Symposium

Control of Blood Pressure and Prevention of End-Organ Damage in Patients with Accelerated Hypertension by Combination with Arotinolol and Extended Release Nifedipine

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In patients with accelerated (malignant) hypertension, end-organ damage is the determinant factor for prognosis. Although recent advances in antihypertensive therapy have improved the outcome of patients with accelerated hypertension, the effectiveness of antihypertensive therapy still remains less convinced.

In this study, we followed 13 patients clinically diagnosed with accelerated hypertension (defined as diastolic blood pressure > 130 mmHg, retinopathy with K-W IV and accelerated renal impairment) for 3 yr. One patient died due to acute myocardial infarction arising from poor compliance with antihypertensive therapy. One patient was maintained on hemodialysis for 3 yr. One patient was introduced for continuous ambulatory peritoneal dialysis (CAPD) for a year and then lived without dialysis therapy. The remaining 10 patients were followed for 3 yr. All patients were initially treated with intravenous administration of calcium antagonist for reduction of blood pressure, followed by hemodialysis therapy if needed. After stabilization of blood pressure, combination therapy with extended release nifedipine (40 to 80 mg daily) and arotinolol (20 mg daily) was started. The targets for blood pressure control were a systolic pressure of 135 mmHg and a diastolic pressure of 80 mmHg. If blood pressure control was unsatisfactory, guanabenz (2 to 4 mg before bedtime), a central acting drug, was added. At presentation, the mean diastolic blood pressure (mDBP) among the 10 remaining patients was 134 ± 2 mmHg, the mean serum creatinine (mScr) was 4.5 ± 0.7 mg/dl and the left ventricular mass index (LVMi) as measured by echocardiography was 150 ± 9 g/m². At 1 yr, the mDBP was reduced to 90 ± 3 mmHg, the mScr to 2.9 ± 0.9 mg/dl and the LVMi to 140 ± 9 g/m². At 3 yr, the mDBP was stabilized at 79 ± 3 mmHg, the mScr maintained at 2.2 ± 0.4 mg/dl, and the LVMi reduced to 128 ± 9 g/m². These results indicate that appropriate blood pressure control is important for improvement of renal impairment and cardiac damage in patients with accelerated hypertension. Moreover, combination therapy with arotinolol and extended release nifedipine may be beneficial for this purpose. (Hypertens Res 2000; 23: 159-166)

Key Words: accelerated hypertension, renal failure, left ventricular hypertrophy, calcium antagonist, αβ blocker

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Introduction

Although the recent development of new antihypertensive agents and the prevalence of antihypertensive therapies are thought to have reduced the incidence of accelerated hypertension and to have improved prognosis, the evidence for these improvements remains limited (1, 2). Thus, although several authors have posited that the incidence of accelerated hypertension is in decline and the prognosis improving (3, 4), this is not collaborated by the recent study of Lip et al. (5), who found no decline in the incidence of accelerated hypertension and a relatively poor prognosis for cases compromised by renal impairment.

In hypertensive emergencies, intravenous antihypertensive therapy is mandatory, and oral agents can be started after the stabilization of blood pressure. As the choice of oral antihypertensive agents, angiotensin converting enzyme (ACE) inhibitors are recommended because several human clinical trials have demonstrated that ACE inhibitors reduced proteinuria and also prevented progressive renal failure in patients with renal insufficiency from hypertension (6-8). However, in cases of moderate to severe renal dysfunction, antihypertensive treatment with ACE inhibitors can actually exacerbate renal dysfunction and hyperkalemia (9). There have been few reports on renal impairment due to accelerated hypertension. At present, some studies provide evidence of the renoprotective effects of calcium antagonists (10), such as retardation of renal growth, reduction of mesangial entrapment of macromolecules, and etc. (11).

Cases of accelerated hypertension are often complicated by myocardial ischemia, left ventricular hypertrophy, and/or renal insufficiency (12-14). For patients with such complications, Nolan and Linas have indicated that intravenous administration of sodium nitroprusside followed by combination therapy with hydralazine and propranolol is highly effective (15). Additionally, it is reported that the addition of nifedipine to β receptor blockade, has been provoked to have cardioprotective effects (16, 17). Arotinolol (18, 19), which was developed in Japan, has a structure and action similar to those of carvedilol (20).

In the present study, we performed a three-year follow-up of patients with accelerated hypertension in order to quantify the efficacy of combination therapy with arotinolol and extended release nifedipine.

Patients and Methods

Thirteen patients were presented with a symptom of accelerated hypertension to our hospital, over the 3 yr period from 1995 to 1997. We diagnosed these patients as accelerated hypertension by three major symptoms as follows, (1) severe hypertension (diastolic blood pressure >130 mmHg), (2) retinal damage (the presence of bilateral linear or flame-shaped haemorrhages and/or cotton-wool spots) and progressive renal failure (serum creatinine >2.0 mg/dl and/or glomerular filtration rate <50 ml/min/1.73 m²). The diagnosis of any of the underlying causes has greater significance in accelerated hypertension, therefore, secondary causes of hypertension were excluded by endocrinological and radiological examinations, including ultrasonography and computed tomography. Especially, when a renal arterial abnormality or a unilaterally diseased kidney was strongly suspected, magnetic resonance image angiography was applied to deny these possibilities. And when we diagnosed the patient as secondary hypertension from endocrine abnormality or renovascular hypertension, we excluded these patients from our study. Each patient gave their informed written consent to participate in the protocol, which had been approved by our institutional review board.

Blood pressure was controlled by intravenous administration of nicardipine (2-10 μg/kg/min; Yamanouchi Co., Tokyo, Japan). Hemodialysis therapy was utilized for patients experiencing acute renal failure or volume overload. After blood pressure was well controlled and renal deterioration improved, patients were discharged from our hospital. They were followed-up routinely with visits to the hospital every 2 wk to ensure that they had a good blood pressure control under the medication for 6 mo and after that patients were checked every month for next 30 mo.

Antihypertensive treatment was performed using extended release nifedipine at a dose of 40 to 80 mg twice daily and arotinolol 20 mg twice daily. The goal target blood pressure levels were less than 135/80 mmHg. If blood pressure was not sufficiently enough, guanabenz reduction was added at a dose of 2 to 4 mg at bedtime.

One patient died due to acute myocardial infarction following poor compliance with antihypertensive therapy. One patient was maintained on hemodialysis for 3 yr. One patient was introduced for continuous ambulatory peritoneal dialysis (CAPD) for a year and then lived without dialysis therapy.

Blood Pressure Measurements

During our studies, all the subjects were always examined at the same time (10:00 am-12:00 am) at least 2 h after the patients had ingested their medication. Blood pressure was measured in a bed room or an office setting with the conventional cuff method and mercury manometer. Patients were seated for at least 10 min before the measurement. Diastolic blood pressure was determined at Korotokoff phase V.
Laboratory Measurements

We measured the serum creatinine, serum blood urea nitrogen, serum sodium and potassium at admission, during the hospitalization, and at adequate point during the follow-up period. Other biochemical examinations were adequately checked.

Echocardiography

All echocardiography recordings were performed by two experienced investigators using a Hewlett Packard Sonos 1000 system (Hewlett Packard Japan Co., Tokyo, Japan) with a 2.5-MHz transducer according to recommendations of the American Society of Echocardiography (21). M-mode recordings were guided by 2-dimensional views. Left ventricular mass index (LVMI) was calculated according to the formula of Devereux et al. (22). Left ventricular end-diastolic and end-systolic volumes were determined by 2-dimensional echocardiography, and left ventricular ejection (EF) was calculated with standard formulas.

Values from at least 3 beats were measured and averaged, and intraobserver variability was determined to be 6.8%, 6.2% and 3.8% for end-diastolic septal thickness, end-diastolic posterior wall thickness and left ventricular internal diameter, respectively.

Renal Biopsy

In 4 patients, additional informed consent was obtained, and renal biopsy was performed within at least 4 mo after the onset of accelerated hypertension.

Statistical Analysis

Values are expressed as mean ± SEM. For comparisons within groups at different time points, one-way ANOVA by repeated measures was performed. A simple regression analysis was performed for correlations among the variables. Statistical significance was considered to be achieved at $p < 0.05$.

Table 1. Basal Characteristics of Patients with Accelerated Hypertension

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>42 ± 5</td>
</tr>
<tr>
<td>Male/Female</td>
<td>9/1</td>
</tr>
<tr>
<td>Blood Pressure (Systolic/Diastolic) (mmHg)</td>
<td>237/134 ± 6/1</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dl)</td>
<td>4.5 ± 0.7</td>
</tr>
<tr>
<td>Left Ventricular Mass index (g/m²)</td>
<td>150 ± 9</td>
</tr>
</tbody>
</table>

(n=10)

Results

Baseline Characterization of 10 Patients with Accelerated Hypertension

Clinical characterization of our patients were listed in Table 1. One woman and 9 men (mean age 42 ± 5) were studied. Mean systolic and diastolic blood pressure were 237 ± 6 and 134 ± 1 mmHg, respectively. Serum creatinine level was elevated in all patients and mean serum creatinine level was 4.5 ± 0.7 mg/dl. Left ventricular mass index was 150 ± 9 g/m².

Changes in Blood Pressure after Treatment (Fig. 1a and b)

Figure 1 shows the changes in systolic and diastolic blood pressure after combined oral administration of calcium antagonist and $\alpha\beta$ blocker. One year after the antihypertensive treatment, systolic and diastolic blood pressure decreased significantly 141 ± 5 and 90 ± 3 mmHg ($p < 0.001$). Then at the end of the study, systolic and diastolic blood pressure were stabilized around 128 ± 3 and 79 ± 3 mmHg.
Changes in Serum Creatinine after Treatment (Fig. 2)
Intermittent haemodialysis therapy was introduced in 5 patients. In these patients, after oral administration of antihypertensive drugs started, serum creatinine levels gradually decreased. One year later, serum creatinine level decreased to 3.1 ± 0.7 mg/dl (p < 0.05). Except one patient, renal function of all of these patients was completely recovered to allow withdrawal of haemodialysis therapy. However, during the first one year, another one patient needed CAPD therapy. And 36 mo later, serum creatinine level decreased significantly to 2.2 ± 0.4 mg/dl (p < 0.01).

Echocardiographic Data
After 1 yr of combination treatment with calcium antagonist and αβ blocker, LVMI decreased slightly, from 150 ± 9 to 140 ± 9 g/m², whereas a significant decrease could be observed after 3 years to 128 ± 9 g/m² (89 ± 12 reduction vs. control) (Fig. 3). Septal and posterior wall thickness were reduced significantly by antihypertensive ther-
apy from 15 ± 1 to 12 ± 1 mm and 13 ± 2 to 12 ± 1 mm respectively after 3 yr (both, p < 0.01).

After 3 yr, antihypertensive therapy had significantly reduced both septal and posterior wall thickness, the former from 15 ± 1 to 12 ± 1 mm and the latter from 13 ± 2 to 12 ± 1 mm (both, p < 0.01).

Ejection fraction was significantly increased from 72 ± 3 to 82 ± 4% after 3 years’ treatment (p < 0.05, Fig. 4).

Correlations among Variables
Highly significant correlations were found between each pair of LVMI, left ventricular end-diastolic diameter, septal wall thickness, and posterior wall thickness (each, p < 0.0001). The diastolic blood pressure was significantly correlated with the left ventricular end-diastolic diameter (r = 0.565, p < 0.0001) and with LVMI (r = 0.351, p < 0.05) (Fig. 5a and 5b). The systolic blood pressure was also correlated with the serum creatinine levels (r = 0.515, p < 0.0005) (Fig. 6).

Renal Biopsy
Typical histopathological changes are shown in Fig. 7. One of the glomeruli showed fully developed hypertensive glomerulopathy with glomerular capillaries adhered to each other, and swelling and fatty degeneration of the endothelial cells. Another glomerulus was largely obliterated with PAS-positive hyalinosis. Diffuse tubular atrophy and interstitial fibrosis were observed. The characteristic findings of malignant nephrosclerosis, such as striking “onion peel” thickening of the intima of a small artery and fibrinoid necrosis of an arteriole at the glomerular hilus, were not found in any of the specimens obtained from the 4 patients.

Discussion
In the present study, we confirmed that appropriate blood pressure control is effective for preserving renal function with amelioration of left ventricular hypertrophy even in patients with accelerated hypertension.

The prognosis of accelerated hypertension remains controversial. Lip et al. have demonstrated that good blood pressure control was associated with an improved survival rate (23). On the other hand, other workers have suggested that blood pressure control does not necessarily reduce the incidence of, or progression to, chronic renal failure (24). In addition, the presence of severely impaired renal function has been related to outcomes of patients with accelerated hypertension (25-27). In general, many patients who develop accelerated hypertension have previously existing essential hypertension (5, 28), although the prevalence of pre-existing renal disease among patients presenting with accelerated hypertension has been variously reported as from 40% (5) to as much as 80% (3). In patients with chronic glomerulonephritis as an underlying renal disease, IgA nephropathy is the most common cause of accelerated hypertension (29). In the present study, one patient was documented to have proteinuria before onset of accelerated hypertension; however, the other patients did not have a past history of hematuria and/or proteinuria. Moreover, high blood pressure was noted in more than half the patients prior to the development of accelerated hypertension. It is therefore unlikely that the patients enrolled in this study had chronic glomerulonephritis as an underlying renal disease.

Fahr (30) provided the first clinical description of decompensated benign nephrosclerosis, distinguishing it
from compensated benign nephrosclerosis and from malignant nephrosclerosis. Recently, Ratschek et al. (31) revised these findings. According to their description, the most prominent difference between decompensated benign nephrosclerosis and malignant nephrosclerosis lies in the changes in the glomeruli; in decompensated benign nephrosclerosis, hyalinized glomeruli are most common alteration, while in malignant nephrosclerosis, so-called glomerular loop collapse is the most frequent pathologic change, though such collapse is still quite rare. In decompensated benign nephrosclerosis, postglomerular interstitial fibrosis with tubular atrophy is in the foreground of pathologic changes. These changes are highly similar to the histopathological changes found in 4 of the present patients. Further, these studies by Fahr and Ratschek et al. provided evidence that these histological changes are found predominantly in male patients. The present cohort included only two female patients, vs. 11 males. It is therefore likely that, in clinical practice, the clinical feature of accelerated hypertension without hemolysis due to destruction of red blood cells, appears as a result of decompensated benign nephrosclerosis but not as a result of malignant nephrosclerosis. At present, although renal biopsy in patients with accelerated hypertension is generally considered to be less informative than clinical features and is not carried out unless a diagnosis of lupus nephritis and vasculitis is suspected (32), it is important to remember that similar manifestations appeared from these pathologically different alterations.

The prevalence of left ventricular hypertrophy (LVH) in patients with accelerated hypertension is also controversial. In one series (15), LVH was less frequently found, and this lower incidence was attributed to the fact that accelerated hypertension develops abruptly, such that the duration of high blood pressure is insufficient for development of LVH. On the other hand, other groups have reported variable results for the prevalence of LVH in malignant hypertension (12-14). In the present study, echocardiographic examination was made for all patients. Moreover, in 3 yr, the LVH of all patients disappeared, even in patients maintained on hemodialysis. This provides evidence that LVH would improve with good blood pressure control. Shapiro et al. (12) demonstrated using echocardiography that treatment to reduce blood pressure did not change LVH with resolution of incoordinate contraction. In their study, no precise antihypertensive drug regimen for treatment of malignant hypertension was described. In the present study, all patients were treated with a combination of extended release nifedipine, a long releasing calcium antagonist, and arotinolol, an aβ blocker. There have been a few reports demonstrating the improvement of cardiac dysfunction with calcium antagonists. Carvedilol has been shown a lot of evidences for improvement of LVH in patients with heart failure and hypertension in a large scale study (20). Arotinolol has been shown to have a structure similar to carvedilol, and to exert similar actions (18, 19). In light of these findings, the present results revealed that good blood pressure control by means of extended release nifedipine and the cardioprotective action of arotinolol can ameliorate LVH and stabilize renal dysfunction.

In our previous study (33), we clearly demonstrated that combination therapy with arotinolol, an aβ blocker, and nifedipine, an extended release calcium antagonist, is effective for both the reduction of highly elevated blood pressure and the protection of the kidney. In the present study, we extended this previous investigation to a follow-up of 3 years’ duration, and added another important finding, i.e., that this therapy improved LVH in patients with accelerated hypertension.

At the present time, since decompensated benign nephrosclerosis has been completely forgotten, accelerated or malignant hypertension is defined based on clinical findings. Also, the underlying or pre-existing renal disease remains uncertain without renal biopsy. We therefore cannot exclude the possibility that our patients might represent some special population of accelerated-malignant hypertension. Second, we might ask why combination treatment with calcium antagonist and aβ-blocker is effective in improving renal dysfunction. Previously, the combination of a aβ-blocker and minoxidil, a direct vasodilator, was reported to be effective in treatment of patients with malignant hypertension and severe side effects including headache and hypertrichosis (34). Currently, it seems possible that extended release nifedipine might be a suitable substitute for minoxidil. Also, most clinical trials have demonstrated the usefulness of ACE inhibitors in slowing the progression of renal failure and in improving the renal impairment in malignant hypertension (6-8), in spite of few reports supporting the efficacy of calcium antagonists (10). However, it should be noted that the most important intervention for retarding the progression of renal disease and improving renal function in malignant hypertension is adequate and sustained reduction of blood-pressure (10). It is therefore reasonable that in the present study the combination treatment produced improvement of renal impairment with good blood pressure control. Third, it remains controversial whether adequate blood pressure control per se improves LVH or not when antihypertensive agents other than ACE inhibitors are applied. In the present study, arotinolol was used instead of carvedilol. This aβ blocker might be effective for reducing LVH in cooperation with adequate blood pressure reduction.

In conclusion, combination therapy with an extended release calcium antagonist and a β blocker was here shown to be effective in improving the renal and cardiac dysfunction associated with highly elevated blood pressure.
### References