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CLINICAL INVESTIGATION

Progressive renal disease: Role of race and antihypertensive medications

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Progressive renal disease: Role of race and antihypertensive medications. Hypertension is associated with an accelerated rate of decline in renal function in patients with chronic renal disease. To identify factors that might alter the rate of decline in renal function, we reviewed records of 200 patients from the Nephrology Clinic of the Durham VA Medical Center who had chronic progressive renal insufficiency. The average rate of decline in renal function (slope of reciprocal plasma creatinine versus time) was -0.80 ± 0.62 (SD) ml/mg month in 112 black patients and -0.84 ± 0.59 in 88 white patients. Multiple regression analysis indicates that the patient's age, level of diastolic blood pressure and type of antihypertensive treatment had a significant effect on the slope of reciprocal creatinine whereas the patient's race and diagnosis did not. In individual patients, addition of minoxidil or a calcium channel blocker to other medications significantly lowered blood pressure and slope of reciprocal creatinine. Some antihypertensive medications lowered blood pressure without significantly affecting the slope. These data suggest that specific medications may have a favorable effect on the progression of chronic renal disease by mechanisms in addition to reduction of blood pressure.

Systemic hypertension appears to be associated with declining renal function in "normal" people and in patients with underlying renal insufficiency. In a longitudinal, prospective study of aging "normal" men, Lindeman, Tobin and Shock [1] found a negative effect of mean blood pressure on the rate of decline in creatinine clearance. In patients with renal insufficiency from diabetic nephropathy, control of hypertension was associated with a 33% reduction in the rate of decline in glomerular filtration rate [2]. In a retrospective study of a large group of chronic dialysis patients, the average rate of progression to end-stage renal disease (ESRD) was faster in patients with diastolic hypertension than in normotensive patients [3]. Thus, the presence of systemic hypertension appears to have an adverse effect on renal function over time.

Studies are needed to address the question of whether the effect of systemic hypertension on progressive renal disease is due solely to the elevation of blood pressure or due to other factors that are involved in the pathogenesis of hypertension. The latter possibility is suggested by observations in black patients with primary hypertension (hypertension with no other known cause of renal disease). These patients appear to progress to ESRD more frequently than hypertensive white patients [4] even when blood pressure was "controlled" [5]. The pathogenesis of essential hypertension in blacks as a group differs from that in whites and this difference may relate to the increased frequency of ESRD in black patients [6]. Further evidence would be finding a specific antihypertensive medication that blocks the mechanism of renal injury and slows the progression of renal disease to a greater extent than is observed from equivalent reductions in diastolic blood pressure with other medications. Alternatively, if there is no difference between the effect of antihypertensive medications on the rate of decline in renal function, then the presence of systemic hypertension would appear to be the main pathogenetic factor.

The objectives of this study were to determine if there were any differences in the rate of decline in renal function between black and white patients with progressive renal disease and to examine the effects of specific types of antihypertensive medication on the relationship between diastolic blood pressure and the rate of decline in renal function. We reviewed data from 200 patients (112 black and 88 white) with progressive renal disease who were followed prior to dialysis at the Durham VA Medical Center Nephrology Clinic. The relationship between diastolic blood pressure and rate of decline in renal function as determined by the slope of reciprocal creatinine versus time was not different between the races. However, specific antihypertensive medications, minoxidil and calcium channel blockers, slowed the rate of decline in renal function more effectively than other commonly used drugs. These data suggest that specific antihypertensive medications may modify the course of progressive renal disease by mechanisms in addition to a reduction in systemic blood pressure.

Methods

The Nephrology Section of the Durham VA Medical Center has a computerized medical record of all patients seen since January, 1979 [7]. From this database we performed a retrospective and longitudinal study of patients who had progressive renal insufficiency. The database was screened for patients with renal insufficiency (plasma creatinine > 1.5 mg/dl) who had at least four determinations of plasma creatinine and blood pressure over at least six months prior to ESRD treatment and showed progression of disease as indicated by at least a 20% decrease in the value of the reciprocal plasma creatinine. From

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Table 1. Characteristics of patients by race

	Black patients	White patients
Age at last contact *years*	58.9 ± 11.2	56.4 ± 12.3
Initial creatinine *mg/dl*	3.2 ± 1.8	3.0 ± 1.7
Last creatinine *mg/dl*	8.4 ± 4.5	7.7 ± 4.2
Duration of follow-up *months*	38.2 ± 25.4	39.7 ± 27.7
Slope of 1/Creat vs. time *ml/mg month*	−0.80 ± 0.62	−0.84 ± 0.59
Systolic blood pressure *mm Hg*	155.5 ± 19.2	147.2 ± 16.1
Diastolic blood pressure *mm Hg*	91.5 ± 8.7[a]	87.7 ± 9.1

Values are mean ± SD for 112 black patients and 88 white patients.
[a] Indicates values for black patients that are significantly different from those of white patients by a Mann-Whitney U test ($P < 0.05$).

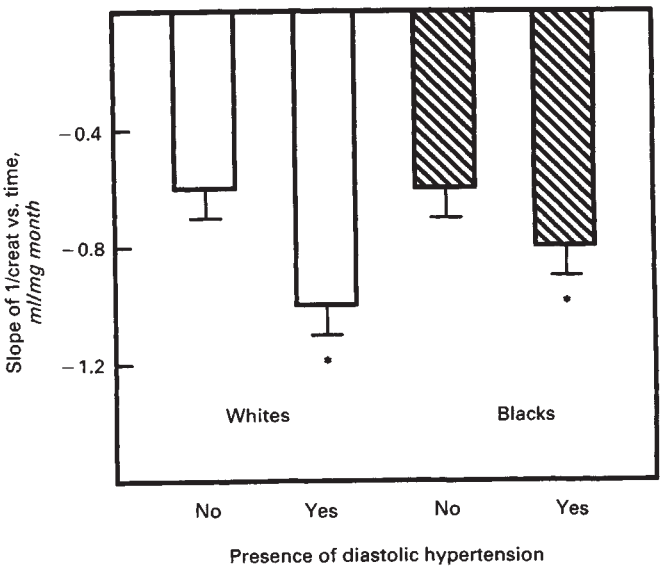

Fig. 1. *Effect of diastolic blood pressure on rates of decline in renal function by race.* Bars represent mean + SE of slope from reciprocal creatinine versus time plots for patients who had diastolic hypertension (>90 mm Hg) and for patients who were normotensive. Black patients are represented by hatched bars; white patients are represented by open bars. * indicates values that are significantly different from race-matched, normotensive values by analysis of variance and a Fisher's protective least significant difference test ($P < 0.05$).

the time period between January 1, 1979 and June 1, 1988, we identified 200 patients who met these criteria; 107 of them had already reached ESRD. Data from 86 of these patients were used in our previous report [3]. For this study we collected data on race, primary renal diagnosis, plasma creatinine, blood pressure, weight, and prescribed medications. The average number of determinations of plasma creatinine per patient was 15.5 ± 1.2 (SE). The medications were prescribed by several physicians according to their preference. At the time of this study very few of these patients had a renin profile or treatment with angiotensin converting enzyme inhibitors. Patients with moderate renal insufficiency were instructed in a low protein (0.8 g/kg/day), no added salt diet. Patient compliance with prescribed medications or diet was not assessed directly.

As in our previous report [3], the change in renal function was estimated by the slope of the plot of reciprocal plasma creatinine versus time [8, 9]. The data of these plots were usually well described by a single line with the R values for linear regression analyses being greater than 0.8 in 85% of patients selected by the above criteria. This determination may not accurately reflect glomerular filtration rates in these patients [10] but it was the only quantitative measure of renal function available retrospectively on this population. To evaluate the effect of specific antihypertensive therapy on the rate of change of renal function, the reciprocal creatinine versus time plots were determined for each therapeutic plan. When the type of antihypertensive medications was changed, a new slope was determined. The minimum criteria for calculation of a slope were a duration of at least six months and at least four determinations of plasma creatinine. We had data from 280 such intervals with data from two different treatment plans on 80 patients and data from a single treatment plan on the remaining 120 patients.

Statistical comparisons and linear regression analyses were determined with Statview II software (Abacus Concepts, Berkeley, California, USA). For comparisons of data that were arranged into multiple groups, we did an analysis of variance to all groups and applied Fisher's protective least significant difference test to compare mean values between groups. For comparison of data between black and white patients we used the nonparametric Mann-Whitney U test. A paired *t*-test was used to compare slope data from a single individual at two periods of time.

Results

Effect of race

Two hundred patients met the selection criteria. These patients were mostly men (98%); 112 of them were black and 88 were white. Average values of age at last visit, plasma creatinine at first and last visit, duration of follow-up, slope of reciprocal creatinine versus time, systolic and diastolic blood pressures (mean values from clinic visits during follow-up) are shown for each race on Table 1. The mean level of diastolic blood pressure in black patients was significantly higher than that of white patients ($P < 0.01$). Other values were not significantly different. Thus, black patients appeared to be more hypertensive than white patients, but their rate of change of reciprocal creatinine was not any faster.

Next we determined if in each race, diastolic hypertension was associated with a faster rate of decline in reciprocal creatinine as was previously reported [3]. For this analysis, patients were sorted by race and the presence or absence of diastolic hypertension (>90 mm Hg) based on the average value measured during clinic visits. The average slope for the reciprocal creatinine versus time plot was determined for each subgroup (Fig. 1). Statistical analyses of these data indicate no difference between the races at each level of blood pressure, but both hypertensive groups had significantly more negative slopes than their corresponding normotensive group ($P < 0.05$). These data confirm our previous observation [3] and indicate that the relationship of diastolic hypertension and more rapid decline in renal function holds for both black and white patients.

Table 2. Characteristics of population by diagnosis and race

	Diastolic BP *mm Hg*	Slope of 1/Creat vs. time *ml/mg month*
Primary hypertension		
Black patients; $N = 45$	94.2 ± 1.1[a]	−0.76 ± 0.09
White patients; $N = 22$	87.3 ± 1.6	−0.61 ± 0.09
Diabetes mellitus		
Black patients; $N = 38$	90.2 ± 1.7	−0.93 ± 0.10
White patients; $N = 19$	86.1 ± 2.3	−1.00 ± 0.10
Glomerulonephritis		
Black patients; $N = 10$	89.4 ± 2.5	−0.67 ± 0.10
White patients; $N = 21$	89.6 ± 1.9	−0.76 ± 0.10
Interstitial nephritis		
Black patients; $N = 12$	86.7 ± 1.6	−0.58 ± 0.20
White patients; $N = 11$	81.6 ± 2.7	−0.60 ± 0.13

Values are mean ± SE for N number of patients with each diagnosis.
[a] Indicates values for black patients that are significantly different from white patients with the same diagnosis by a Mann-Whitney U test ($P < 0.05$)

Table 3. Characteristics of population by age

	Diastolic BP *mm Hg*	Slope of 1/Creat vs. time *ml/mg month*
Patients <45 years old $N = 34$	92.8 ± 1.3[a]	−0.98 ± 0.10[b]
Patients 45 to 65 years old $N = 108$	89.2 ± 0.9	−0.80 ± 0.06
Patients >65 years old $N = 58$	89.2 ± 1.3	−0.76 ± 0.08

Values are means ± SE. N is the number of patients. Statistical comparisons by Fisher's protective least significant difference test.
[a] Indicates a value that is significantly different from the diastolic blood pressure of the other two groups
[b] Indicates a value that is significantly different from the oldest group

Table 4. Frequency of prescribed antihypertensive medications

	Black patients	White patients
Diuretic	76%	84%
Beta-blocker	56%	53%
Prazosin	32%	18%
Clonidine	22%	10%
Minoxidil	16%	9%
Ca-channel blocker	8%	12%
Hydralazine	8%	6%
ACE inhibitors	3%	1%

Table 5. Effect of antihypertensive treatment on rate of decline in renal function in normotensive patients

Treatment	N	Diastolic BP *mm Hg*	Slope 1/Creat vs. time *ml/mg month*
No treatment	26	81.4 ± 1.3	−0.56 ± 0.09[b]
Diuretics	28	82.4 ± 1.1	−0.82 ± 0.11[a]
+ Beta blockers	15	83.8 ± 0.9[a]	−0.58 ± 0.14
+ Prazosin	17	86.3 ± 0.8[a,b]	−0.84 ± 0.14
+ Two drugs	27	83.5 ± 1.0[a]	−0.52 ± 0.13[b]
+ Ca-blockers	8	78.4 ± 2.6	−0.46 ± 0.10[b]
+ Clonidine	11	84.6 ± 1.7	−0.48 ± 0.10[b]
+ Minoxidil	13	85.2 ± 0.9[a,b]	−0.20 ± 0.06[a,b]

Values are means ± SE. N is the number of patients. Comparisons between diastolic blood pressure and slope data between groups were by analysis of variance and a Fisher's protective least significant difference test.
[a] Indicates values that are significantly different ($P < 0.05$) from the no treatment group
[b] Indicates values that are significantly different from the diuretic treatment group

Average values for diastolic blood pressure and slope of reciprocal creatinine versus time plots as grouped by specific diagnosis and race are presented on Table 2. Primary hypertension was present in 40% of black patients and 25% of white patients. Diabetes mellitus (usually type II) was present in 34% of black patients and 22% of white patients. The average value of diastolic blood pressure for black patients with primary hypertension was significantly higher ($P < 0.01$) than that observed in white patients with primary hypertension. Otherwise, there were no significant differences in the data on this table.

We used a multiple regression analysis of age, diagnosis, diastolic blood pressure, and antihypertensive treatment to determine which factors appeared to have an effect on the slope of reciprocal creatinine versus time. In this analysis, race ($P = 0.70$) and diagnosis ($P = 0.86$) had no significant effect on the slope, whereas diastolic blood pressure ($P = 0.012$), type of antihypertensive treatment ($P = 0.012$) and age ($P = 0.04$) did.

Effect of age

To analyze the effect of age on the slope of reciprocal creatinine versus time, we sorted the data into three groups: patients less than 45 years old at the time of the last creatinine determination; patients between the age of 45 and 65 years old; and patients greater than 65 years old. The data for diastolic blood pressure and slope of reciprocal creatinine versus time are presented on Table 3. The youngest age group had an average slope that was significantly different from that of the oldest ($P < 0.05$). The mean diastolic blood pressure of the youngest group was significantly greater than that of either the middle or older age groups. The patients in the youngest group were more likely white (53%) and more likely to have a diagnosis of glomerulonephritis or vasculitis (50%) than patients in the other age groups. In each age group, the slope of reciprocal creatinine versus time was the same for black and white patients.

Effect of specific antihypertensive medications

We determined the slope of the reciprocal creatinine versus time plot for the time interval that each patient was on a specific regimen of antihypertensive medications. The frequency of prescribed antihypertensive medications for black and white patients are given on Table 4. Because the presence of hypertension has an effect on the slope of reciprocal creatinine versus time, we separated the data into two groups on the basis of a normal or hypertensive diastolic blood pressure.

Normotensive patients who were not treated with either a diuretic or antihypertensive medications had an average slope of reciprocal creatinine which was significantly less than that of patients who were treated with diuretics alone, even though the levels of diastolic blood pressure were equal (Table 5). Addition of specific antihypertensive drugs such as a combination of two drugs (beta blocker or clonidine and a vasodilator), a calcium channel blocker (usually verapamil or nifedipine), clonidine or

Table 6. Change in diastolic blood pressure and slope of reciprocal creatinine versus time with addition of specific antihypertensive treatments in individual patients

Treatment	*N*	Diastolic BP *mm Hg*	Slope 1/Creat vs. time *ml/mg month*	*P*
Time controls	40	−2.5 ± 1.3	−0.05 ± 0.09	0.78
+ Beta blocker	12	−6.2 ± 1.5	−0.16 ± 0.17	0.18
+ Prazosin	18	−2.6 ± 1.9	+0.12 ± 0.20	0.50
+ Minoxidil	18	−14.2 ± 1.8	+0.53 ± 0.18	0.006
+ Clonidine	12	−4.3 ± 1.8	+0.34 ± 0.24	0.21
+ Ca-blocker	7	−8.8 ± 2.7	+0.53 ± 0.16	0.02
+ Two drugs	11	−7.6 ± 1.6	+0.47 ± 0.30	0.17

Values are mean paired differences ± SE for data (after minus before addition of medication) in *N* number of patients. *P* values indicate comparisons by a paired *t*-test for the slope data.

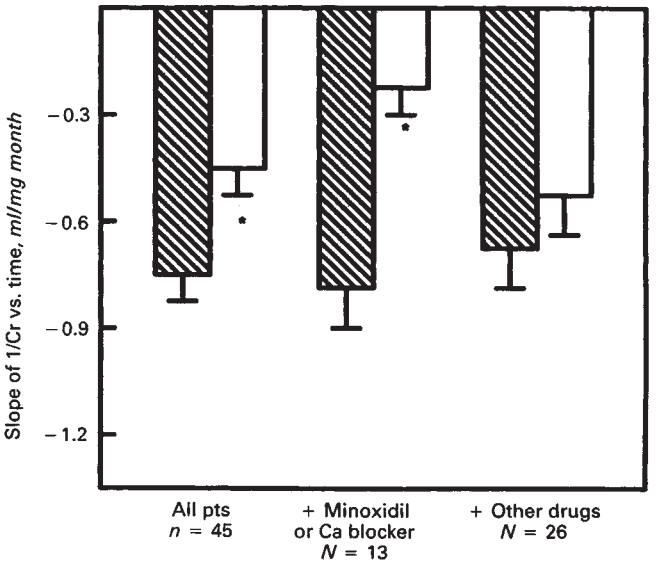

Fig. 2. *Effect of specific medications on rate of decline in renal function in individual patients.* Bars represent mean + SE of slope from reciprocal creatinine versus time plots for individual patients when they were hypertensive (hatched bars, dBP > 90) and when they were normotensive (open bars, dBP < 90). The pair of bars on the left are the data for all patients, including six patients who had no change in medication. The middle pair of bars are data from patients who received either minoxidil or a calcium channel blocker to reduce their blood pressure. The pair of bars on the right are data from patients who received another drug to lower their blood pressure. * indicates values that are significantly different by a paired *t*-test.

minoxidil was associated with significantly slower rates of change in reciprocal creatinine than treatment with diuretic alone. Treatment with other antihypertensive medications such as beta blockers (usually propranolol or atenolol) or prazosin with a diuretic did not significantly slow the rate of decline in renal function in this population as compared to patients treated with only a diuretic. Patients who were treated with minoxidil had rates of change in reciprocal creatinine that were significantly lower than both no treatment and diuretic treatment groups, even though their average level of diastolic blood pressure was significantly greater than the control groups. There were no significant differences between black and white patients in these responses. These data imply that specific medications may have a beneficial effect on the rate of decline in renal function in addition to that observed with control of diastolic hypertension. In patients who remained hypertensive, treatment with antihypertensive drugs was associated with no significant reduction in the rate of change of reciprocal creatinine as compared to patients treated with only diuretics (data not shown). This lack of an effect may be due to an inability to control diastolic hypertension.

Effect of specific antihypertensive drugs in individual patients

In 80 patients we had sufficient data to determine the slope of reciprocal creatinine before and after a change in the antihypertensive treatment. Because the reciprocal creatinine versus time plots are remarkably linear in this population, we can use the slope of the first treatment interval in a given patient as a control value to be compared with the slope of the second treatment interval [3]. In 40 patients who did not have a change in antihypertensive medication we had enough data to determine the slope of reciprocal creatinine versus time before and after an arbitrarily defined mid-point of their follow-up. These data are time controls and showed no significant change in either slope or mean value of diastolic blood pressure (Table 6). In patients who had a new antihypertensive drug prescribed, we compared the slope of reciprocal creatinine versus time and the average diastolic blood pressure in time periods following and preceding the change in medication. These paired differences are shown on Table 6. Significant improvement in diastolic blood pressure was observed with all medication changes except prazosin. Significant slowing of the slope of the reciprocal creatinine versus time plot was observed with the addition of minoxidil or calcium channel blockers. Additions of other antihypertensive medications except beta blockers tended to improve the slope but were not significant because the beneficial effects were not seen in a majority of patients. Addition of beta blockers, usually propranolol or atenolol, significantly reduced diastolic blood pressure but had no effect on the slope of the reciprocal creatinine versus time plot.

Previously, we have shown that a reduction in diastolic blood pressure from hypertensive to normotensive values in individual patients was associated with a less negative slope of the reciprocal creatinine versus time plot [3]. We repeated this analysis in the 45 cases where average values of diastolic blood pressure were lowered from greater than 90 mm Hg to below 90 mm Hg during the time of follow-up. The average slope improved from −0.76 ± 0.09 ml/mg month during the hypertensive period to −0.46 ± 0.09 during the normotensive period (Fig. 2). Thus as a group, these data confirmed our previous observation. In subsets of these patients the data were different. In patients who received minoxidil or calcium channel blockers and responded with a reduction of their diastolic blood pressures from hypertensive to normotensive values, the slope of the reciprocal creatinine plot changed from −0.78 ± 0.12 ml/mg month to −0.24 ± 0.07 (Fig. 2). However, in patients who were treated with addition of a beta blocker, prazosin, clonidine or a combination of two of these drugs, the slope of the reciprocal creatinine was −0.68 ± 0.11 ml/mg month when they were hypertensive and was not different at −0.56 ± 0.13 ml/mg month after addition of the medication when they were normotensive.

Discussion

In a previous study we showed that the presence of diastolic hypertension in patients with pre-existing renal insufficiency was associated with a more rapid rate of decline in renal function as determined by the slope of the reciprocal serum creatinine versus time plot [3]. The objective of the present study was to extend this observation by determining if this phenomenon was a function of diastolic blood pressure alone or a function of other pathogenetic processes associated with hypertension.

One question which we wished to address is whether black patients with renal insufficiency progress to ESRD more rapidly than white patients. Hypertensive black patients reach ESRD more frequently than can be explained by the prevalence of hypertension [4]. Renal function in black patients with primary hypertension is associated with decreased renal blood flow [11], sodium retention [12], and reduced urinary kallikrein excretion [13] as compared to that in hypertensive white patients. These factors may predispose the kidneys of hypertensive black patients to a more rapid progression of disease. The data from our study indicate that black and white patients had equivalent rates of progression of renal disease as determined by the reciprocal creatinine versus time plot as a group (Table 1) and when divided by the presence or absence of diastolic hypertension (Fig. 1) or type of renal disease (Table 2). Thus, once renal insufficiency is established and shown to be progressive, black men do not progress more rapidly than white men, notwithstanding the significantly higher level of diastolic blood pressure in the black patients as a group (Table 1). These findings were true for a subgroup of patients with primary hypertension as the probable cause of their renal disease (Table 2). Therefore, the increased prevalence of blacks with ESRD probably relates to other factors such as an increased rate of progressive renal disease in younger blacks or black females which make up most of the increased prevalence [4], or to an increased rate of development of renal insufficiency in blacks with hypertension as compared to whites [5]. These possibilities were not addressed in this study.

A second objective of this study was to determine if specific types of antihypertensive medication have effects on the progression of renal disease and slow its rate more than expected with control of hypertension. Numerous studies show that various treatments preserve renal function in animal models of progressive renal disease. For example, in rats with reduced renal mass, inhibitors of angiotensin converting enzyme preserve renal morphology and function better than other antihypertensive medications at the same level of systemic blood pressure [14, 15]. Thus we hypothesized that specific antihypertensive drugs may have a beneficial effect on the progression of renal disease even in patients whose diastolic blood pressures were controlled.

To address this hypothesis, we compared rates of change in reciprocal creatinine versus time plots for groups of patients treated with a specific antihypertensive regimen (Table 5). These data indicate that patients who require diuretic treatment to control blood pressure or extracellular fluid volume had faster rates of decline in reciprocal creatinine than patients who do not, and that patients treated with minoxidil had rates of decline in reciprocal creatinine that were significantly slower than that of patients who received only diuretics or no treatment for blood pressure control. Our interpretation of these observations is limited because of nonrandom assignment to treatment group, small numbers, unknown patient compliance and the presence of other medications. Therefore, in a second approach, we examined data from individual patients whose slope of reciprocal creatinine versus time was determined before and after addition of a specific antihypertensive medication. In these patients (Table 6) the diastolic blood pressure was lowered significantly by the addition of all drugs except prazosin. The effect of these additions on the slope of the reciprocal creatinine versus time plot was variable. Addition of beta blockers or prazosin had no effect. Addition of two drugs or clonidine tended to slow the rate of decline, but these changes were not significant because of individual variability and a small number of observations. However, additions of minoxidil or calcium channel blockers had a significant, positive effect on the slope. These drugs were also the most effective in lowering the diastolic blood pressure, and the effect on the slope of the reciprocal creatinine versus time plot could be a result of better control of blood pressure.

To examine this possibility, we looked at data from individual patients who had a reduction in mean diastolic blood pressure from greater than 90 mm Hg to a normotensive value. In our previous study this change was associated with a beneficial effect on the rate of change of the reciprocal creatinine [3]. In this study, we found that this effect was dependent upon the type of medication used to control the blood pressure. Addition of minoxidil or a calcium channel blocker was associated with a 40% slower rate of change in reciprocal creatinine when diastolic hypertension was controlled. Addition of a beta blocker, prazosin, clonidine or a combination of two of these drugs had no significant effect on the rate of change in reciprocal creatinine even when diastolic blood pressure was controlled (Fig. 2). Thus these data suggest that the medication itself and not just the reduction in systemic blood pressure may have a beneficial effect on the course of progressive renal disease.

In early literature minoxidil was reported to preserve or improve renal function acutely in malignant hypertension [16, 17]. Only two of the patients in our study had malignant hypertension with papilledema, so the present data are not due to that effect of minoxidil. The effectiveness of minoxidil in "benign" hypertension and renal insufficiency is less clear in the literature. Mitchell, Graham and Pettinger [17] followed 32 such patients who were treated with minoxidil for an average of 39 months. They reported that many of these patients showed progression of renal disease even when blood pressure was adequately controlled [17]. From their data, however, we calculate the average rate of change of reciprocal creatinine for these patients to be -0.35 ml/mg month. This value is nearly the same as reported for our patients (Table 5) and appears to be significantly lower than the average value for our normotensive patients who were not treated. The mechanisms involved in slowing progressive renal disease with minoxidil are unknown. Our data suggest that the mechanisms are not limited to a reduction in systemic blood pressure because lowering blood pressure to a similar extent with other medications did not have the same beneficial effect (Fig. 2). However, prospective, randomized studies are needed to confirm this hypothesis.

Calcium channel blockers have been shown to preserve renal

function during several types of acute [18] and chronic [19] renal failure in animals. Chronic verapamil treatment of rats with the five sixths nephrectomy model of renal insufficiency preserved renal function without significantly lowering mean arterial blood pressure [19]. This suggests that mechanisms other than blood pressure control underlie this protective effect. These mechanisms may include blocking tissue calcium accumulation during injury [19, 20] or blocking the hypermetabolism that appears to be associated with a reduction in renal mass [21]. Similar mechanisms may occur in patients. Renal tissue from patients with renal disease had a higher calcium content than renal tissue from autopsied controls [22]. These authors suggest that tissue calcium content was elevated early in the course of renal disease and aggravated by elevations in plasma phosphate. Eliahou et al [23] recently reported on a randomized trial in patients with progressive renal disease comparing treatment with a calcium channel blocker to treatment with other antihypertensive medications (beta blockers, prazosin or hydralazine). The 17 patients treated with nisoldipine, a calcium channel blocker, showed a significant improvement in the slope of the reciprocal creatinine (from −0.75 ml/mg month to −0.49) whereas the 17 patients in the control group had no change (−0.46 ml/mg month to −0.52) during the 17 month follow-up period. There was no significant change in diastolic blood pressure during the treatment period. These data and the data from our study support the hypothesis that treatment with calcium channel blockers may preserve renal function in the setting of renal insufficiency by mechanisms in addition to a reduction in systemic blood pressure.

The results of our study may be limited by the patient population on which it is based. The patients were derived from a VA Nephrology Clinic over a 9.5 year period. The Durham VA Medical Center provides care for all eligible veterans in a region that includes most of North Carolina, a population of older males. Therefore, the conclusions drawn from this study may not be applicable to young patients or women. The average rate of decline in the slope of reciprocal creatinine versus time in this population, however, was similar to that reported for other populations. For example, the mode for the slope of reciprocal creatinine plots was −0.6 ml/mg month for predialysis patients followed by clinics at Johns Hopkins and Montreal General Hospitals [24]. Diabetic patients with renal disease followed at the Joslin Clinic had an average reciprocal creatinine slope of −0.2 ml/mg month when diastolic blood pressure was normal and −0.7 ml/mg month when it was not [25]. Walker et al [26] reported that patients followed at Johns Hopkins Hospital with diabetic nephropathy and hypertension had an average reciprocal creatinine slope of −0.8 ml/mg month if they were insulin-dependent and −1.0 ml/mg month if they were non-insulin dependent. Thus, these preliminary reports from other medical centers indicate that their patient populations have comparable rates of change in reciprocal creatinine to those observed in our population.

In summary, this retrospective study of a large population of veterans with progressive renal insufficiency indicates that there are no differences between black and white patients in the rate of progression as determined by the slope of the reciprocal creatinine versus time or in the response of renal disease to the presence of hypertension. Additionally, in this population, the use of specific antihypertensive medications such as minoxidil and calcium channel blockers was associated with a significant slowing of the progression of renal disease. This effect was not seen with other antihypertensive medications and appeared to be additive to the beneficial effect of lowering the diastolic blood pressure. The mechanisms involved in this protective effect are unknown. These data, however, indicate that it may be possible to slow the rate of progressive renal disease with medications. Prospective studies are needed to directly address this possibility and to determine pathogenetic mechanisms.

Acknowledgments

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