Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.0438-17
Intern Med 57: 2459-2466, 2018
http://internmed.jp

【 ORIGINAL ARTICLE 】

Effect of Eplerenone on the Glomerular Filtration Rate (GFR) in Primary Aldosteronism: Sequential Changes in the GFR During Preoperative Eplerenone Treatment to Subsequent Adrenalectomy

Yujiro Nakano[1], Takanobu Yoshimoto[1], Tatsuya Fukuda[1], Masanori Murakami[1], Ryotaro Bouchi[1], Isao Minami[1], Koshi Hashimoto[1,2], Yasuhisa Fujii[3], Kazunori Kihara[3] and Yoshihiro Ogawa[1]

Abstract:

Objective Eplerenone (EPL) is a mineralo-corticoid receptor antagonist that is highly selective and has few side effects. This study was conducted to examine whether or not EPL treatment was able to reverse glomerular hyperfiltration, as an indicator of aldosterone renal action, in primary aldosteronism (PA) patients.

Methods Changes in the estimated glomerular filtration rate (ΔGFR) were examined in 102 PA patients with EPL treatment. Furthermore, the sequential ΔGFR in 40 patients initially treated with EPL followed by adrenalectomy was examined in order to evaluate the extent of the remaining glomerular hyperfiltration in the patients treated with EPL.

Results EPL decreased the GFR at 1 month after treatment. The GFR at baseline was the sole significant predictor for the ΔGFR. Patients initially treated by EPL followed by adrenalectomy showed three different ΔGFR patterns during the treatment, despite having comparable doses of EPL and comparable control of blood pressure and serum potassium levels. The urinary aldosterone excretion was significantly different among these three groups, and the group with no decrease in the GFR after EPL treatment showed greater urinary aldosterone excretion. Glomerular hyperfiltration was completely restored only in 17.5% of our unilateral PA patients after EPL treatment.

Conclusion The present study revealed that blockade of aldosterone action by EPL could, at least partially, reverse glomerular hyperfiltration in PA. Whether or not these differential effects on the GFR affect the long-term outcome needs to be investigated, especially in patients with unilateral PA who do not want adrenalectomy and choose the EPL treatment option.

Key words: primary aldosteronism, chronic kidney disease, mineralocorticoid receptor antagonist, glomerular hyperfiltration

(Intern Med 57: 2459-2466, 2018)
(DOI: 10.2169/internalmedicine.0438-17)

Introduction

Primary aldosteronism (PA) is a major cause of secondary hypertension, accounting for approximately 10% of patients with hypertension (1, 2). Recent epidemiologic studies have revealed that patients with PA are more frequently associated with severe cardiovascular and renal complications than

[1]Department of Molecular Endocrinology and Metabolism, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Japan, [2]Department of Preemptive Medicine and Metabolism, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Japan and [3]Department of Urology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Japan
Received: October 31, 2017; Accepted: January 28, 2018; Advance Publication by J-STAGE: April 27, 2018
Correspondence to Dr. Takanobu Yoshimoto, tyoshimoto.mem@tmd.ac.jp

age-, sex-, and blood pressure-matched patients with essential hypertension (3, 4). Two therapeutic options are recommended for the treatment for PA: either unilateral laparoscopic adrenalectomy for patients with unilateral aldosterone-producing adenoma (APA) or a medical treatment based on mineralocorticoid receptor antagonists (MRAs), spironolactone (SPL), or eplerenone (EPL) for patients with bilateral PA (1). The goal of treatment for PA is preventing cardiovascular and renal damage by resolving hyperaldosteronism through adrenalectomy for unilateral cases or through MRA treatment for bilateral cases and those who do not want surgery. With MRA treatment, however, insufficient suppression of aldosterone action may result in cardiovascular and renal damage even when the blood pressure and serum potassium are well controlled.

Glomerular hyperfiltration is a major cause of renal damage in various renal diseases. A series of clinical studies have suggested the possibility of reversible glomerular hyperfiltration due to renal hemodynamic alteration by hyperaldosteronism (5, 6), wherein the glomerular filtration rate (GFR) rapidly decreases after the removal of aldosterone excess by adrenalectomy (5, 7-9). A similar rapid reversal of glomerular hyperfiltration has also been shown in PA with high-dose MRA treatment using SPL (100-300 mg) (7, 9, 10). SPL has been widely used as an MRA treatment for PA for a long period of time. However, high-dose SPL has many sex hormone-related side effects, such as gynecomastia, often making it difficult for patients to receive the necessary doses of SPL. EPL, another MRA, is a highly selective MRA with few sex hormone-related side effects (1, 11). However, clinical data for EPL in the treatment of PA are limited, and few studies-with only small patient populations-have examined the effects of EPL on glomerular hyperfiltration in patients with PA (12, 13). Furthermore, whether or not EPL can sufficiently block the aldosterone action in PA remains unclear, since the approved dosage of EPL is limited to 100 mg/day in Japan, which is approximately equivalent to 50 mg SPL (14).

In the present study, we examined whether or not EPL treatment can reverse glomerular hyperfiltration, as an indicator of aldosterone renal action, in 102 patients with PA. Furthermore, we analyzed the sequential changes in the GFR in 40 patients initially treated with EPL followed by adrenalectomy, which can fully restore hyperaldosteronism, in order to evaluate the extent of the remaining glomerular hyperfiltration in the patients treated with EPL.

Materials and Methods

Patients

The study group comprised patients who had been diagnosed with PA at Tokyo Medical and Dental University Hospital between April 2007 and March 2014. PA was diagnosed based on at least 1 out of 3 abnormal results on the following confirmatory tests: 1) the aldosterone renin ratio (ARR) exceeded 200 after administration of captopril (50 mg), 2) the plasma renin activity (PRA) was less than 2.0 ng/mL/h after intravenous administration of furosemide (40 mg) with upright posture, and 3) the plasma aldosterone concentration (PAC) exceeded 60 pg/mL after intravenous infusion of 2,000 mL saline, as recommended by the Japanese Society of Hypertension and the Japan Endocrine Society (15, 16).

A total of 179 patients were diagnosed with PA. Of these patients, those treated with any antihypertensive agents other than EPL with or without calcium channel blockers (CCBs) after the confirmation of lateralization (n=39) were excluded. The remaining 140 patients were treated with EPL with or without CCBs (confined to slow-release nifedipine or amlodipine). Of these 140 patients, those with diabetes diagnosed according to the criteria of the Japan Diabetes Society (17) (n=11), those with an estimated GFR (eGFR) of less than 30 mL/min/1.73 m^2 (n=1), those whose data were not available (n=21), and those lost to follow-up (n=5) were excluded from the study (Fig. 1). The remaining 102 patients were included in the study population for EPL treatment. On a diagnosis of PA, antihypertensive agents were limited to a CCB and an alpha-receptor antagonist, according to the clinical practice guidelines of The Endocrine Society (1), until lateralization of aldosterone hypersecretion by adrenal vein sampling (AVS) was confirmed. In AVS, blood samples were collected 15 minutes after bolus intravenous injection of tetracosactide acetate (250 μg). Assessment of successful catheterization and lateralization for AVS was conducted according to the Japanese Society of Endocrinology Guidelines for the Management of PA (16).

The patients with PA were treated with EPL after the confirmation of lateralization by AVS. EPL with a CCB was administered to these patients depending on the drug availability and the condition of the patient, including their blood pressure, serum potassium level, and/or renal function. Alpha-receptor antagonist treatment was discontinued after the initiation of EPL treatment. Among the 102 patients, 51 underwent adrenalectomy a few months after EPL treatment (Fig. 1). Of these 51 patients, the 40 with available data were analyzed for sequential changes in the GFR during treatment (Fig. 1).

This retrospective study was approved by the Ethics Committee of Tokyo Medical and Dental University Hospital (No. 2198).

Data collection

Extensive clinical data were extracted from patients' charts, including the age, sex, duration of hypertension, body mass index (BMI), blood pressure at first visit, laboratory test results, and medication. PAC and PRA were measured in the morning after a 30-minute rest, in a sitting position, by radioimmunoassay. Serum creatinine (Cre), serum potassium, and urinary albumin excretion (UAE) tests were performed in the morning. Urinary aldosterone excretion and urinary potassium excretion were measured when the pa-

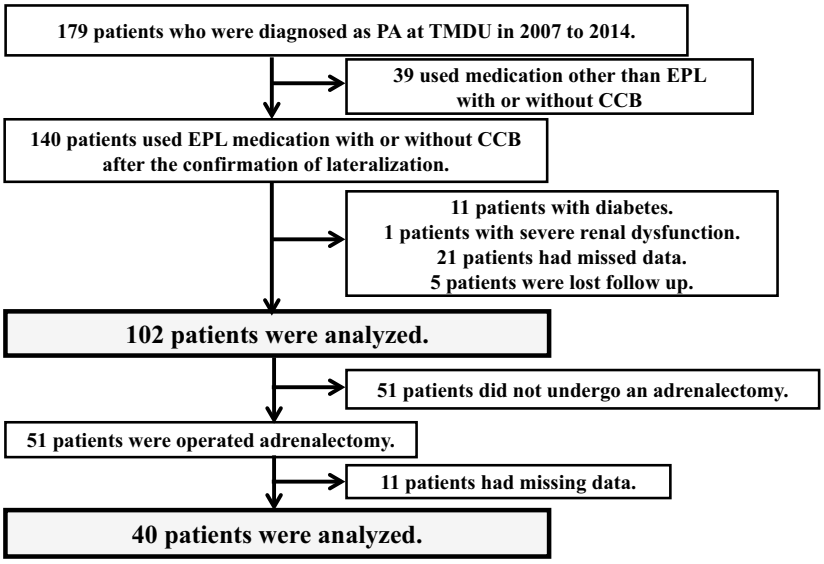

Figure 1. **Patient recruitment criteria. In our hospital, 179 patients were diagnosed with PA in 2007 to 2014. Due to either a lack of EPL treatment, missing data, and/or withdrawal from follow-up, 77 patients were not able to be included in the study. For the first analysis, 102 patients were studied. Of these 102 patients, 62 did not undergo adrenalectomy or had missing data. Therefore, the 40 remaining patients were studied for the second analysis. PA: primary aldosteronism, TMDU: Tokyo Medical and Dental University Hospital, EPL: eplerenone**

tients were hospitalized after PA confirmation and/or the subgrouping of PA. Cre was collected both before and after the initiation of EPL treatment or adrenalectomy. Blood pressure, serum potassium, and brain natriuretic peptide (BNP) were measured after a one-month interval and in the follow-up period post-EPL administration.

The evaluation of the renal function

We calculated the eGFR as a marker of the renal function. The formula used to calculate the eGFR was the Japanese equation for the GFR estimation, established by the Japanese Society of Nephrology: eGFR (mL/min/1.73 m^2) = 194× $Cre^{-1.094}$ × $age^{-0.287}$(×0.739 if the patient was a woman) (18). We calculated the defined ΔGFR as the difference of the eGFR before and after the initiation of EPL or adrenalectomy.

Statistics analyses

The data are presented as the mean ± standard deviation or geometric mean (95% confidence interval), and the doses of medication data (CCB, doxazosin and EPL) are presented as the mean (range). Only PRA is presented as the median (quartile). The duration of hypertension, the GFR, PAC, ARR, urinary aldosterone excretion, and UAE were log-transformed for the statistical analysis due to their skewed distribution. A one-way analysis of variance (ANOVA) followed by Gabriel's post hoc test was used for the comparison among three groups, except for PRA, the dose of CCB, and the dose of EPL, which were analyzed by a Kruskal-Wallis test. Univariate correlations were evaluated as Pearson's correlation coefficient, except for PRA, which was evaluated as Spearman's rank correlation coefficient. In this multivariate regression analysis with a stepwise procedure, the following covariates were incorporated into the analysis: GFR at baseline, BMI, changes in the blood pressure after EPL treatment, and PAC.

A p value <0.05 was considered to indicate statistical significance. All statistical analyses were performed using the SPSS version 21.0 statistical package (IBM SPSS Statistics for Windows, Version 21.0; IBM, Armonk, USA)

Results

Treatment with EPL decreased GFR at 1 month in PA

The baseline characteristics of PA (n=102) are shown in Table 1. The GFR baseline was 76.6 (73.3-79.8) mL/min/1.73 m^2, and PAC was 319 (259-378) pg/mL. All patients started administration of EPL at 83.7 (25-100) mg/day with a CCB [slow-release nifedipine 39 (20-80) mg, n=45 or amlodipine 6.7 (2.5-10) mg, n=33] after confirmation of the laterality of aldosterone hypersecretion by AVS. A total of 62% of patients were diagnosed with unilateral APA, based on the AVS results.

A statistically significant (p<0.001) decrease in the GFR was observed at 1 month after EPL administration. However, the GFR subsequently remained stable at the three-month follow-up evaluation.

Table 1. Baseline Characteristics of PA before EPL Treatment.

Variables	All patients (n=102)
Age at diagnosis (years)	53±10
Sex (male/female)	51/51
Duration of HT (years)	11 (9-13)
BMI (kg/m^2)	24.3±4.2
Systolic BP (mmHg)	137±17
Diastolic BP (mmHg)	84±10
Cre (mg/dL)	0.76±0.19
GFR (mL/min/1.73m^2)	76.6 (73.3-79.8)
PRA (ng/mL/h)	0.3 (0.1-0.4)
PAC (pg/mL)	319 (259-378)
u-Aldo (μg/day) n=78	19.6 (15.3-24.0)
ARR	1,940 (1,380-2,500)
Potassium (mEq/L) n=60	3.81±0.49
u-potassium (mEq/day)	48.2 (43.7-52.8)
UAE (mg/gCre) n=76	46.6 (23.7-69.4)
BNP (pg/mL) n=87	22.9±14.3
AVS Result (uni/bi) n=82	51/31

Data are expresses as mean±SD, geometric mean (95% confidence interval) or percentage. Only PRA are expressed as median (quartile).

PA: primary aldosteronism, EPL: eplerenone, HT: hypertension, BMI: body mass index, BP: blood pressure, Cre: creatinine, GFR: estimated glomerular filtration rate, PRA: plasma renin activity, PAC: plasma aldosterone concentration, u-Aldo: urinary aldosterone excretion, ARR: aldosterone renin ratio, u-potassium: urinary potassium excretion, UAE: urinary albumin excretion, BNP: brain natriuretic peptide, AVS: adrenal vein sampling, uni: unilateral, bi: bilateral

Table 2. Univariate Correlation between ΔGFR and Parameters of the Study Population.

Variables	R	p value
Age at Diagnosis (years)	-0.068	0.496
Sex (%male)	0.024	0.810
Log Duration of HT (years)	-0.120	0.231
BMI (kg/m^2)	0.036	0.723
Systolic BP (mmHg)	-0.034	0.735
Diastolic BP (mmHg)	-0.100	0.322
Cre (mg/dL)	0.299	0.002
Log GFR (mL/min/1.73m^2)	-0.453	<0.001
PRA (ng/mL/h)	0.036	0.718
Log PAC (pg/mL)	0.070	0.485
Log u-Aldo (μg/day) n=86	0.142	0.215
Log ARR	0.029	0.776
Potassium (mEq/L) n=67	0.130	0.322
Log UAE (mg/gCre)	-0.079	0.497
BNP (pg/mL) n=87	-0.204	0.058
AVS Result (%Unilateral)	0.017	0.879
Δsystolic BP (mmHg)	0.026	0.799
Δdiastolic BP (mmHg)	0.137	0.182
ΔBNP (pg/mL) n=34	0.546	0.001

ΔGFR, Δsystolic BP, Δdiastolic BP and ΔBNP was defined as changes in GFR systolic BP, diastolic BP and BNP at 1 month after eplerenone treatment.

Univariate correlations were evaluated as Pearson's correlation coefficient, except PRA that was evaluated as Spearman's rank correlation coefficient.

HT: hypertension, BMI: body mass index, BP: blood pressure, Cre: creatinine, GFR: estimated glomerular filtration rate, PRA: plasma renin activity, PAC: plasma aldosterone concentration, u-aldo: urinary aldosterone excretion, ARR: aldosterone renin ratio, UAE: urinary albumin excretion, BNP: brain natriuretic peptide

Table 3. Multivariate Analysis of Candidate Predictors of ΔGFR.

Variables	Standardized β	p value
GFR at baseline	-0.450	<0.001

ΔGFR was defined as changes in GFR at 1 month after eplerenone treatment. Stepwise regression analysis followed multi regression analysis was performed. GFR at baseline, body mass index, changes in the systolic blood pressure after eplerenone treatment and plasma aldosterone concentration were assessed. Other variables were not significant. Adjusted R^2: 0.194

GFR: estimated glomerular filtration rate

Predictors of changes in the GFR (ΔGFR) after EPL treatment

We then analyzed the data further to identify the clinical parameters influencing ΔGFR during the month after EPL treatment among the 102 patients. Cre and the GFR at baseline were shown to be significantly (p<0.001) correlated with the ΔGFR in a univariate analysis (Table 2). A multivariate stepwise regression analysis revealed that the GFR at baseline was the sole significant predictor for the decrement in the GFR after EPL treatment (Table 3). Changes in the systolic or diastolic blood pressure during EPL treatment did not correlate with the ΔGFR.

In our 102 patients, changes in BNP during EPL treatment were assessed in 34 patients. The changes in the BNP level were significantly (p=0.001) correlated with the ΔGFR.

The decremental patterns of GFR after EPL treatment and subsequent adrenalectomy

In our cohort of patients with PA, 40 patients were initially treated by EPL followed by adrenalectomy (Fig. 1). We then analyzed the sequential changes in the GFR during treatment. Since several previous studies and the present study have clearly shown that decremental changes in the GFR occur within 1 month following adrenalectomy or the initiation of MRA treatment, we examined the ΔGFR at 1 month after EPL treatment as well as the ΔGFR at 1 month after subsequent adrenalectomy in these 40 patients.

As shown in Fig. 2a, these 40 patients were categorized into the following three groups based on the patterns of ΔGFR during treatment: Groups A, B, and C. Group A in-

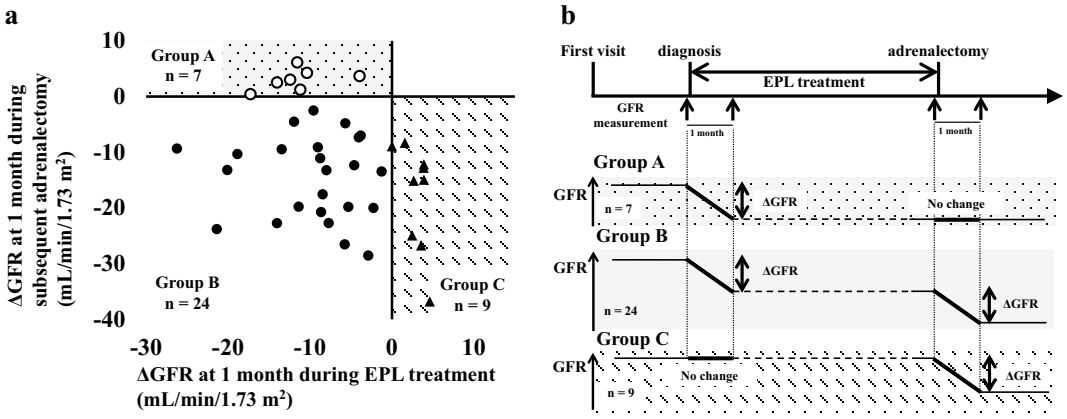

Figure 2. **The changes in the GFR (ΔGFR) during EPL treatment (x-axis) and after subsequent adrenalectomy (y-axis) in PA. (a) The 40 patients initially treated by EPL followed by adrenalectomy were categorized into 3 groups by the decremental pattern of GFR: Groups A, B and C. Group A: GFR decreased after EPL administration but did not change after following adrenalectomy. Group B: GFR decreased after EPL administration and further decreased after subsequent adrenalectomy. Group C: GFR did not change after EPL administration but decreased after subsequent adrenalectomy. (b) Graphic abstract of the sequential changes in the GFR among the three groups. GFR: estimated glomerular filtration rate, EPL: eplerenone, PA: primary aldosteronism**

cluded the patients in whom the GFR decreased after EPL administration but did not change following adrenalectomy. Group B included the patients in whom the GFR decreased after EPL administration and further decreased after subsequent adrenalectomy. Group C included the patients in whom the GFR remained unchanged after EPL administration but decreased after subsequent adrenalectomy (Fig. 2). Of note, the doses of EPL and CCB, and the changes in blood pressure were not significantly different among the three groups, and EPL treatment was able to achieve control of the blood pressure and hypokalemia in all patients in all three groups (Table 4). A comparison of the clinical parameters showed that the urinary aldosterone excretion before EPL treatment was significantly different among the three groups and that marked urinary aldosterone excretion before EPL treatment was observed in Group C compared with Groups A and B (Table 4).

Discussion

We examined whether or not treatment with EPL can reverse glomerular hyperfiltration, as an indicator of aldosterone renal action. In addition, we analyzed the sequential changes in the GFR in 40 patients initially treated with EPL followed by adrenalectomy, which can fully resolve hyperaldosteronism, in order to evaluate the extent of the remaining glomerular hyperfiltration in the patients treated with EPL.

Our study clearly indicated that our EPL treatment (mean 83.7 mg/day range: 25-100 mg/day) significantly decreased the GFR at 1 month after the treatment. A multivariate analysis revealed that the GFR at baseline was the sole significant predictor of the ΔGFR (Table 3). In cases of unilateral PA initially treated by EPL followed by adrenalectomy, the patients were able to be clearly categorized into three subgroups depending on the ΔGFR pattern during treatment (Fig. 2).

Few studies have reported the effects of EPL on the renal function in PA (12, 13). Fourkiotis et al. reported in their cross-sectional cohort study that the GFR in patients with PA was comparable between the adrenalectomized group and the EPL treatment group approximately five years after the initial diagnosis (12). Another study on the effect of MRA treatment on the GFR was largely based on patients treated with SPL, and an individual analysis of patients treated with EPL was not described, as the numbers included in the EPL group were relatively small (13). The present study clearly indicated that a modest but significant decline in the GFR was observable within 1 month after EPL treatment, suggesting that blockade of the aldosterone action by EPL could, at least partially, reverse glomerular hyperfiltration in PA. The MR-antagonizing activity elicited by our EPL treatment (mean 83.7 mg/day) was assumed to be virtually equivalent to the previous study using low-dose SPL treatment (50 mg/day) (1, 18), which was found to be less effective than surgery for achieving the reversal of glomerular hyperfiltration (19). Other studies, with SPL uptitrated as needed (100-300 mg/day), have documented a comparable effect on the GFR between patients receiving surgical treatment and those receiving SPL treatment (7, 9, 10) Therefore, the effect of our EPL treatment on the GFR appeared to be modest compared with adrenalectomy, which resulted in the complete resolution of hyperaldosteronism. Our results also showed that the ΔBNP was positively correlated with the ΔGFR during EPL treatment. Gaddam et al. reported that elevated plasma aldosterone levels induced cardiovascular volume overload in patients with resistant hypertension, and MRA treatment reduced the plasma BNP levels, as an indicator of cardiovascular volume overload (20). Our

Table 4. Comparison of Various Parameters between the Groups Based on the Decline GFR Patterns after EPL Treatment and Subsequent Adrenalectomy.

Variables	Group A (n=7)	Group B (n=24)	Group C (n=9)	p value[a)]
Before EPL treatment				
Age at diagnosis (years)	57±8	47±10	52±13	0.123
Sex (male/female)	4/3	13/11	5/4	0.861
Duration of HT (years)	11 (0-24)	9 (5-12)	9 (1-16)	0.869
BMI (kg/m^2)	22.1±2.9	23.1±3.9	22.0±3.0	0.682
Systolic BP (mmHg)	124±12	138±15	134±12	0.132
Diastolic BP (mmHg)	80±8	84±12	88±11	0.391
Cre (mg/dL)	0.72±0.15	0.72±0.15	0.84±0.24	0.228
GFR (mL/min/1.73m^2)	75.7 (68.0-83.5)	84.0 (76.6-91.5)	72.1 (56.9-87.2)	0.121
PRA (ng/mL/h)	0.3 (0.1-0.5)	0.3 (0.1-0.4)	0.2 (0.1-0.4)	0.728
PAC (pg/mL)	297 (143-452)	454 (320-588)	723 (258-1,188)	0.096
u-Aldo (μg/day)	9.5 (1.2-17.8)	23.3 (14.2-32.4)	38.0 (18.6-57.4)	0.014[b)]
ARR	1,450 (870-2,810)	2,400 (1,360-3,450)	5,580 (2,880-10,870)	0.117
Potassium (mEq/L)	3.60±0.26	3.66±0.66	3.15±0.21	0.547
u-potassium (mEq/day)	42 (22 -62)	56 (43-69)	57 (36-78)	0.423
UAE (mg/gCre)	24.0 (0.0-51.4)	61.3 (4.2-118.3)	75.1 (0.0-213.4)	0.442
Medication				
Nifedipine (mg)	46 (40-80) n=6	47 (20-80) n=14	44 (20-80) n=5	0.937
Amlodipine (mg)	5.0 (n=1)	7.1 (2.5-10) n=8	7.5 (5.0-10) n=4	0.743
Doxazosin (mg)	2 (n=1)	3 (2-8) n=6	None	n.e.
After EPL treatment				
Systolic BP (mmHg)	127±11	127±9	127±3	0.990
Diastolic BP (mmHg)	80±6	80±7	72±3	0.368
Potassium (mEq/L)	4.40±0.11	3.89±0.58	4.10±0.70	0.286
Medication				
Nifedipine (mg)	40 (40-40) n=3	41 (20-80) n=14	28 (20-40) n=5	0.248
Amlodipine (mg)	5.0 (n=1)	6.6 (2.5-10) n=9	6.2 (5-10) n=4	0.918
EPL (mg)	85.7 (50-100)	80.7 (25-100)	77.7 (50-100)	0.830

Data are expresses as mean±SD, geometric mean (95% confidence interval), medication (nifedipine, amlodipine, doxazosin and EPL) are expressed as mean (range), only PRA is expressed as median (quartile).

a) One way ANOVA. PRA, nifedipine, amlodipine and EPL were analyzed by Kruskal-Wallis test.

b) A vs. C (p=0.012), and B vs. C (p=0.039) in post hoc analysis by Gabriel's test.

GFR: estimated glomerular filtration rate, EPL: eplerenone, HT: hypertension, BMI: body mass index, BP: blood pressure, Cre: creatinine, PRA: plasma renin activity, PAC: plasma aldosterone concentration, u-Aldo: urinary aldosterone excretion, ARR: aldosterone renin ratio, u-potassium: urinary potassium excretion, UAE: urinary albumin excretion, n.e.: not examined

data suggest that EPL treatment for PA patients reduces the cardiovascular volume overload, similarly to Gaddam's study (20).

The present study further indicated that the GFR at baseline was a significant predictor of a decreasing GFR after EPL treatment (Table 3). This finding is in agreement with previous studies showing that a greater baseline GFR was associated with a more marked fall in the postoperative GFR (7, 21, 22), supporting the notion that the post-treatment GFR decline in patients with PA, either by adrenalectomy or MRA treatment, results from the cancellation of glomerular hyperfiltration caused by hyperaldosteronim. Although several previous studies have shown that serum potassium levels, PRA, PAC, and/or ARR were also predictors of a decreasing GFR after adrenalectomy (12, 13, 21, 22), these factors were not indicated to be significant predictors in the present study. This discrepancy may be due to the difference in treatment conditions from previous studies based on the complete reversal of the aldosterone action by adrenalectomy or by sufficient doses of MRA. In the present study, the effects of these factors on GFR may have been blurred under EPL treatment, which is not sufficient to fully resolve hyperaldosteronism.

To evaluate the extent of the remaining glomerular hyperfiltration in the patients treated with EPL, we analyzed the sequential changes in the GFR in 40 patients initially treated with EPL followed by adrenalectomy, which can fully restore hyperaldosteronism. No study has yet documented the sequential changes in the GFR during preoperative MRA treatment through to the subsequent adrenalectomy. The present study showed that our 40 patients with unilateral APA could be clearly categorized into three groups (A, B, and C) based on the sequential changes in the GFR during preoperative EPL treatment through to subsequent adrenalectomy,

despite the doses of EPL and CCBs used being comparable among the three groups (Fig. 2b, Table 4). Differences among these three groups may be due to the modest antagonizing effect of our EPL treatment on hyperaldosteronism. For example, in Group A, our initial EPL treatment alone may have completely reversed the glomerular hyperfiltration; therefore, no additional effect was seen after adrenalectomy. In Group B, our EPL treatment may have partially reversed and subsequent adrenalectomy completely reversed the glomerular hyperfiltration. In Group C, our initial EPL treatment may have been ineffective, leaving the subsequent adrenalectomy solely responsible for reversing the glomerular hyperfiltration. These hypotheses are also supported by our findings that the urinary aldosterone excretion was significantly different among the three groups, and marked urinary aldosterone excretion was observed in Group C compared with those in Groups A and B (Table 4). Of note, the glomerular hyperfiltration was completely restored only in group A (17.5%). This finding suggests that, at the current approved upper dose of EPL, the inhibition of renal effects of aldosterone remains inadequate in at least 82.5% of operable PA cases. A series of long-term observational studies has shown that surgical and medical treatment are equally beneficial for cardiovascular and renal protection in patients with PA; however, this is based on a comparison between patients with unilateral APA treated with adrenalectomy and those with bilateral idiopathic hyperaldosteronism treated with spironolactone, which was uptitrated as needed and tolerated (7, 23, 24). No studies have reported the effects of EPL treatment on cardiovascular and renal outcomes in patients with PA. Taken together, our present findings suggest that detailed studies with careful observation are needed to determine whether or not Japanese PA patients treated with EPL truly have the same cardiovascular prognosis as those who undergo surgery.

Of note, EPL treatment with combination of CCBs was able to restore control of blood pressure and hypokalemia to comparable levels among the three groups, despite the groups' different responses with regard to the GFR during preoperative MRA treatment through to subsequent adrenalectomy. These findings suggest that, under EPL treatment, some APA cases show dissociation between the therapeutic effect on blood pressure and serum potassium control and the inhibitory effect on aldosterone-induced glomerular hyperfiltration by EPL treatment. Long-term prospective observational studies will be required to establish whether or not this dissociation affects the long-term renal and cardiovascular outcomes, especially in patients with unilateral APA who opt for medical treatment.

Several limitations associated with the present study warrant mention. First, the retrospective nature of the study and relatively small number of patients may have masked the significance of the data. A prospective research design including control patients, such as those with essential hypertension, would be preferable for future studies. Second, we used the Cre-based GFR rather than the cystatin C-based GFR; Cre may be influenced by muscle volume or the amount of meat consumed. In addition, the renal function might have been underestimated in the present study because of the formula used to evaluate the GFR. The formula that we applied was based on the data from chronic kidney disease (CKD) patients in Japan (17), which may not be suitable for application in the patients in our study, who showed a nearly normal renal function (mean GFR 76.5 mL/min/1.73 m^2). Third, in assessing renal injury, we did not measure the UAE at the outpatient clinic after discharge and did not check for structural injuries of the kidneys. Fourth, the doses of EPL and CCBs were not standardized in the present study. Finally, the follow-up period was relatively short for the most studied patients, precluding any determinations arising from longer-term outcomes.

In conclusion, the present study showed that the blockade of aldosterone action by EPL could, at least modestly, reverse glomerular hyperfiltration in PA. Furthermore, the present study showed for the first time that our EPL treatment during the preoperative MRA treatment through to subsequent adrenalectomy results in three different patterns of sequential changes in the GFR among patients with unilateral APA, despite the doses of EPL and CCBs used and the control of blood pressure and serum potassium being comparable among the patients. Whether or not these differential effects on the GFR by EPL treatment affect the long-term renal or cardiovascular outcomes remains to be elucidated, especially in patients with unilateral APA who opt for medical treatment. The present study therefore indicates the need for long-term prospective studies on the effects of EPL treatment on the cardiovascular and renal outcomes in patients with PA.

The authors state that they have no Conflict of Interest (COI).

Financial Support

This research was supported by AMED under Grant Number * JP17ek0109122*, conducted as a part of the Japan Primary Aldosteronism Study (JPAS), and partly supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan (T.Y., 16K08962 and M.M, 16K 19392).

Acknowledgement

The authors thank all other staff members of the Molecular Endocrinology and Metabolism Department, Tokyo Medical and Dental University.

References

1. Funder JW, Carey RM, Mantero F, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab **101**: 1889-1916, 2016.

2. Rossi GP, Bernini G, Caliumi C, et al. A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. J Am Coll Cardiol **48**: 2293-2300, 2006.

3. Milliez P, Girerd X, Plouin PF, et al. Evidence for an increased

rate of cardiovascular events in patients with primary aldosteronism. J Am Coll Cardiol **45**: 1243-1248, 2005.
4. Rossi GP, Bernini G, Desideri G, et al. Renal damage in primary aldosteronism: results of PAPY Study. Hypertension **48**: 232-238, 2006.
5. Ribstein J, Cailar GD, Fesler P, Mimran A. Relative glomerular hyperfiltration in primary aldosteronism. Clin J Am Soc Nephrol **16**: 1320-1325, 2005.
6. Sechi LA, Fabio AD, Bazzocchi M, et al. Intrarenal hemodynamics in primary aldosteronism before and after treatment. J Clin Endocrinol Metab **94**: 1191-1197, 2009.
7. Sechi LA, Novello M, Lapenna R, et al. Long-term renal outcomes in patients with primary aldosteronism. JAMA **295**: 2638-2645, 2006.
8. Rossi GP, Sechi LA, Giacchetti G, et al. Primary aldosteronism: cardiovascular, renal and metabolic implications. Trends Endocrinol Metab **19**: 88-90, 2008.
9. Catena C, Colussi G, Nadalini E, et al. Relationships of plasma renin levels with renal function in patients with primary aldosteronism. Clin J Am Soc Nephrol **2**: 722-731, 2007.
10. Reincke M, Rump LC, Quinkler M, et al. Risk factors associated with a low glomerular filtration rate in primary aldosteronism. J Clin Endocrinol Metab **94**: 869-875, 2009.
11. Amar L, Lorthioir A, Azizi M, Plouin PF. Progress in primary aldosteronism. Mineralocorticoid antagonist treatment for aldosterone-producing adenoma. Eur J Endocrinol **172**: R125-R129, 2015.
12. Fourkiotis V, Vonend O, Diederich S, et al. Effectiveness of eplerenone or spironolactone treatment in preserving renal function in primary aldosteronism. Eur J Endocrinol **168**: 75-81, 2012.
13. Iwakura Y, Morimoto R, Kudo M, et al. Predictors of decreasing glomerular filtration rate and prevalence of chronic kidney disease after treatment of primary aldosteronism: renal outcome of 213 cases. J Clin Endocrinol Metab **99**: 1593-1598, 2014.
14. Garthwaite SM, McMahon EG. The evolution of aldosterone antagonists. Mol Cell Endocrinol **217**: 27-31, 2004.
15. Ogihara T, Kikuchi K, Matsuoka H, et al. The Japanese Society of Hypertension guidelines for the management of hypertension (JSH 2009). Hypertens Res **32**: 3-107, 2009.
16. Nishikawa T, Omura M, Satoh F, et al. Guidelines for the diagnosis and treatment of primary aldosteronism -The Japan Endocrine Society 2009- advance publication. Endocr J **58**: 711-721, 2011.
17. Seino Y, Nakajo K, Tajima N, et al. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. Diabetol Int **1**: 2-20, 2010.
18. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis **53**: 982-992, 2009.
19. Wu VC, Kuo CC, Wang SM, et al. Primary aldosteronism: changes in cystatin C-based kidney filtration, proteinuria, and renal duplex indices with treatment. J Hypertens **29**: 1778-1786, 2011.
20. Gaddam K, Corros C, Pimenta E, et al. Rapid reversal of left ventricular hypertrophy and intracardiac volume overload in patients with resistant hypertension and hyperaldosteronism - a prospective clinical study. Hypertens **55**: 1137-1142, 2010.
21. Utsumi T, Kawamura K, Imamoto T, et al. Preoperative masked renal damage in Japanese patients with primary aldosteronism: Identification of predictors for chronic kidney disease manifested after adrenalectomy. Int J Urol **20**: 685-691, 2013.
22. Tanase-Nakao K, Naruse M, Nanba K, et al. Chronic kidney disease score for predicting postoperative masked renal insufficiency in patients with primary aldosteronism. Clin Endocrinol **81**: 665-670, 2014.
23. Catena C, Colussi GL, Nadalini E, et al. Cardiovascular outcomes in patients with primary aldosteronism after treatment. Arch Intern Med **168**: 80-85, 2008.
24. Catena C, Colussi GL, Lapenna R, et al. Long-term cardiac effects of adrenalectomy or mineralocorticoid antagonists in patients with primary aldosteronism. Hypertension **50**: 911-918, 2007.