in response to persistent changes in distal NaCl delivery and influence the renin-angiotensin-aldosterone axis. These later two responses are mechanistically coupled and help to ensure proper maintenance of salt balance on a longer term basis (Figure 5).

IV. Tubuloglomerular Feedback and Development of Hypertension

A normal human subject placed on a high salt diet will reestablish salt balance with minimal to no change in blood pressure. By contrast many hypertensive subjects given the same quantity of salt will establish a new steady state of salt balance only at the expense of a higher blood pressure. This hypertensive shift in the pressure-natriuresis relationship has been linked to an intrinsic abnormality of renal salt excretion (10). The most compelling evidence in support of this concept are studies in animal models of hypertension where transplantation of a kidney from a hypertensive animal transfers the elevated blood pressure to the previously normotensive recipient (11). The are many mechanisms involving the regulation of renal salt transport that can potentially explain the abnormal relationship between renal perfusion pressure and renal sodium excretion. One potential mechanism for which there is experimental support is an abnormal TGF response (10) (Figure 6).

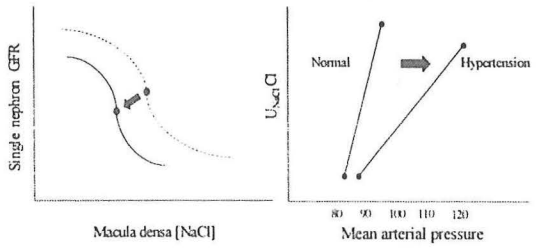

Figure 6

An abnormality in TGF can potentially give rise to hypertension as a result of either a baseline increase in sensitivity or an inability to decrease the sensitivity of the system in response to sustained increases in dietary salt intake. With either one of these disturbances, ingestion of a high salt diet will result in expansion of extracellular fluid volume and the development of hypertension. Eventually a new steady state will be reached in which the characteristics of TGF become normalized but only at the expense of sustained hypertension.

Studies in the spontaneous hypertensive rat (SHR) model of hypertension are consistent with a role for abnormal TGF in the genesis of hypertension (12,13). Between four and six weeks of age these animals begin to show evidence of excessive salt and water retention and start to develop hypertension. At six weeks of age the GFR is significantly decreased due to a reduction in the glomerular ultrafiltration coefficient and glomerular plasma flow. Despite the antecedent salt retention and development of hypertension TGF at this stage of life shows increased sensitivity. Once hypertension is fully established by 12 weeks, differences in GFR and renal plasma flow between hypertensive and control animals have largely disappeared. The TGF response is now normal. This pattern is consistent with a baseline increase in TGF activity being responsible for the initial period of renal salt retention and impaired renal function ultimately resulting in the onset of hypertension. Once hypertension is fully established the TGF response becomes normalized but the activity of the system is still inappropriate for the degree of systemic pressure elevation.

A similar pattern of TGF activity has been noted in the Milan Hypertensive Strain (MHS) rat. Enhanced activity is already present by the time these animals begin to develop hypertension (14-16). As blood pressure progressively rises the characteristics of TGF eventually normalize. Once again however, TGF activity is still inappropriate for the degree of blood pressure elevation. When these animals are challenged with a volume load there is a smaller increase in GFR as compared to control animals indicating an inability to properly desensitize the system.

Under normal circumstances nitric oxide and angiotensin II are important physiologic regulators of the TGF response. Numerous studies have explored the possibility that alterations in the metabolism of these substances may be involved in the abnormal TGF response noted in animal models of hypertension.

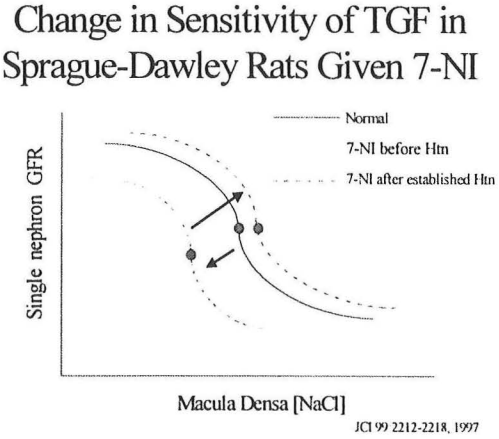

Figure 7

The neuronal or type I isoform of nitric oxide synthase (nNOS) is highly expressed in macula densa cells (17). Increased delivery and reabsorption of sodium at the macula densa activates the enzyme. The subsequent generation of nitric oxide offsets the vasoconstrictive effect of TGF on the afferent arteriole (18). In this manner nitric oxide generation plays an important role in decreasing the sensitivity of TGF in response to sustained increases in distal NaCl delivery (19).

Inhibition of nitric oxide leads to increased sensitivity of TGF (20) (Figure 7). Studies in which a specific inhibitor of nNOS is administered to laboratory animals suggest that this shift in

sensitivity is involved in the development of hypertension (21). Administration of the specific nNOS inhibitor, 7-nitroindazole (7-NI), to rats in their drinking water leads to the onset of hypertension after two weeks of therapy which eventually plateaus after 3-4 weeks. Assessment of TGF characteristics during this time period demonstrate enhanced sensitivity prior to the onset of hypertension. This initial resetting of TGF is associated with a reduction in GFR (22). As hypertension develops the sensitivity of TGF begins to decline and by the time blood pressure plateaus at 4 weeks TGF sensitivity is normalized. This pattern is similar to the previously described patterns in the SHR and MHS rats suggesting that increased sensitivity of TGF is involved in the development of hypertension in these models.

Indirect evidence suggests that decreased nitric oxide synthesis or a reduced ability to respond to nitric oxide may play a role in the heightened sensitivity of TGF in the SHR and MHS rat models of hypertension (23). Intratubular infusion of a nitric oxide inhibitor does not change the sensitivity or magnitude of the TGF response in these animals. By contrast, the respective normotensive control strains respond with a very strong resetting toward a higher sensitivity. These findings suggest that nitric oxide-mediated vasodilation that normally counteracts TGF-induced vasoconstriction of the afferent arteriole is far less pronounced in the hypertensive animals than their normotensive controls.

Studies have also examined the role of renal nitric oxide production in the development of hypertension in the Dahl salt-sensitive (DS) and Dahl salt-resistant rat (DR) (24,25). Renal nitric oxide production is decreased during high salt intake in the DS rats as compared to the DR rats. Administration of L-arginine to DS rats increases nitric oxide production and prevents the development of salt-sensitive hypertension. These observations suggest that a decrease in renal nitric oxide production may play a role in salt sensitivity.

Studies examining the specific isoforms of nitric oxide have shown that DR rats given a high salt diet result in a much greater increase in renal medullary nNOS protein as compared to DS rats (25). When nNOS is inhibited with 7-nitroindazole (7-NI), the DR rats become salt sensitive and develop an increased MAP in response to the high salt diet. MAP is not significantly affected by the inhibitor in the DS rats. These results suggest that nNOS normally plays an important role in the DR rat in preventing salt-sensitive hypertension and that a decrease in nNOS in the DS rat may be partly responsible for its salt-sensitivity. Although not specifically examined in these studies, a decrease in nNOS activity could result in salt sensitivity as a result of heightened activity of the TGF response.

As previously mentioned, the sensitivity of the TGF response is also influenced by changes in the circulating or tissue levels of the renin-angiotensin system. Tissue or systemic levels of AII are directly related to the sensitivity of the TGF system. In this regard, hypertension in the SH and MHS rats has been attributed to a baseline increase in the sensitivity of TGF to AII at any given level of salt intake or extracellular volume. This possibility is somewhat analogous to the ability of infused angiotensin II to restore TGF sensitivity in normal animals that are volume expanded (26). Administration of an ACEI to SH rats prevents the development of hypertension and is associated with an increase in GFR and renal blood flow (27,28). In addition, administration of an AT_1 receptor antagonist normalizes the exaggerated TGF activity present in young SH rats (29,30).

In summary, nitric oxide and angiotensin II are important regulators of the TGF response. The relationship between AII activity and TGF sensitivity is direct while the relationship with nitric oxide is indirect.

Several observations suggest that changes in the activity of nitric oxide and AII may be

related. For example, inhibition of nitric oxide production enhances renin release from rat cortical kidney slices. Studies in dogs are consistent with an inhibitory effect of nitric oxide on renin release that is dependent upon a macula densa mechanism (31). Specific inhibition of the macula densa enriched nNOS increases renin release in rats at a time that TGF activity is enhanced (16). These data suggest that the increased TGF sensitivity associated with inhibition of nNOS is mediated in part by activation of the renin-angiotensin system. Conversely, AII can down regulate macula densa nNOS activity. As a result there is diminished contribution of nNOS in counteracting TGF-mediated afferent arteriole constriction. This decrease in nNOS activity partially accounts for the enhanced TGF activity in AII-dependent hypertension (32)

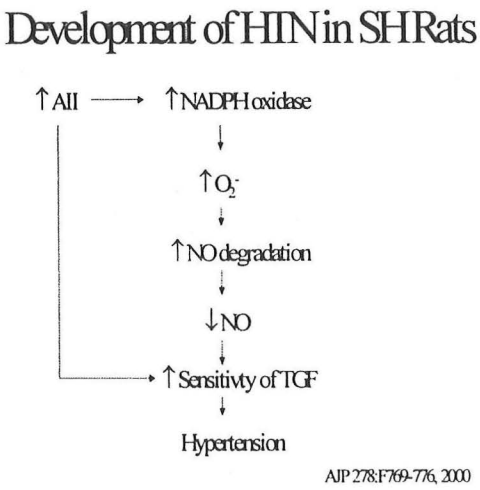

Figure 8

Studies in the SH rat have attempted to better define the role of nitric oxide and AII in the enhanced sensitivity of TGF (33-36). In these animals synthesis and delivery of the various isoforms of nitric oxide and cofactors to the juxtaglomerular apparatus is intact. Despite the intact synthetic machinery, studies suggest there is loss of nitric oxide effect secondary to enhanced degradation. This degradation is mediated by increased oxidation by O_2^- generated within the juxtaglomerular apparatus. The source of the O_2^- is not clear but a likely candidate is the enzyme NADPH oxidase. This enzyme is found in several locations within the kidney and is known to be stimulated by AII. Overactivity of the renin-angiotensin system at the level of the juxtaglomerular apparatus could decrease the bioactivity of locally produced nitric oxide secondary to overproduction of O_2^- (Figure 8). Several observations support this possibility. First, the exaggerated TGF response of the SHR kidney is dependent upon AT_1 receptors (29). Second, the baseline exaggerated response of TGF is blunted after administration of the superoxide dismutase mimetic agent (tempol). This agent would be expected to prevent O_2^- mediated degradation of nitric oxide. Third, short and long term administration of tempol lead to a normalization of renal vascular resistance that is accompanied by a reduction in systemic blood pressure (33-36).

In summary, numerous studies in animal models of hypertension suggest that an exaggerated TGF response can be a potential cause of hypertension. Such an abnormality is a particularly attractive explanation for the development of salt sensitive hypertension. Although it is not possible to directly assess the components of renal autoregulation in humans it is likely that increased TGF sensitivity is responsible for some forms of human hypertension.

V. Autoregulation and Susceptibility to Hypertension-Induced Renal Injury

Chronic renal failure is a known complication of uncontrolled hypertension. However, the

risk for renal failure is quite variable with certain patient groups exhibiting a greater susceptibility that others. It is believed that genetic factors play an important role is determining this susceptibility. A similar difference in the risk for renal failure has been noted in animal models of hypertension. The 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 much more modest degrees of hypertension. 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 (37). In these studies uninephrectomized animals receive a 2nd 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 (37).

Differences in renal autoregulatory ability may explain the difference in sensitivity of the BN and SH rat kidney to hypertension-induced renal injury. Autoregulation in the SH rat model is highly efficient and remains so even in the setting of high arterial pressures. The ability to maintain adequate tone of the afferent arteriole in the setting of high systemic pressure minimizes the development of intraglomerular hypertension and as a result glomerular injury is minimized. By contrast the autoregulatory response of the BN rat is limited and rapidly fails under conditions of increased arterial pressure (38). Decreased ability to maintain adequate tone of the afferent arteriole allows pressure to be more easily transmitted into the glomerular circulation resulting in vascular injury (Figure 9).

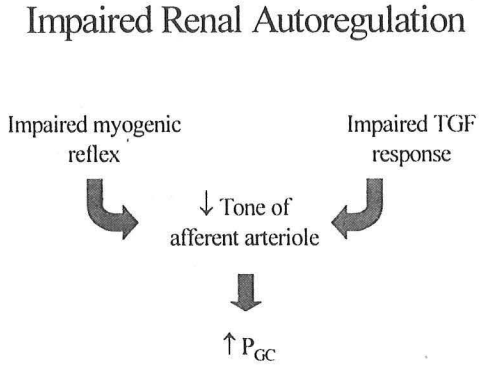

Figure 9

A similar link between a failure of autoregulation and susceptibility to renal injury has been noted in the FHH rat (39). This strain is characterized by the early onset of hypertension and development of proteinuria and glomerulosclerosis. 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. Studies comparing these two strains demonstrate that renal autoregulation is impaired in the FHH rat before the development of glomerular disease while autoregulation is intact in the FHL animals. As in the BN rat, insufficient vasoconstriction of the afferent arteriole is responsible for the abnormal autoregulatory response (40).

Just as an intrinsic abnormality in renal autoregulation may help explain differences in susceptibility to hypertension-induced renal disease, acquired derangements can similarly render an animal susceptible to renal injury or accelerate the progression of already established renal disease.

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 (41). The impaired ability to vasoconstrict the afferent arteriole allows for high systemic pressures to be transmitted to the renal vasculature resulting in severe microvascular disease. In this manner what was originally benign hypertension is transformed into malignant nephrosclerosis.

The Dahl salt-sensitive rat is characterized by the development of hypertension and the rapid onset of renal failure following the institution of a high salt diet. Renal autoregulation is intact while on a low salt diet but becomes impaired as a consequence of the increased salt intake (42). 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 serves as a buffer to limit changes in intraglomerular pressure in response to rapid fluctuations in systemic arterial pressure. In the setting of hypertension, an increase in preglomerular vascular tone prevents the transmission of excessive pressure into the glomerular circulation thereby preventing renal microvascular injury. Differences in the 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 efficiency 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, and DS rats may explain the rapid and severe renal injury that develops in association with increases in systemic pressure.

It is interesting to speculate that baseline differences in the efficiency of renal autoregulation may also explain the varying risk of renal disease is human hypertension (Figure 10). African American patients with hypertension are generally considered to be salt sensitive and are at increased risk for development of renal failure. When challenged with a high salt diet these patients exhibit a much greater increase in GFR as compared to age- and blood pressure-matched white subjects (43). The increase in GFR is accompanied by a similar increase in renal blood flow such that filtration fraction is unchanged. These hemodynamic changes are consistent with preglomerular vasodilation. This impairment in GFR autoregulation is reminiscent of the impaired autoregulatory capacity observed in the Dahl salt-sensitive rat following the institution of a high salt diet and suggests a potential mechanism that may contribute to the increased risk of renal failure in these patients.

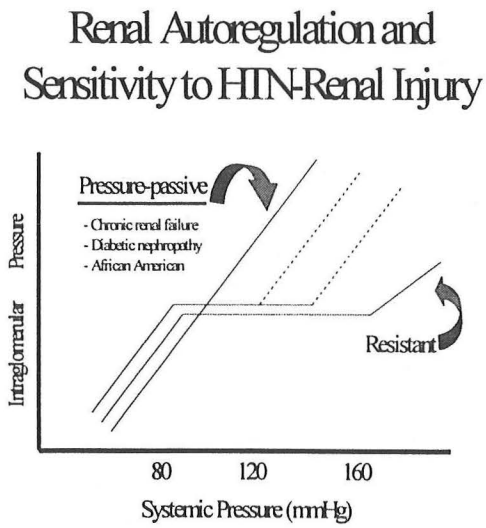

Figure 10

Hypertension is one of the most important factors that can contribute to accelerated loss of renal function in patients with chronic renal failure. Partial loss of kidney function is associated with decreased preglomerular renal vascular resistance, increased intraglomerular pressure and hyperfiltration in the remaining renal tissue (44-46). The loss of an intact autoregulatory capacity creates a situation in which increases in systemic pressure are accompanied by proportionate increases in intraglomerular pressure. This situation is analogous to the loss of autoregulation and severe renal injury that develops in the SH rat subjected to renal ablation.

Diabetic patients are also at particular risk to develop accelerated renal function loss due to hypertension. In the very earliest stages of the disease renal function is characterized by increased renal blood flow and hyperfiltration. These hemodynamic changes have been linked to impaired renal autoregulation. Direct assessment in experimental models of diabetes have confirmed that renal autoregulation is impaired in the earliest stages of diabetes and is one of the factors contributing to hyperfiltration (47). In a manner similar to chronic renal failure from other causes, inefficient autoregulation will allow the preglomerular circulation to simply serve as a passive conduit for the transmission of damaging systemic pressure into the glomerular circulation.

VI. Therapeutic Implications of Impaired Renal Autoregulation

Studies in experimental animals have shown that glomerular capillary hypertension is the most important hemodynamic alteration associated with the development of glomerular sclerosis and progressive kidney failure (48). Maneuvers designed to lower intraglomerular pressure have consistently resulted in a renoprotective effect. The two most effective strategies to lower intraglomerular pressure are aggressive lowering of systemic blood pressure and inhibition of the renin-angiotensin system.

Angiotensin converting enzyme inhibitors (ACEI) are effective antihypertensive agents that also possess the unique ability to lower intraglomerular pressure. Since angiotensin II preferentially constricts the efferent arteriole, inhibiting the synthesis or blocking the actions of AII leads to dilation of the efferent vessel and a decline in intraglomerular pressure. 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. Based on the results of numerous large trials ACEI have become the drugs of choice to protect against progressive renal dysfunction particularly in diabetic nephropathy and proteinuric renal disease. Similar trials are currently in progress examining the renal effects of angiotensin receptor blockers (ARBs). Based on experimental models and short term human studies it is likely that these trials will show the ARB class to be at least as effective as the ACEI class in providing renal protection (49).

In addition to hemodynamic benefits, the ACEI and ARB class also interfere in other AII-mediated effects that may play a role in the progression of renal disease (50). These effects include compensatory hypertrophy, stimulation of fibrosing cytokines, inflammatory cell recruitment, proteinuria, and alteration in lipids. Whether in the setting of maximal reduction in intraglomerular pressure these non-hemodynamic benefits are of clinical relevance is currently not known.

A second strategy to lower intraglomerular pressure is to lower systemic arterial pressure. This approach is particularly relevant to conditions associated with impaired renal autoregulation where intraglomerular pressure starts to become a direct function of systemic pressure. Just as an

increase in systemic pressure tends to raise intraglomerular pressure, control of systemic hypertension should effectively lower intraglomerular pressure. However, the relationship between systemic arterial pressure and intraglomerular pressure in the downward direction is not readily predictable (48). In experimental models of renal disease a mild or moderate reduction in mean arterial pressure (MAP) does not necessarily predict a reduction in intraglomerular pressure (48,51,52). On the other hand, more aggressive lowering of MAP does provide a more predictable reduction in intraglomerular pressure as well as subsequent renal damage. The greater the decline in systemic pressure the more likely it is that glomerular hypertension and injury will be averted.

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

Griffen et al., compared the effects of enalapril and nifedipine on development of glomerulosclerosis in the rat remnant kidney model (53). In this study both enalapril and nifedipine decreased blood pressure as compared to controls but only enalapril significantly decreased the amount of glomerulosclerosis. There was a leftward shift in the slope relating glomerular injury and MAP in the nifedipine group such that more injury was sustained at any given level of blood pressure as compared to the untreated animals. The steeper slope in the nifedipine group is consistent with a loss of autoregulation resulting in more direct transmission of pressure into the glomerular capillaries and as a result more severe renal injury.

A similar study comparing various classes of hypertensive agents and how they impacted on renal autoregulation was performed in the uninephrectomized SH rat (54) (Figure 11). Enalapril reduced intraglomerular pressure at all levels of blood pressure studied and renal autoregulation remained intact although reset to a lower limit. By contrast, nifedipine significantly increased intraglomerular pressure as MAP was lowered from the control value of 169 mmHg to 120 mmHg. Renal autoregulation was found to be abolished. When MAP was lowered to 85 mmHg, intraglomerular pressure became normalized. These data are consistent with the idea that monotherapy with CCBs can potentially result in deleterious effects on intraglomerular pressure when systemic pressure is not sufficiently controlled.

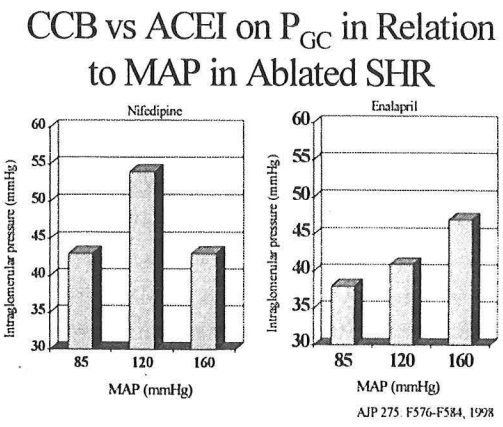

Figure 11

Recent evidence suggests that there are class differences between the CCBs on how they affect renal autoregulation (55). In the rat remnant kidney model renal autoregulation was found impaired

to a similar degree in control, diltiazem-, and verapamil-treated rats. By contrast the impairment in the felodipine-treated group was significantly worse as these animals had a complete loss of autoregulatory ability. Although not statistically significant, both proteinuria and glomerulosclerosis tended to be worse in the felodipine-treated rats as compared to the control and other CCB groups. In addition, the relationship between average systolic blood pressure and glomerulosclerosis was shifted to the left and was significantly steeper in the felodipine group. As a consequence, a given increase in blood pressure resulted in a disproportionately greater increase in glomerulosclerosis in the rats treated with felodipine (Figure 12).

Class Differences in the Effects of CCB in the Rat Remnant Kidney

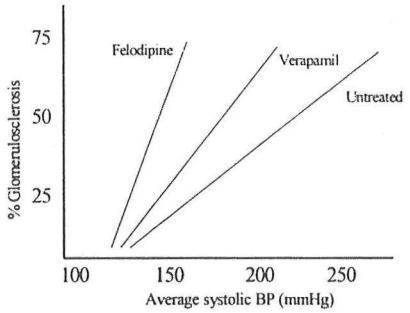

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Figure 12

While most clinical and experimental data have supported a renal protective effect of ACEI, studies examining the renal protective properties of CCBs have produced conflicting results (56,57). In addition, class differences between CCBs have also been noted (58). It is likely that part of the controversy surrounding these agents lies in their variable ability to lower intraglomerular pressure due to differing effects on the autoregulatory response as well as to differences in their ability to dilate the efferent vessel. It is also likely that differences in systemic blood pressure control also explain part of the conflicting data. Inadequate blood pressure control can lead to an increase in intraglomerular pressure while aggressive lowering of systemic arterial pressure can overcome the negative effect of afferent dilation and result in a net lowering of intraglomerular pressure (59).

From a clinical standpoint the level of blood pressure control needed to overcome the negative effect of afferent vasodilation is not readily predictable and likely varies from patient to patient. One strategy to ensure that intraglomerular pressure does not increase following the initiation of CCB therapy is to first or concomitantly administer an ACEI. The efferent vasodilatory effects of an ACEI ensures that intraglomerular pressure will decrease no matter what the change is in systemic blood pressure control. In this manner use of the ACEI protects against any potential detrimental effect of CCB therapy on intraglomerular pressure during the time period required to maximally control MAP.

Ruggenentl et al recently examined the impact of dihydropyridine CCBs on urinary protein excretion and GFR decline in a group of patients with nondiabetic proteinuric chronic renal disease. (60). The effects on urinary protein excretion were examined as a function of blood pressure control and whether or not the patient was also taking an ACEI. In patients with a MAP 117 or 105 mmHg, 24 hour urine protein excretion was greater in patients receiving dihydropyridine CCBs as compared to subjects treated with drugs other than CCBs or ACEIs. In patients with a lower MAP (94 mmHg) this adverse effect of CCB therapy on urinary protein excretion was no longer present. In contrast to CCB therapy, use of ACEIs was associated with a reduction in urinary protein excretion at the high levels of MAP (117 and 105 mmHg). However, similar to the CCB group, urinary protein excretion was no different in patients treated with ACEI as compared to non ACEI therapy when MAP was 94

mmHg. In patients with a MAP of 108 mmHg use of an ACEI and CCB together resulted in significantly less proteinuria as compared to patients on CCB therapy alone. These data demonstrate that in proteinuric patients monotherapy with CCBs can adversely effect the level of urinary protein excretion. The increase in proteinuria can be prevented by either a greater reduction in systemic blood pressure of concomitant use of an ACEI.

To summarize to this point, aggressive lowering of systemic blood pressure and ACEI therapy are the most effective means to lower intraglomerular pressure. In the setting of impaired renal autoregulation, reducing systemic blood pressure can decrease intraglomerular pressure but the relationship is complex and is critically dependent upon the degree of blood pressure lowering and the antihypertensive agent utilized. A more predictable fall can be achieved with ACEIs as these agents preferentially lead to vasodilation of the efferent arteriole even in the setting of inadequate blood pressure control. These agents may produce greater declines in glomerular pressure for any given reduction in systemic pressure than other hypertensive agents. In addition these agents may offer renal protective effects through nonhemodynamic mechanisms. As a result, it would seem reasonable to consider ACEIs as first line therapy in hypertensive patients with chronic renal failure in whom renal autoregulation is likely impaired.

It is not known if there is a point at which the degree of benefit achieved by blood pressure reduction is sufficiently large that any potential difference between ACEI and other drugs is no longer demonstrable. In studies of diabetic and nondiabetic patients ACEI are more effective in preserving renal function than conventional agents when the target MAP is between 100-102 mmHg. Preliminary data suggest that the superiority of ACEI over other drugs becomes less apparent when MAP is lowered to values below this range (48). In the Collaborative Diabetic Nephropathy Study better blood pressure control (126/81 mmHg vs 140/85 mmHg) was correlated with remission from nephrotic range proteinuria. The benefit of lower blood pressure was observed regardless of whether an ACEI or other type of antihypertensive agent was used (61).

A similar conclusion was reached in the United Kingdom Prospective Diabetes Study (62). In this study 758 patients with type 2 diabetes were randomized to aggressive blood pressure control with captopril or atenolol. Patients who did not reach goal blood pressure were given other medications but not either of the two primary drugs. The attained blood pressure was similar in the two groups (144/82 mmHg) and, at nine years follow-up, there was no difference between the two groups in the frequency of microalbuminuria (31 versus 26 percent with atenolol), progression to overt proteinuria (protein excretion >300 mg/L, 5 versus 10 percent, P = 0.09), or a doubling of the plasma creatinine concentration.

There are no completed studies that have compared drugs in patients treated with a MAP pressure in the range of 90 mmHg or less. A recent report suggests that greater renal protection can be achieved when ACEIs are combined with aggressive blood pressure control (63). This study randomly assigned diabetic patients to a MAP goal of ≤92 mmHg or 100-107 mmHg. The primary drug used to control blood pressure in both groups was ramapril. There was no statistically significant difference in the rate of decline in renal function between the two groups. However, patients assigned to the lower blood pressure goal did have a significantly greater reduction in the amount of proteinuria. In this group 12/43 (23%) patients experienced a remission of proteinuria as compared to 5/46 (11%) in the high MAP group. The authors concluded that the combination of an ACEI with good blood pressure control may not only arrest the progression of diabetic renal disease

but may result in regression or in some instances remission of clinical evidence of renal disease.

VII. Complications of Therapy with Impaired Renal Autoregulation

The level at which blood pressure is considered to be adequately controlled has fallen over the last decade. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) recommends a treatment goal of < 130/85 mmHg for diabetic persons or those with renal impairment. A blood pressure goal of <125/75 mmHg is recommended in hypertensive chronic renal failure patients excreting at least 1 gram of proteinuria over 24 hours. Since the publication of the JNC VI guidelines, recent clinical trials have confirmed the clinical benefit of aggressively lowering blood pressure (64-66).

The Hypertension Optimal Treatment (HOT) was a prospective study in which approximately 19,000 hypertensive patients were randomized to target diastolic pressures of ≤90, ≤85, or ≤80 mmHg (67). Treatment was initiated with the long-acting dihydropyridine CCB felodipine. ACEIs, beta-blockers, and diuretics were added if the target pressure was not obtained with initial therapy. The fewest number of cardiovascular events occurred at an average blood pressure of 138/83 while the lowest cardiovascular mortality was noted at 139/86 mmHg. By comparison, aggressive antihypertensive therapy appeared to be particularly beneficial in the subset of approximately 1500 patients with diabetes. In these patients, there was a significant reduction in the relative risk of a cardiovascular events when blood pressure was reduced to ≤80 mmHg as compared to ≤90 mmHg.

In the (UKPDS) trial, 1148 patients with type 2 diabetes were randomized to a goal blood pressure <150/85 or <180/105 using captopril or atenolol as primary therapy (68). The blood pressures in the two groups by the end of the study were 144/82 and 154/87 mmHg, respectively. Significantly fewer diabetic micro- and macrovascular complications and diabetic-related deaths occurred in the more aggressively treated group as compared to those with a mean blood pressure of 154/87 mmHg.

The results of these studies clearly argue for an aggressive approach to the treatment of hypertension. One factor that is oftentimes cited as a reason to be less aggressive is the development of an acute rise in the serum creatinine concentration. Azotemia that develops in the setting of aggressive antihypertensive therapy is unusual in the setting of normal renal function but, rather, is more commonly encountered in hypertensive patients with preexisting chronic renal failure. An increased serum creatinine concentration can occur with ACEI therapy as well as other antihypertensive agents particularly in association with better blood pressure control. A 20-30% increase in the serum creatinine concentration that remains stable thereafter should not be viewed as a contraindication to continued aggressive therapy in such patients (69,70). In fact, chronic renal failure patients who develop a mild stable increase in serum creatinine concentration may have a better renal outcome than those whose serum creatinine remains stable. In patients who develop a more excessive or progressive rise in serum creatinine concentration, the physician should consider several underlying predisposing factors that may be readily reversible.

Use of the ACEI and ARB class can lead to an azotemic response by virtue of their ability to interfere in the renin-angiotensin system. The reason for this phenomenon appears to be related to the role AII plays in sustaining the renal circulation under conditions of hypoperfusion. GFR is largely governed by the relative tone of the afferent and efferent arterioles. The initial response to a drop in renal perfusion pressure is afferent arteriolar vasodilation as a result of the myogenic reflex. As renal perfusion pressure drops further an increase in efferent arteriole resistance may be required to maintain intracapillary glomerular pressure at a level sufficiently high to sustain glomerular filtration. The increase in efferent vascular tone that occurs under renal hypoperfusion conditions is in large part secondary to the vasoconstrictive effect of AII. It is under these conditions that the administration of an ACE inhibitor can lead to a fall in GFR. What appears to occur is the ACE inhibitor blunts the vasoconstrictive effect of AII at the efferent arteriole and therefore leads to a decline in efferent arteriolar resistance. This decline in efferent arteriole resistance leads to a fall in the glomerular capillary pressure and then to a fall in GFR.

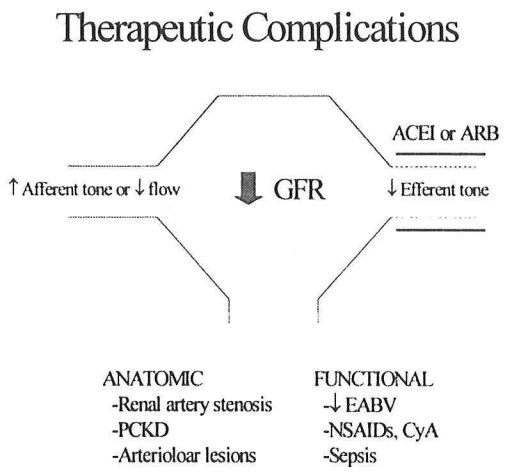

Figure 13

There are several clinical settings in which this physiology becomes important (Figure 13). The first setting involves significant (usually >70%) bilateral renal artery obstruction or unilateral renal artery obstruction to a solitary functioning kidney. In these two examples increased tone of the efferent arteriole acts to restore intraglomerular pressure so that the GFR is maintained at a level necessary to ensure homeostasis. The tradeoff is that renal function and GFR are now dependent upon sustained constriction of the efferent vessel by AII. In addition to intraluminal obstruction as in the setting of atherosclerosis, the same physiology has been noted in the setting of polycystic kidney disease in which the renal arteries are extrinsically compressed by large cysts. In such patients the use of ACE inhibitors have rarely been reported to cause acute renal failure (71).

ACEI can also cause an azotemic response under conditions of an absolute or effective reduction in circulatory volume. In these settings perfusion pressure may be low enough to mimic the conditions in which there is actual physical obstruction of the renal arteries. Such an occurrence would be in a setting of moderate to severe congestive heart failure. Under these circumstances, increased efferent arteriolar tone sustains GFR by raising intraglomerular pressure so as to counterbalance the decrease in renal perfusion. In heart failure patients who fail to increase cardiac output and improve renal perfusion, ACE inhibitor therapy can precipitate acute renal failure due to the decrease in efferent tone and the loss of this counterbalancing effect. The same physiology would explain ACEI-induced acute renal failure in patients who are volume contracted from other conditions

such as gastroenteritis or aggressive diuresis.

A similar mechanism is responsible for the decline in renal function that can occur in certain patients given ACE inhibitors in the setting of nonsteroidal antiinflammatory drugs (NSAID) or cyclosporin A (72,73). The unopposed vasoconstriction that results from NSAID-induced inhibition of vasodilatory prostaglandins can result in exaggerated falls in the GFR when efferent tone cannot be increased. An inability to increase efferent tone can also explain the worsening of renal function with cyclosporin A since this drug preferentially constricts the afferent arteriole. ACE inhibitors can also be expected to magnify the decline in GFR that occurs in the setting of sepsis. In the early stages of sepsis renal function resembles pre-renal failure primarily due to the effects of lipopolysaccharide on nitric oxide metabolism that result in an increase in renal vasoconstriction (74).

A major cause of acute azotemia in association with aggressive antihypertensive therapy is related to the presence of an impaired autoregulatory capacity. In this setting there develops a more direct relationship between blood pressure and GFR. Presumably, chronic hypertension leads to hyalinosis of the afferent arteriole thereby rendering the vessel stiff and less able to vasodilate in response to a drop in blood pressure. Following the institution of antihypertensive therapy, improved blood pressure control may lead to decreased renal perfusion and decreased intraglomerular pressure resulting in a slight rise in the serum creatinine concentration. By this mechanism, an increased creatinine concentration can occur regardless of the type of antihypertensive agent used. As long as the increase is not excessive nor progressive, discontinuation of the drug is not warranted. The renal deterioration is hemodynamic in nature and reversible and should not distract from the long term benefit afforded by better blood pressure control.

Christianson et al. has found evidence of impaired autoregulation in studies of diabetic patients with nephropathy as well as in patients with other forms of proteinuric renal disease (75,76). In these studies administration of intravenous clonidine resulted in a comparable decline in MAP in patients with nephropathy as well as control subjects without evidence of renal disease. In patients with renal disease this decrease in blood pressure was accompanied by a significant decline in the GFR as compared to subjects without nephropathy. In some of the renal failure patients a complete pressure-passive vasculature was found indicating a total loss of autoregulatory capacity.

This decline in GFR is hemodynamic in nature and is reversible even after several years of therapy (77-79) (Figure 14). Apperloo et al., measured the GFR in patients with mild to moderate renal function after receiving either an ACEI or a beta blocker (77). They then compared the long term renal outcome in patients who exhibited a large initial treatment-induced fall in GFR to those who had only a small initial fall in GFR. During a 4 year follow up, renal function remained more stable in the patients with the largest initial decline in GFR as compared to

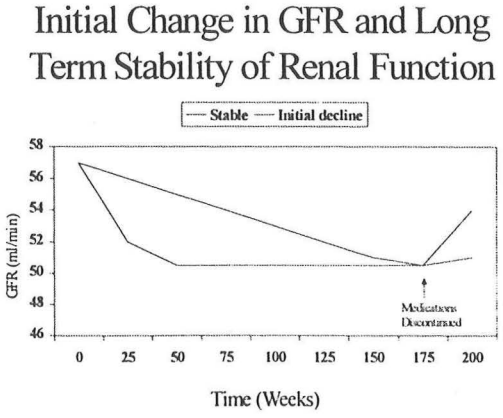

Figure 14

the patients with only a small initial change in GFR. In addition, GFR increased after discontinuation of therapy at 4 years in the group with the large initial decline in GFR while GFR did not change in the other group. The results were the same whether patients were treated with an ACEI or a beta blocker. These data suggest that an initial fall in GFR following the institution of antihypertensive therapy may reflect renal protection. It is likely that a slight rise in the serum creatinine concentration in this setting serves as an indirect marker that intraglomerular pressure has ben successfully reduced.

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