Long-Term Improvement in Renal Function After Short-Term Strict Blood Pressure Control in Hypertensive Nephrosclerosis

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Seventy-nine hypertensive nephrosclerosis patients entered a prospective randomized single-blind study to 1) establish the pattern of decay of renal function in this population and the variability therein and 2) to determine if strict diastolic blood pressure (DBP) control (<80 mm Hg) is more effective than conventional levels (90–95 mm Hg) in conserving renal function. Because of unexpected significant improvement in renal function in patients from both groups, which changed the perspectives on the course of this disease as described herein, this report is being published before completion of the trial. The selection criteria were 1) serum creatinine concentration of 1.6–7.0 mg/dl, 2) glomerular filtration rate of less than 70 ml/min/1.73 m², and 3) absence of diseases (other than hypertension) known to destroy renal function. Renal function was assessed by glomerular filtration rate ([¹²⁵I]iothalamate clearance) and serum creatinine concentration. Before randomization, DBP was aggressively treated to reduce it to less than 80 mm Hg. Twenty-two subjects (14 in the strict DBP control group and eight in the conventional DBP control group) have been enrolled in the study for 36 months. In contrast to results from previous studies in humans and rats, renal function improved in both patient groups. Thus, irrevocable progression of renal damage after onset of renal failure from high blood pressure does not necessarily occur, and in fact, long-term improvement of renal function resulted from the effects of the study itself. The study design involving the 2–4-month initial period of aggressive DBP control at 80 mm Hg or less followed by control of DBP at less than 90 mm Hg was associated with long-term improvement in renal function. (Hypertension 1989;13:766–772)

Mitch et al. have proposed that renal disease progression, once established, has a predictable and irrevocable pattern of decay in individuals. They reported that the reciprocal of the serum creatinine (1/S_Cr) concentration declined linearly as creatinine concentration rose from a mean of 3.0 mg/dl to 14 mg/dl during a mean interval of 77 months in three patients with hypertensive renal disease. Rutherford et al. made similar observations in 30 hypertensive patients. The rate of nephron destruction assumed a straight-line function, the slope of which remained constant for each individual. However, the slope could vary among individuals. Such a pattern should provide a rationale for demonstrating efficacy of interventions in relatively small patient populations. Thus, in this project, we attempted to determine whether strict (diastolic blood pressure [DBP] ≤80 mm Hg) control of DBP is better than conventional (DBP 90–95 mm Hg) control in the control of renal disease progression by measuring the slope of 1/S_Cr and glomerular filtration rate (GFR).

It is generally accepted that control of BP partially allays progression of renal disease in essential hypertension. However, there are no long-term carefully controlled prospective trials of treated hypertensive nephrosclerosis patients that characterized the course of the disease. Thus, there is no published basis for calculation of sample size required for design of a trial to study intervention efficacy. Thus, in addition to the goal described above, we attempted to define characteristics of the progression of hypertensive renal disease by GFR and the slope of 1/S_Cr versus time while treating patients with currently available antihypertensive agents.

Although this is a preliminary report, it appears that progression of renal disease in hypertensive nephrosclerosis is not necessarily progressive. Dur-
Patients and Methods

Patients with long-standing hypertension and an S_Cr concentration of 1.6–7.0 mg/dl with a GFR of less than 70 ml/min/1.73 m² of body surface area between the ages of 21 and 68 years were invited to participate in this study. Patients with any of the following conditions were excluded from the study: 1) history of acute renal failure, chronic glomerulonephritis, nephrotic syndrome, analgesic abuse, diabetes mellitus, polycystic kidneys, systemic lupus erythematosus, or scleroderma; 2) known renal artery stenosis or evidence thereof, primary aldosteronism, or other reversible causes of hypertension; 3) pregnant or lactating women or women who were likely to become pregnant; 4) cerebrovascular accident, transient ischemic attacks, or hypertensive encephalopathy within the past year; and 5) myocardial infarction within the last 3 months.

The general design of the protocol is illustrated in Figure 1. In all patients, we attempted to control DBP to 80 mm Hg or less on three out of four outpatient visits to exclude patients with severe refractory hypertension, noncompliance from the randomization, or both. Patients whose DBP was not controlled to 80 mm Hg or less were also monitored as a “nonrandomized” group. After qualifying, the patients were randomized (at zero time) to either the strict (DBP < 80 mm Hg) or the conventional (DBP 90–95 mm Hg) blood pressure level, this level being blinded from the patients and so maintained by the use of currently available antihypertensive agents. No dietary intervention was suggested during or before the study.

Patients were stratified according to initial S_Cr concentration into the low (S_Cr 1.6–2.5 mg/dl) or high (S_Cr 2.6–7.0 mg/dl) creatinine group to prevent randomization of an inappropriately high number of high-creatinine patients into either the strict or conventional group.

DBPs were recorded as the mean± standard error of the mean of all values on outpatient clinic visits between the time of GFR determinations. Renal function, neuroendocrine, and clinical chemistry studies were done before the initial aggressive BP control phase, at randomization (zero time), and at 3, 9, 18, 24, and 36 months of the study. GFR was measured according to the technique of Israelit et al5 with [125I]iothalamate, plasma renin activity by the technique previously published from this laboratory,6 and catecholamines by a radioenzymatic technique (Cat-a-kit, Upjohn Laboratories, Kalamazoo, Michigan).7

To illustrate trends in antihypertensive drug usage, we developed a semiquantitative index based on Table 1. Each drug dose given in the table is equivalent to one unit. The pharmaceutical company that contributed the drug is listed with each agent. The antihypertensive drug score for each patient was calculated with multiples of the above doses if the doses were higher than those listed above for the one-unit value.

The protocol was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center at Dallas, and written informed consent was obtained from each patient before study entry.

Statistical methods included two-way repeated measures analysis of variance to assess the effect of BP control (conventional or strict) over time for various measurements made at baseline and at 3, 9, 18, 24, and 36 months. If the group-by-time interaction was significant at the p<0.10 level, two-tailed pairwise comparisons were made for treatment groups at each time and within a group for different time periods. The p<0.05 level was considered significant.8,9
Results

Seventy-nine hypertensive nephrosclerotic patients were recruited to this project. Eighty-nine percent of the patients were black, and 78% were men. The age ranged from 27 to 68 years at entry with a mean age of 58. Twenty-two patients have now been enrolled for 36 months after zero time of the study. Fourteen patients were in the strict and eight patients in the conventional DBP control group.

The mean DBP was maintained at or near planned levels in both groups of randomized patients before 24 months, but from 24 to 36 months, mean DBP could not be maintained at proposed levels of 80 mm Hg or less and 90-95 mm Hg in the strict and conventional control groups, respectively. The mean±SEM in the strict group was 83 ±2 mm Hg at 36 months. In the conventional group, DBP was 86±3 mm Hg, even though the dose, the number of antihypertensive drugs, or both were markedly reduced (Figure 2). Therefore, the results were also pooled and considered as one treatment group.

The status of renal function in these patients (n=22) was analyzed. The GFR increased from 35.8±2.7 to 44.2±3.3 ml/min (p<0.05), and S Cr decreased from 2.56±0.14 to 2.26±0.24 mg/dl (p>0.05). Because the initial level of renal function is an important determinant of the subsequent progression to renal failure,3 patients were stratified into low initial S Cr (<2.5 mg/dl) or high initial S Cr (>2.6 mg/dl) groups and analyzed. In the low-creatinine group (n=18), the GFR increased in the overall group from 40.5±2.5 to 49.1±3.1 ml/min (p<0.05) at 36 months while the S Cr decreased from 2.3±0.2 to 1.9±0.2 mg/dl (p<0.05) (Figure 3). In patients (n=4) with initial high S Cr, the GFR increased from 19.55 to 27.44 ml/min at 36 months, and the S Cr changed from 3.38±0.29 to 3.75±0.87 mg/dl. These changes were not significant (p>0.05).

Some of the patients have been followed for more than 4 years. The entire course for each patient is illustrated in Figure 4 as 1/S Cr versus time including the slope thereof. Fourteen of 18 patients with an initial S Cr of 1.6-2.5 mg/dl had positive slopes (x=0.003). Two of four patients with an initial S Cr >2.6 mg/dl also had positive slopes (x=0.0008). Therefore, the overall picture is improvement in renal function, particularly in patients with initial low creatinine.

Treatment with the angiotensin converting enzyme inhibitor enalapril has been shown to preserve renal function in hypertensive rats with subtotal nephrectomy.10,11 We therefore analyzed the status of renal function in patients treated with enalapril (n=13; range of doses, 10-20 mg/day). There was no statistically significant difference in the degree of improvement of renal function in patients treated with and without enalapril.

There was no significant change in body weight, plasma cholesterol, triglyceride, low density lipoprotein, high density lipoprotein, glucose, uric acid, potassium, phosphorus, plasma renin activity, epinephrine, norepinephrine, or 24-hour urine protein and sodium from zero time through the ensuing 3-year period (Table 2).

Treatment Problems

One patient in the strict BP control group (1/31 in the whole study) experienced a myocardial infarction after 45 months in the study. He continues in the project and is asymptomatic. This is one nonfatal myocardial infarction in at least 717 patient-
months in the strict BP control (DBP ≤80 mm Hg) group at high risk for myocardial infarction. Two patients in the strict BP control group (2/48) and one patient in the conventional group (1/31) developed reversible renal dysfunction while taking a converting enzyme inhibitor. S\textsubscript{Cr} increased more than twofold above the baseline level after these patients took enalapril for more than 2 months. Each of these patients had renal arteriograms performed that demonstrated absence of renal artery stenosis. Of the 22 patients reported herein, two developed nephrotic syndrome but were continued in the study. One patient (patient 3 in Figure 4) with an initial S\textsubscript{Cr} of 3.6 mg/dl has progressed slowly to hemodialysis at 37 study months. Therapy with enalapril was discontinued in two patients because of angioneurotic edema and in two others because of hyperkalemia.
TABLE 2. Metabolic Parameters in 22 Patients Before and After 36 Months of Good Blood Pressure Control

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Initial</th>
<th>36-Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dl)</td>
<td>107.0±4.6</td>
<td>102.7±3.8</td>
</tr>
<tr>
<td>Potassium (meq/l)</td>
<td>4.0±0.2</td>
<td>4.2±0.1</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>218.2±7.2</td>
<td>228.1±8.4</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>168.9±20.6</td>
<td>199.6±28.0</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>144.5±6.4</td>
<td>150.0±12.8</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>43.0±2.1</td>
<td>44.8±2.9</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>9.5±0.4</td>
<td>7.7±0.4</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>9.74±0.07</td>
<td>9.47±0.14</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>3.56±0.12</td>
<td>3.42±0.13</td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>5.47±1.93</td>
<td>7.77±2.50</td>
</tr>
<tr>
<td>Norepinephrine (pg/ml)</td>
<td>493.2±85.4</td>
<td>526.0±81.9</td>
</tr>
<tr>
<td>Epinephrine (pg/ml)</td>
<td>69.6±12.3</td>
<td>68.6±10.1</td>
</tr>
<tr>
<td>24-hr urine sodium (meq/24 hr)</td>
<td>179.4±20.9</td>
<td>156.2±22.2</td>
</tr>
<tr>
<td>24-hr urine protein (mg/24 hr)</td>
<td>338.9±103.1</td>
<td>446.8±150.0</td>
</tr>
</tbody>
</table>

Values are mean±SEM.
LDL, low density lipoprotein; HDL, high density lipoprotein; PRA, plasma renin activity.

Discussion

Increased intraglomerular pressure is presumably a contributing factor to progression of hypertensive nephrosclerosis in rats.10,11 In 1939, Wilson and Byrom12 found that the glomerular damage in rats with unilateral renal artery stenosis hypertension was restricted to the unclipped kidney, the one exposed to high BP. Hill and Heptinstall13 in 1968 reported that the earliest microangiographic change in the uninephrectomized rat with steroid-induced hypertension was marked dilatation of glomerular arterioles. In subsequent years, Brenner and his colleagues14,15 have confirmed and extended these observations, which suggest that intraglomerular hypertension or hyperfiltration plays a role in the progression of nephrosclerosis in rats with initial loss of renal mass by surgery,16 infarction,17 or a result of genetically reduced number of nephrons.18 Also, they have pharmacological evidence that the progression of glomerulosclerosis can be retarded by lowering intraglomerular pressure in rats.19,20

Lowenstein et al21 found that wedged renal vein pressure is increased in hypertensive patients. This observation suggests that increased systemic arte-
rial pressure is transmitted through the glomerulus to the renal vein. Thus, according to one hypothesis, hypertension-induced renal insufficiency is caused by glomerular hypertension, which results from transmission of high systemic arterial pressure through the afferent arteriole to the glomerulus. According to this hypothesis, sufficient reduction of systemic arterial pressure in hypertensive patients may reduce intraglomerular pressure and thereby prevent further glomerular hyperfiltration-induced damage. This rationale describes the basis for the hypothesis in this study.

The results from this prospective study indicate that the progression of hypertensive nephrosclerosis in most patients can be halted by control of BP as achieved in this protocol. In fact, improvement in renal function occurred in most patients. Seventy-eight percent (14/18) of patients with initial low SCr concentration had partial restoration of renal function. While improvement is less frequent in patients with initial high SCr levels, one half (2/4) of the patients with initial high SCr levels had improvement in renal function.

Thus, the overall improvement in renal function during the 3-year interval of study was an unexpected result. The differences between this study and previous reports are that 1) most are retrospective studies whereas this is a prospective study, 2) most had difficulty in patient compliance whereas we had a very high compliance rate (95%) after zero time, 3) other studies had not maintained the quality control of actual BP as rigorously as ours, and 4) no previous studies had initial aggressive DBP (<80 mm Hg) control. We suggest that these factors contribute to the differences in results from previous reported observations. We controlled DBP to 80 mm Hg or less in all patients during the first three of four outpatient visits. It is a possibility that this 2-4-month period of aggressive BP control may have been the factor that permitted long-term improvement in renal function in both groups regardless of treatment with an angiotensin converting enzyme inhibitor.

Several metabolic factors have been proposed to contribute to the progression of hypertensive nephrosclerosis including gout, diabetes mellitus, dyslipoproteinemia, low dietary potassium or linoleic acid, and high dietary protein or phosphate. First, there were no systematic dietary changes during the study. Also, there was no significant overall change in plasma uric acid, glucose, cholesterol, triglyceride, low density lipoprotein, high density lipoprotein, potassium, phosphorus, and 24-hour urine urea nitrogen between groups nor with time during the 3-year trial period. Therefore, the improvement of renal function observed in this study is unlikely to be due to changes in any metabolic factor that has been suggested for the etiology of progression of renal disease.

Complications from aggressive control of BP were uncommon in our study. There were no myocardial infarctions, strokes, transient ischemic attacks, or increases in anginal attacks in any patients during the strict (DBP ≤80 mm Hg) 2-4-month prerandomization phase of this study. Thus, the previously suggested worsening of coronary heart disease with aggressive antihypertensive therapy did not occur in these patients at high coronary artery disease risk from long-standing severe hypertension. One patient in the strict BP control group developed a myocardial infarction after 45 months in the study. He continues asymptotically in the strict BP control group.

Three patients developed reversible renal dysfunction while taking enalapril. These patients were also noted to have exaggerated reactive hyperreninemia to enalapril despite β-adrenergic receptor blockade and severe diuretic-resistant fluid retention while taking minoxidil. However, renal arteriographic studies were negative, suggesting a syndrome of pseudo renal artery stenosis.

We were unable to maintain the mean DBP at proposed levels in both groups of randomized patients after 2 years of good BP control. A similar observation was noted in the Framingham study and other previous studies. The hypertension became easier to control after a period of effective treatment with antihypertensive drugs. In the conventional group, DBP was 86±3 mm Hg even though the doses of antihypertensive drugs were markedly reduced. The mechanism of this change is unclear. It may be related to the natural history of these patients and a resetting of baroreceptor mechanisms.

In summary, this preliminary study is limited by the small number of patients evaluated. However, the results clearly indicate that marked destruction of renal function does not lead inevitably to predictable further decay of renal function in treated hypertensive nephrosclerosis patients. Good (DBP <90 mm Hg) BP control per se, preceded by a 2-4-month period of DBP at 80 mm Hg or less, has the potential for producing a significant improvement of renal function in hypertension-induced renal disease.

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References


KEY WORDS • renal arteries • antihypertensive agents • minoxidil • hypertensive nephrosclerosis • hypotension • renal function
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