Change of Glomerular Hemodynamics in Patients with Advanced Chronic Kidney Disease after Cilnidipine Therapy

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Abstract: Cilnidipine, a dual calcium channel antagonist, is assumed to regulate hypertension *via* N- and L-type calcium channel. The N-type calcium channel is associated with sympathetic nerve activation. This effect may improve the glomerular hemodynamics in the injured nephron, and may mitigate the progression of renal injury. To clarify the effect of cilnidipine in instances of already existing decreased renal blood flow, we examined the alteration of renal hemodynamics before and after cilnidipine therapy in patients with advanced chronic kidney disease (CKD). Cilnidipine was administrated daily to 17 CKD patients with hypertension for 12 months. Another 16 patients were similarly administered amlodipine during this study, a long-acting L-type calcium channel antagonist has also been shown to be renoprotective. Glomerular filtration rate (GFR), effective renal plasma flow (ERPF), and protein excretion in 24-hour accumulated urine were measured at the start and end of the study. The parameters of renal hemodynamics were calculated by Gomez's estimation equation. Systolic blood pressure decreased to 80 % of the level at the beginning of the study, and ERPF increased to 127 % of the level at baseline. Glomerular capillary pressure on single nephron was reduced to 90 %, although total GFR decreased within the non-statistical change. Especially, renal vascular resistance ratio (RA/RE) on single nephron improved to 120 %. Cilnidipine improves ERPF and glomerular hypertension without worsening total renal function. N- and L-type calcium channel antagonist is effective and safe for patients with advanced CKD as a result of improvement of glomerular capillary resistance.

Keywords: N- and L-type calcium channel antagonist, glomerular hemodynamics, renal vascular resistance, glomerular capillary pressure, chronic kidney disease.

INTRODUCTION

Renal blood flow and glomerular filtration rate (GFR) decrease along with the progression of renal dysfunction in patients with chronic kidney disease (CKD) [1,2]. Continuous glomerular injury causes a decrease in normal nephron count in the bilateral kidney, and compensative increase of GFR in the residual individual nephron [3]. This phenomenon, called hyperfiltration, is one factor contributing to the progress of glomerular sclerosis. Hypertension, a complication in most CKD patients, also accelerates the progression rate of glomerular sclerosis [4]. Angiotensin converting enzyme inhibitor and angiotensin II receptor 1 blocker are known as renoprotective, anti-hypertensive drugs [5,6]. However, its single use is not enough for the renoprotective level of blood pressure in the most cases. Ca channel antagonists, especially dihydropyridine derivatives, are commonly used for the treatment of hypertension due to their property to maintain organ blood circulation [7,8]. However, the increase of renal blood flow brings hyperfiltration, and this ultimately accelerates glomerular sclerosis [9]. Recently, the long-acting dihydropyridine-type Ca channel antagonist is reported to play a role in the prevention of renal injury in addition to decreasing blood pressure [10]. Ca channels are classified as L-type, N-type, T-type, and P/Q-type by structure and distribution [11]. These subtypes are known to present in the kidney and serve to modulate the renal vascular tone. L-type Ca channel is substantially distributed within the vascular bed. It is established that the inhibition of L-type Ca channel cause predominant dilatation of the afferent arteriole. T-type channel is reported to mediate the aldosterone secretion [12]. P/Q-type channel contributes the KCl-induced constriction of the afferent arteriole [13]. Stimulation of the sympathetic nerve *via* the N-type Ca channels causes norepinephrine excretion and increased heart rate, and contraction of the heart and vascular smooth muscle [14]. Thus, N-type Ca channel antagonists may regulate the excitation of the renal sympathetic nerve, decrease renal vascular resistance [15]. Moreover, L- and N-type Ca channel antagonists are expected to play a role in the improvement of renal hemodynamics in patients with already advanced CKD. To clarify this hypothesis, we administrated cilnidipine, an L- and N-type Ca channel antagonist, to advanced CKD patients with hypertension, and examined the effect to hemodynamics.

PATIENTS AND METHODS

Subjects

Subjects included in the study were non-diabetic patients with chronic renal failure visiting to our hospital. All patients were clinically diagnosed as chronic renal failure due to chronic glomerulonephritis. Informed consent of 33 patients was obtained for participation in the study. 17 were assigned to the cilnidipine group, and the other 16 were assigned to the amlodipine group, mutually. Cilnidipine and amlodipine were continuously administered for 12 months during the

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Table 1. Background of Advanced CKD Patients with Cilnidipine or Amlodipine Therapy

		Cilnidipine Group	Amlodipine Group
n		**17**	**16**
Age	(yo)	66 ± 6	60 ± 17
Sex	(M/F)	9 / 8	7 / 9
Heart rate (HR)	(/min)	85 ± 14	86 ± 12
Systolic blood pressure (SBP)	(mmHg)	165 ± 12	155 ± 7
Diastolic blood pressure (DBP)	(mmHg)	93 ± 10	88 ± 9
Total protein (TP)	(g/dL)	7.1 ± 0.8	6.9 ± 0.9
Hemoglobin (Hb)	(g/dL)	11.6 ± 1.5	10.6 ± 1.9
24-hour urinary protein (24UP)	(g/day)	1.7 ± 2.5	1.5 ± 2.2
24-hour creatinine clearance (GFR)	(mL/min)	27 ± 11	31 ± 17
24-hour urine volume (24UV)	(L/day)	1.8 ± 0.4	1.8 ± 0.6
Effective renal plasma flow (ERPF)	(mL/min)	105 ± 35	140 ± 54

Values express mean ± SD, There are no significant differences in each parameters.

study. The background of cilnidipine group and amlodipine group were as following, respectively: mean age 66 ± 6 years and 60 ± 17 years; sex (male / female) 9:8 and 7:9; systolic blood pressure (SBP) express 165 ± 12 mmHg and 155 ± 7 mmHg, respectively; diastolic blood pressure (DBP) express 93 ± 10 mmHg and 88 ± 9 mmHg, respectively; heart rate (HR) express 85 ± 14 /min and 86 ± 12 /min, respectively; glomerular filtration rate (GFR) express 27 ± 11 mL /min and 31 ± 17 mL /min, respectively; 24-hour accumulated urine protein excretion (24UP) express 1.7 ± 2.5 g /day and 1.5 ± 2.2 g /day, respectively. There were no significant differences between either group (Table **1**).

Study Protocol

Patients were confirmed on several occasions as having systolic blood pressure above 150 mmHg, or diastolic blood pressure remaining over 90 mmHg, and then given a 12-month treatment regimen of 10mg/day of cilnidipine or 5mg/day of amlodipine mutually according to the entry. Blood pressure was measured three times on every hospital visit by the digital oscillometric blood pressure monitor (Omuron HEM-907, Mie), and expressed as M ± SD. GFR was estimated by 24-hour creatinine clearance (24CCr), and effective renal plasma flow (ERPF) was calculated by Tc-99m-mercaptoacetyltriglycine (MAG3) scintigram [16] at the start and end of the study. 24UP and 24-hour accumulated urine volume (24UV) were measured simultaneously. Parameters of renal hemodynamics were calculated by Gomez's estimation equation [17]. We assumed here that KF stayed within normal and stable ranges. There were few errors in KF due to comparison between the same patients or between subjects with similarly decreased renal function within a short period. Student's t-test was used for statistical analysis between pre- and post-treatment or between two therapy groups. The study was approved by the institutional ethical committee. Authors drew attention to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964).

Estimation of Glomerular Hemodynamics

Parameters of renal hemodynamics were calculated by Gomez's estimation equation as the following:

$$FF = GFR / ERPF$$

$$CM = (TP/FF) \times \log_e \{1/(1-FF)\}$$

$$\Pi GC = 5 \times (CM - 2)$$

$$PGC = \Pi GC + PT + \Delta PF$$

$$\Delta PF = GFR / KF$$

$$RBF = RPF \times \{1/(1-Hct)\}$$

$$RA = 1.328 \times (MBP - PGC) / RBF$$

$$RE = 1.328 \times GFR / KF \times (RBF - GFR)$$

Abbreviations here are Used to Express

FF = filtration fraction

CM = intraglomerular capillary protein concentration

TP = plasma total protein concentration

ΠGC = intraglomerular capillary osmotic pressure

PGC = intraglomerular capillary blood pressure

PT = capillary hydraulic pressure (10 mmHg)

ΔPF = effective filtration pressure

KF = ultrafiltration coefficient (0.812 (mL/sec)/mmHg)

RBF = renal blood flow, Hct: hematocrit

RA = afferent arteriole resistance

RE = efferent arteriole resistance

MBP = mean blood pressure

We assumed here that KF stayed within normal and stable ranges. There were few errors in KF due to comparison

between the same patients or between subjects with similarly decreased renal function within a short period.

RESULTS

Alterations in Clinical Data and Total Renal Function After Medication

HR significantly decreased in the cilnidipine group, on average from 85 ± 14 /min to 79 ± 15 /min. SBP also significantly decreased from 165 ± 12 mmHg to 132 ± 17 mmHg, and DBP decreased significantly from 93 ± 10 mmHg to 84 ± 10 mmHg. GFR express significant decrease from 27± 11 mL/min to 22 ± 10 mL/min. However, the other parameters changed within non-significant range. For example, ERPF increased from 105 ± 35 mL/min to 124 ± 34 mL/min, and 24UP decreased from 1.7 ± 2.5 g /day to 1.0 ± 1.1 g /day. It is a point to take attention that the non-increase of GFR in spite of ERPF increasing. This indicates that cilnidipine could improve glomerular hyperfiltration. Following the same group average comparison expressed as percentage of pretreatment measurement in the amlodipine group, statistical significance was recognized only in SBP decreasing from 155 ± 7 mmHg to 136 ± 8 mmHg. The other parameters stayed within non-significant range. 24UP non-significantly increased from 1.5 ± 2.2 g /day to 2.1 ± 3.3 g /day, and GFR and ERPF stayed in the previous level. The percentage of pretreatment measurement of 24UP decreased in cilnidipine group, but increased in the amlodipine group (Table **2**).

Comparison of Alteration Rate in Clinical Data and Renal Function Between Cilnidipine and Amlodipine Therapy

Alteration rate in HR, SBP, GFR, ERPF, and 24UP was measured over 12 months, and was compared between cilnidipine and amlodipine groups. HR was reduced 7.4 ± 8.1% by cilnidipine, and 5.8 ± 10.5% by amlodipine. SBP showed a 20.0 ± 7.6 % reduction with cilnidipine, and 12.3 ± 5.2% with amlodipine. GFR levels decreased by 19.6 ± 13.6% with cilnidipine and showed a 6.3 ± 16.6% increase by amlodipine. ERPF increased 27.0 ± 51.7% with cilnidipine and 0.8 ± 30.0% for amlodipine. 24UP decreased 6.4 ± 53.3% in the cilnidipine group while increasing 92.0 ± 192.1% in the amlodipine group. A similar level of desirable efficacy was recognized in the tested two calcium channel antagonists. Cilnidipine rather expressed a stronger drug effect on ERPF and 24UP (ERPF: 127% vs. 101%, 24UP: 94% vs. 192%) (Fig. **1**).

Alterations in Glomerular Hemodynamics After Medication

Glomerular hemodynamic parameters in a single nephron were calculated by Gomez's estimation equation. The obtained data were compared between prior to administration and after 12 months' cilnidipine treatment, and alteration rate of the above markers with cilnidipine treatment was compared to amlodipine. For cilnidipine, GFR decreased from 26.2 mL/min to 21.5 mL/min; ERPF increased from 104.9 mL/min to 123.7 mL/min, and FF decreased from 0.25 to 0.18. ΠGC decreased from 46.1 mmHg to 41.5 mmHg, in other words, the improvement of hyperfiltration. RA/RE also improved from 12.9 to 15.5. With amlodipine, on the other hand, GFR showed slight reduction from 31.4 mL/min to 31.3 mL/min, ERPF changed from 140.2 mL/min to 141.1 mL/min, FF from 0.22 to 0.21, ΠGC from 45.1 mmHg to 43.9 mmHg, and RA/RE from 10.5 to 10.8. There were no remarkable changes by amlodipine treatment in all parameters. These findings indicated that cilnidipine improved glomerular capillary hypertension and glomerular afferent/efferent arteriole resistance ratio more notably than amlodipine (Table **3**).

DISCUSSION

The authors propose that L-type and N-type calcium channel antagonist cilnidipine may improve glomerular

Table 2. Change of Clinical Parameters in Advanced CKD Patients with Cilnidipine or Amlodipine Therapy

		Cilnidipine Group		Amlodipine Group	
		Before	**After**	**Before**	**After**
n		**17**	**17**	**16**	**16**
HR	(/min)	85 ± 14	79 ± 15*	86 ± 12	80 ± 7
SBP	(mmHg)	165 ± 12	132 ± 17*	155 ± 7	136 ± 8*
DBP	(mmHg)	93 ± 10	84 ± 10*	88 ± 9	81 ± 11
24UP	(g/day)	1.7 ± 2.5	1.0 ± 1.1	1.5 ± 2.2	2.1 ± 3.3
GFR	(mL/min)	27 ± 11	22 ± 10*	31 ± 17	31 ± 22
24UV	(L/day)	1.8 ± 0.4	1.8 ± 0.5	1.8 ± 0.6	1.7 ± 0.6
ERPF	(mL/min)	105 ± 35	124 ± 34	140 ± 54	141 ± 61
24UNa	(mEq/day)	186 ± 51	172 ± 54	131 ± 45	131 ± 45
24UK	(mEq/day)	46 ± 26	32 ± 21	63 ± 44	66 ± 30

Before: value prior to treatment, After: value after treatment, Values express mean±SD, HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, 24UP: 24-hour urine protein excretion, GFR: glomerular filtration rate estimated from 24-hour creatinine clearance, ERBF: effective renal blood flow estimated from MAG3 scintigram, 24UNa: 24-hour urinary sodium excretion, 24UK: 24-hour urinary potassium excretion, *: statistically significant vs Before treatment.

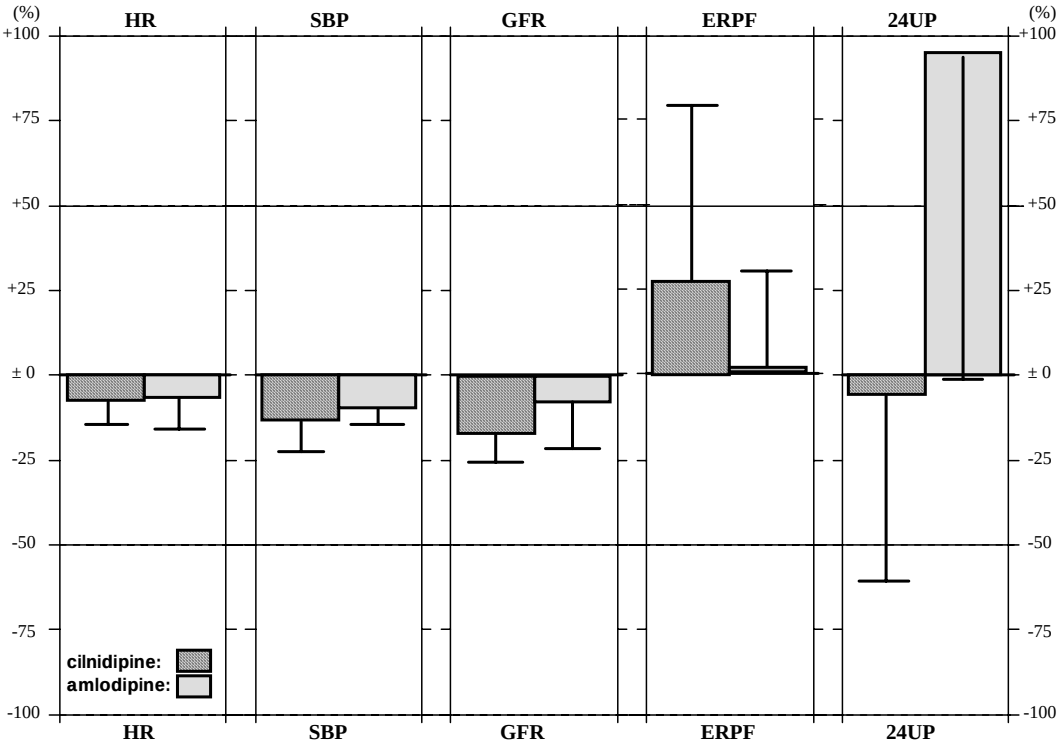

Fig. (1). Comparison of alteration rate in clinical data and renal function between cilnidipine and amlodipine therapy. Alteration rate in HR, SBP, GFR, ERPF, and 24UP was measured, and was compared in each group. A similar level of desirable efficacy was recognized in the tested two calcium channel antagonists. Cilnidipine rather expressed a stronger drug effect on ERPF and 24UP.

Table 3. Change of Renal Hemodynamics in Advanced CKD Patients with Cilnidipine or Amlodipine Therapy

		Cilnidipine Group		Amlodipine Group	
		Before	**After**	**Before**	**After**
n		**17**	**17**	**16**	**16**
GFR	(mL/min)	27 ± 11	22 ± 10	31 ± 17	31 ± 22
ERPF	(mL/min)	105 ± 35	124 ± 34	140 ± 54	141 ± 61
FF		0.25 ± 0.06	0.18 ± 0.09	0.22 ± 0.05	0.21 ± 0.06
RBF	(mL/min)	162 ± 58	187 ± 51	211 ± 98	210 ± 107
CM	(mmHg)	8.13 ± 0.81	7.43 ± 0.99	7.72 ± 0.89	7.49 ± 1.23
PGC	(mmHg)	30.67 ± 4.05	27.13 ± 4.94	28.61 ± 4.46	27.47 ± 6.15
ΠGC	(mmHg)	46.1 ± 4.5	41.5 ± 6.0	45.1 ± 5.1	43.9 ± 8.4
RA	(dyn • s • cm-7)	39392 ± 16380	27419 ± 13265	28541 ± 11744	28547 ± 20284
RE	(dyn • s • cm-7)	3233 ± 822	2244 ± 1.56	2890 ± 814	2800 ± 866
RA/RE		12.9 ± 6.5	15.5 ± 9.8	10.5 ± 5.0	10.8 ± 6.4

Before: value prior to administration, After: value after treatment, Values express mean ± SD.
GFR: glomerular filtration rate, ERPF: effective renal plasma flow, FF: filtration fraction, RBF: renal blood flow, CM: intraglomerular capillary protein concentration, PGC: intraglomerular capillary osmotic pressure, **Π**GC: intraglomerular capillary blood pressure, RA: afferent arteriole resistance, RE: efferent arteriole resistance.

hypertension and the decrease of renal blood flow. Furthermore, it is concluded that cilnidipine has a similar level of desirable efficacy as well as amlodipine, a known renoprotective L-type calcium channel blocker, in patients with advanced CKD. L-type calcium channel antagonists block the calcium channel of vascular smooth muscle cells and heart muscle cells, resulting in a decrease in systemic blood pressure. However, as shown in the first generation calcium channel antagonist, this induces reactive sympathetic nerve reflex and dilates the glomerular afferent arteriole, resulting in an increase of renal blood flow and glomerular filtration rate [7,8]. Because glomerular hypertension and glomerular hyperfiltration accelerate sclerosis over long periods of time, the safety of calcium channel antagonists in patients with advanced renal dysfunction has not been established [4,9].

Recently, long-acting L-type calcium channel blocker amlodipine was reported to have a renoprotective effect [10]. Amlodipine has been shown to increase renal blood flow without causing increase in GFR, and is expected to improve long-term prognosis. Cilnidipine has already demonstrated renoprotective effect in hypertensive animal models [18]. and similar effect was reported in human hypertensive non-CKD subjects [19,20]. In the present study, it is a unique aspect that most subjects were patients with advanced chronic renal failure due to chronic glomerulonephritis, and that hypertension is a secondary complication of primary renal disease. Renal blood flow and total glomerular filtration rate have already decreased at the start of antihypertensive drugs in spite of the increase in single nephron GFR [4,21].

We examined renal hemodynamics using Gomez's estimation equation, and suggested the benefit of calcium channel antagonists in respect to the improvement of glomerular hypertension. As Gomez's estimation equation being unsuitable for using in case of inconstant Kf, the comparison was performed between the groups of similarly decreased renal function. In this investigation, we focused on the hemodynamic benefit of calcium channel antagonists in patients known to already have advanced chronic renal failure. Therefore, the background of subjects was stable in terms of renal dysfunction due to non-hypertensive mechanisms. In considering various clinical regulations Gomez's estimation equation may be a permissible assessment.

Study results revealed that L- and N-type calcium channel antagonist cilnidipine increased renal blood flow and effective renal plasma flow, and decreased glomerular filtration rate and capillary pressure. The resistances of glomerular afferent and efferent arterioles decrease, and the resistance ratio of both arterioles also improved. Moreover, the non-significant decrease of total GFR and the improvement of filtration fraction would suggest the improvement of elevated single nephron GFR. Amlodipine, a long-acting L-type calcium channel antagonist, also made no significant worsening of hemodynamic parameters in this study, and was recognized to be renoprotective. In comparing hemodynamic parameters of both groups, cilnidipine seems to be more desirable in rate of change. The cause of difference is considered to be *via* N-type calcium channel.

In conclusion, cilnidipine improves glomerular blood flow and glomerular hypertension without worsening total renal function. Dual calcium channel antagonist is effective and safe for patients with advanced CKD as a result of improvement of glomerular capillary resistance.

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