Original Paper

Effects of L- and N-Type Ca Channel Blocker Cilnidipine on Changes in Heart Rate and QT Interval During Dialysis

Takeshi Iida^{a,b} Satoshi Morimoto^a Yoshifumi Amari^{a,b} Takashi Ando^a
Atsuhiko Ichihara^a

^aDepartment of Medicine II, Endocrinology and Hypertension, Tokyo Women's Medical University, Tokyo; ^bDepartment of Nephrology and Dialysis, Moriguchi Keijinkai Hospital, Osaka, Japan

Key Words

Cardiovascular event • Hemodialysis • Hypertension • Sudden death • Sympathetic nerve activity

Abstract

Background/Aims: Hemodialysis patients have poor prognosis due to increased prevalence of cardiovascular diseases. Treatment to suppress increases in sympathetic nerve activity and QT prolongation may have the potential to reduce the occurrence of these events. The L/N-type Calcium (Ca) channel blocker cilnidipine has unique inhibitory action to inhibit sympathetic nerve activity and in a canine model ameliorates QT prolongation. In this study, we investigated whether cilnidipine has inhibitory effects on heart rate, an index of sympathetic nerve activity, and QT prolongation in patients undergoing dialysis. **Methods:** An L-type Ca channel blocker amlodipine was administered for 4 weeks followed by cilnidipine treatment for 4 weeks. On the last day of each period, heart rate and corrected QT interval were estimated and compared between the two periods. **Results:** Cilnidipine showed greater suppression of heart rate during dialysis than did amlodipine. The corrected QT interval in one dialysis session was significantly increased, and 3 of 17 patients showed prominent QT prolongation during administration of amlodipine but not cilnidipine. **Conclusion:** These data suggested that cilnidipine may inhibit increases in heart rate and QT interval. Cilnidipine may have beneficial effects in reducing cardiovascular events, resulting from increased sympathetic nerve activity and lethal arrhythmias in hemodialysis patients.

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Introduction

Hemodialysis (HD) patients have poor prognosis due to increased prevalence of cardiovascular diseases [1, 2]. The United States Renal Data System showed that sudden death/cardiac arrhythmias accounted for 37% of deaths in patients with end-stage renal disease [3]. Sudden death accounted for 21% of deaths in HD patients in the Dialysis Outcomes and Practice Patterns Study [4]. It has been reported that sudden death is the most common cause in cardiac-derived death [5]. Sympathetic activation is observed during HD sessions [6, 7] and may cause cardiovascular events [8], including sudden death. In addition, arrhythmia is the most common cause for sudden cardiac death [9]. QT prolongation is one of the most important causes of fatal arrhythmias and is frequently observed after HD sessions [10, 11]. Therefore, it is considered that treatment to suppress increases in cardiac sympathetic nerve activity (SNA) and QT prolongation may have the potential to reduce the occurrence of these events. Hypertension in patients with end-stage renal disease on chronic dialysis is a common occurrence [12, 13], and calcium (Ca) channel blockers are used in many dialysis patients. The L/N-type Ca channel blocker cilnidipine has unique inhibitory action on the sympathetic N-type Ca channels, in addition to the traditional inhibitory action of L-type Ca channels [3, 14-16]. Cilnidipine suppresses the overactivity of the cardiac sympathetic system in hypertensive patients more effectively than does amlodipine [17]. Cilnidipine also inhibits the renin-angiotensin system and aldosterone secretion from adrenocortical cells [18], and decreases proteinuria/albuminuria [19]. Interestingly, cilnidipine ameliorated ventricular electrical remodeling, which causes QT prolongation, in a canine hypertrophied heart model [20]. A case report described an HD patient in whom cilnidipine ameliorated the QT prolongation induced by HD [21]. Cilnidipine may have beneficial effects in dialysis patients; however, this hypothesis has not been tested. Therefore, in this study, we investigated whether cilnidipine has inhibitory effects on heart rate (HR), a marker of SNA [22], and QT prolongation in patients undergoing dialysis.

Materials and Methods

Patients

The study was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines, and was approved by the ethical committee of Moriguchi Keijinkai Hospital (approval no.: 2807). All participants were enrolled after providing written informed consent. The participants were outpatients on maintenance dialysis at Kadoma Keijinkai Clinic in Kadoma City and Moriguchi Keijinkai Clinic in Moriguchi City, Osaka, Japan. Patients were selected from those who were undergoing regular dialysis treatment for at least 6 months and were hemodynamically stable during dialysis. Patients with a history of stroke or cardiac infarction within 6 months before study initiation and those with atrial fibrillation were excluded. The enrollment period was from September 2014 to January 2015. During this study, additional treatment or changes in the doses of antihypertensive drugs and changes in the blood purification modality and target dry weight were essentially prohibited.

Background factors

At enrollment, information was collected on age, sex, body mass index (BMI), dialysis history, diabetes mellitus, HD or hemodiafiltration, and antihypertensive drugs administered. Post-dialysis values of the cardiothoracic ratio were obtained on the first dialysis day of the week.

Blood purification

Patients were treated thrice weekly with standard HD or on-line hemodiafiltration using the NCV-2 dialysis device (Nipro, Osaka, Japan) and Lympack TA1 dialysate (Na⁺ 138 mmol/L, K⁺ 2.0 mmol/L, Ca²⁺ 2.5 mmol/L, Mg²⁺ 1.0 mmol/L, Cl⁻ 110 mmol/L, HCO₃⁻ 28 mmol/L, CH₃COO⁻ 8 mmol/L; Nipro) with one dialysis session lasting 3–4 h.

Fig. 1. Study protocol.

Blood pressure and heart rate

Blood pressure (BP) was measured from just before initiation to just after termination of dialysis once or twice per hour in the supine position using a BP recording device that was a part of the dialysis equipment. HR was analyzed with the data obtained with a Holter electrocardiography device (FM-150, Fukuda Denshi, Tokyo, Japan) using SCM-8000 software (Fukuda Denshi). One dialysis session was divided into four periods (periods 1, 2, 3, and 4), and the mean values for each period were calculated.

Blood examinations

Non-fasting blood samples were taken while patients were lying in bed in the supine position after at least 5 min of rest on the first dialysis day of the week. Pre-dialysis values of blood urea nitrogen (BUN), creatinine, uric acid, albumin, Ca, inorganic phosphorus, magnesium, intact parathyroid hormone, sodium (Na), potassium (K), chloride (Cl), total cholesterol, high-density lipoprotein cholesterol, blood sugar, hemoglobin A1c, glycated albumin, brain natriuretic peptide, and post-dialysis values of BUN, creatinine, albumin, Ca, Na, K, and Cl were measured by conventional methods at an external testing laboratory (BML, Inc., Tokyo, Japan). Albumin-corrected Ca (C-Ca) was calculated using the following formula: $C-Ca = Ca + (4 - \text{albumin})$.

Electrocardiogram

Electrocardiograms were recorded just before initiation and just after termination of dialysis (FCP-7431, Fukuda Denshi). QTc was calculated automatically by Bazett's formula [10]:

$$QTc (s) = \text{mean QT interval (s)} / \sqrt{\text{mean RR interval (s)}}$$

Echocardiography

Echocardiography was performed on a non-dialysis day as previously described [23] (Vivid S6 System, GE Healthcare, Milwaukee, WI), and the following indices of cardiac function were estimated: left ventricular ejection fraction (a marker of contractile activity) and left ventricular mass index (a marker of cardiac hypertrophy).

Study protocol

This study was conducted prospectively. An L-type Ca channel blocker amlodipine (5–10 mg/day) was orally administered for 4 weeks (A period; Fig. 1). On the last day of the A period, which was the first dialysis day of the week, blood tests, chest X-ray, measurements of BP and HR, and electrocardiography were performed. Subsequently, cilnidipine was administered for 4 weeks instead of amlodipine (C period). On the last day of the C period, which was also the first dialysis day of the week, the same examinations described above were repeated. The dose of cilnidipine was set to be double that of amlodipine to achieve equal BP reductions between the two groups (e.g., 5 mg of amlodipine was replaced with 10 mg of cilnidipine) [24, 25].

Statistical analysis

Data are expressed as mean $\pm$ standard deviation. Statistical comparisons of data between the A and C periods and between each period of one dialysis session were performed by paired *t*-test or repeated analysis of variance. A *P* value of < 0.05 was considered statistically significant. All analyses were performed using Microsoft Excel 2016 (Microsoft Corp., Redmond, WA).

Results

Patient characteristics

Seventeen patients were enrolled in the study. Table 1 shows details of the following background factors: age, sex, BMI, dialysis history, diabetes mellitus, methods of blood purification, antihypertensive drugs, BP, HR, laboratory data, cardiothoracic ratio, QTc interval, and echocardiography data. The dosage of amlodipine administered was 6.5 ± 2.3 mg/day and that of cilnidipine was 12.9 ± 4.7 mg/day. Other antihypertensive drugs were not changed in any of the patients, and the blood purification modality was also not changed in all patients. Body weight changed in some patients but did not differ significantly between the A (54.6 ± 9.5 kg) and C (54.6 ± 9.6 kg) periods in the group data.

Blood pressure during dialysis

Systolic BP was significantly higher in the C period than in the A period at the *start* time (A period vs. C period, 146 ± 23 mmHg vs. 164 ± 22 mmHg, $P < 0.01$) and at period 3 (143 ± 24 mmHg vs. 158 ± 23 mmHg, $P < 0.01$) of dialysis sessions (Fig. 2). Systolic BP did not change significantly during any dialysis session in both the A and C periods. Systolic BP over a whole dialysis session was significantly higher during the C period than during the A period. Diastolic BP did not change significantly during the dialysis sessions in both the A and C periods, and diastolic BP over a whole dialysis session did not differ significantly between the two groups (Fig. 2).

Table 2. Number of cases showing QTc prolongation over 40 ms and under 40 ms after dialysis. QTc, corrected QT; A, amlodipine; C, cilnidipine

	over 40 ms	under 40 ms
A period	3	14
C period	0	17

Table 1. Characteristics of the study subjects
ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker. C-Ca, albumin-corrected calcium; IP, inorganic phosphorus; Intact PTH, intact-parathyroid hormone; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index. QTc, corrected QT interval; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker

Number of patients	17
Age (y. o.)	71 $\pm$ 11
Gender (Male/Female)	13/4
Body mass index (kg/m ²)	22.7 $\pm$ 4.3
Dialysis history (years)	3.8 $\pm$ 2.8
Diabetes mellitus (yes/no)	7/10
Hemodialysis / Hemodiafiltration	13/4
Antihypertensive drug (except for Ca blockers)	
ACE-I/ARB	15
α blocker	1
β blocker	1
diuretic	2
Systolic blood pressure (mmHg)	147 $\pm$ 22
Diastolic blood pressure (mmHg)	73 $\pm$ 10
Heart rate (/min)	69 $\pm$ 11
Laboratory study	
Blood urea nitrogen (mg/dl)	52.4 $\pm$ 10.5
Creatinine (mg/dl)	9.80 $\pm$ 2.62
Uric acid (mg/dl)	6.6 $\pm$ 1.0
Albumin (g/dl)	3.5 $\pm$ 0.3
C-Ca (mg/dl)	9.1 $\pm$ 0.5
IP (mg/dl)	4.9 $\pm$ 0.8
Mg (mg/dl)	2.4 $\pm$ 0.1
Intact PTH (pg/dl)	152 $\pm$ 77
Na (mEq/l)	139 $\pm$ 2
K (mEq/l)	4.5 $\pm$ 0.7
Cl (mEq/l)	103 $\pm$ 3
Total cholesterol (mg/dl)	160 $\pm$ 32
High-density lipoprotein cholesterol (mg/dl)	45 $\pm$ 16
Blood sugar (mg/dl)	125 $\pm$ 58
Hemoglobin A1c (%)	5.4 $\pm$ 0.7
Glycated albumin (%)	17.9 $\pm$ 2.4
Brain natriuretic peptide (pg/ml)	490 $\pm$ 425
Cardiothoracic ratio (%)	43.7 $\pm$ 16.8
QTc interval (ms)	439 $\pm$ 28
Echocardiogram	
LVEF (%)	63.9 $\pm$ 6.9
LVMI (g/m ²)	138 $\pm$ 23

Fig. 2. Comparison of blood pressure during a dialysis session between the A and C periods. * $P < 0.05$ compared with the A period. sBP, systolic blood pressure; dBP, diastolic blood pressure; A, amlodipine; C, cilnidipine.

Heart rate during dialysis

HR was not significantly different at the start time between the A and C periods (Fig. 3). HR showed a slight but insignificant tendency to be increased during dialysis in the A period. In contrast, HR showed slight, insignificant decreases at periods 1 and 2 in the C period. As a result, HR was significantly lower in the C period than in the A period at period 1 (A period vs. C period, 68 ± 10 vs. 66 ± 9 /min, $P < 0.05$) and at period 2 (69 ± 9 /min vs. 66 ± 9 /min, $P < 0.01$; Fig. 3). The average HR during the dialysis session was significantly lower in the C period than in the A period (70 ± 9 /min vs. 67 ± 10 /min, $P < 0.05$).

Table 3. Laboratory data before and after dialysis

A, amlodipine-period; C-period, Cilnidipine-period; C-Ca, albumin-corrected calcium				
	A period		C period	
	before	after	before	after
Blood urea nitrogen (mg/dl)	52.4±10.5	16.1±5.6	54.3±16.6	17.3±8.4
Creatinine (mg/dl)	9.80±2.62	3.45±1.03	9.80±2.76	3.55±1.19
Albumin (g/dl)	3.5±0.3	3.8±0.4	3.5±0.3	3.8±0.4
C-Ca (mg/dl)	9.1±0.5	9.0±0.3	9.0±0.4	9.0±0.5
Na (mEq/l)	139±2	140±1	139±4	140±1
K (mEq/l)	4.5±0.7	3.2±0.4	4.5±0.7	3.3±0.3
Cl (mEq/l)	103±3	101±1	103±3	101±2

Fig. 3. Comparison of heart rate during a dialysis session between the A and C periods. * $P < 0.05$ compared with the A period and ** $P < 0.05$ compared with the start time of a dialysis session. A, amlodipine; C, cilnidipine.

QTc interval

No patients showed arrhythmia to enable estimations of QT interval while recording the electrocardiogram before and after dialysis. QTc interval was not significantly different before starting dialysis between the two periods, and it significantly increased following dialysis (439 ± 28 ms before dialysis to 456 ± 43 ms after dialysis, $P < 0.05$) during the A period, while it was not significantly changed (451 ± 40 ms to 456 ± 42 ms) during the C period (Fig. 4). In addition, 3 patients showed prominent QTc prolongation of > 40 s by dialysis during the A period (450 ms to 541 ms in patient 1, 446 ms to 500 ms in patient 2, 443 ms to 492 ms in patient 3); however, such prominent QTc prolongation was not observed during the C period in these 3 patients (Table 2).

Fig. 4. Comparison of corrected QT interval before and after dialysis during the A and C periods. * $P < 0.05$ compared with the A period. A, amlodipine; C, cilnidipine.

Laboratory data

There were no significant differences in laboratory data such as BUN, creatinine, albumin, Ca, Na, K, and Cl before and after dialysis between the A and C periods (Table 3). Changes in serum C-Ca (A period, -0.1 ± 0.4 mg/dL; C period, 0.0 ± 0.3 mg/dL) and K (A period, -1.3 ± 0.5 mEq/L; C period, -1.2 ± 0.2 mEq/L), which are thought to affect QTc interval, did not differ significantly between the A and C periods.

Discussion

This study demonstrated four major findings regarding the effects of the L/N-type Ca channel blocker cilnidipine in patients undergoing dialysis. First, cilnidipine showed greater suppression of HR during dialysis than did the L-type Ca channel blocker amlodipine. Second, the use of amlodipine but not cilnidipine showed significant increases in the QTc interval during one dialysis session; 3 of 17 patients showed a prominent prolongation of the QTc interval (> 40 ms) during the A period but not the C period. Third, changes in serum levels of Ca and K did not differ between the A and C periods. All these data suggest that cilnidipine can inhibit increases in HR and QTc interval independent of changes in electrolytes caused by dialysis.

Effects of cilnidipine on heart rate

Increased HR is an important risk factor for cardiovascular death in hypertensive patients [26]. In the general Japanese population, increased HR is a risk factor for increased mortality [27]. HR is significantly positively correlated with indices of SNA, such as plasma norepinephrine and muscle SNA, suggesting that it can be used as a marker of sympathetic activity [22]. SNA triggers the onset of cardiovascular diseases through platelet activation, increased cardiac oxygen consumption, tachycardia, increased oxidative stress, and activation of the renin-angiotensin system [28]. SNA is increased during HD sessions [6]. In the present study, although HR did not differ significantly between the two groups at the start time of dialysis, it showed significantly greater decreases in the first half (periods 1 and 2) of the dialysis session in the C period compared with the A period (Fig. 3), indicating that

cilnidipine may have an inhibitory effect on SNA, especially during dialysis sessions. Systolic BP values during dialysis sessions were significantly higher in the C period than in the A period (Fig. 2). Because antihypertensive treatment in general causes reflex tachycardia [29], it stands to reason that the difference in HR between the A and C periods was due to the difference in the extent of reflex tachycardia caused by these drugs. However, there are a couple of points that do not support this presumption. First, HR did not differ significantly between the two periods at the *start* time of dialysis and was significantly lower in the first half of the dialysis (Fig. 3). Second, although systolic BP at the *start* time was significantly lower in the A period than in the C period, the difference was not apparent in the first half of the dialysis session between the A and C periods (Fig. 2). Thus, we consider it unlikely that lower HR in the C period was due to reduced reflex tachycardia caused by cilnidipine.

Effects of cilnidipine on QT interval

QT interval is a predictor of the risk of both coronary events and cardiovascular death after adjusting for the effects of additional risk factors in hypertension [30, 31]. QT intervals in HD patients are longer than those in the general population, and 65% of these patients show longer QT intervals [32]. QT intervals after dialysis sessions are longer than before dialysis sessions [10, 11]. Moreover, changes in QT intervals depend on the concentrations of Ca and K in the dialysis bath [33]. In HD patients, QT prolongation is considered to be a risk factor for sudden cardiac death [33]. Sudden deaths in HD patients are frequently observed in the 12-h period after starting a dialysis session and in the 12-h period at the end of the dialysis-free weekend interval [23]. QT prolongation due to lowered serum Ca and K levels after dialysis may be one of the main causes of sudden death in the 12-h period after starting with a dialysis session. In previous reports, patients who experienced sudden cardiac arrest were significantly more likely to have been exposed to low-Ca dialysate of < 2.5 mEq/L and K dialysate of < 2 mEq/L [34, 35]. In the present study, administration of cilnidipine for 4 weeks inhibited QT prolongation induced by dialysis. This finding is consistent with a previous report showing that cilnidipine shortened QT interval in the hypertrophied canine heart [20]. The authors speculated that the reversal of electrical remodeling by cilnidipine may be, at least in part, associated with the mechanism of this phenomenon, although their speculation remains to be verified [20]. Future studies are required to determine the precise mechanism by which cilnidipine inhibits QT prolongation.

Limitations

Several limitations of the present study warrant mention. First, this study involved a small number of patients. Second, a crossover trial, where cilnidipine treatment for 4 weeks was changed to amlodipine treatment for 4 weeks was not conducted. Third, the precise mechanism by which cilnidipine inhibits QT prolongation remains undetermined as described above. Larger-scale crossover or randomized controlled studies investigating the mechanism by which cilnidipine inhibits QT prolongation are required.

Conclusion

In this study, cilnidipine showed greater suppression of HR during dialysis than did amlodipine. Amlodipine but not cilnidipine significantly increased the QTc interval during one dialysis session, and 3 of 17 patients showed prominent prolongation of QTc during treatment with amlodipine but not with cilnidipine. Changes in serum levels of Ca and K did not differ between the A and C periods. In sum, these data suggest that cilnidipine could inhibit increases in HR and QTc interval independent of changes in electrolytes caused by dialysis. It is possible that cilnidipine has beneficial effects in reducing the occurrence of cardiovascular events, including sudden death resulting from increased SNA and lethal arrhythmias. Future studies investigating the prognostic value of cilnidipine in dialysis patients are needed to address this issue.

Disclosure Statement

The authors have nothing to disclose.

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References

- 1 Levey AS, Beto JA, Coronado BE, Eknoyan G, Foley RN, Kasiske BL, Klag MJ, Mailloux LU, Manske CL, Meyer KB, Parfrey PS, Pfeffer MA, Wenger NK, Wilson PW, Wright JT, Jr.: Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. *Am J Kidney Dis* 1998;32: 853-906.
- 2 Tong J, Liu M, Li H, Luo Z, Zhong X, Huang J, Liu R, He F, Fu J: Mortality and Associated Risk Factors in Dialysis Patients with Cardiovascular Disease. *Kidney Blood Press Res* 2016;41:479-487.
- 3 Saran R, Li Y, Robinson B, Abbott KC, Agodoa LY, Ayanian J, Bragg-Gresham J, Balkrishnan R, Chen JL, Cope E, Eggers PW, Gillen D, Gipson D, Hailpern SM, Hall YN, He K, Herman W, Heung M, Hirth RA, Hutton D, Jacobsen SJ, Kalantar-Zadeh K, Kovesdy CP, Lu Y, Molnar MZ, Morgenstern H, Nallamothu B, Nguyen DV, O'Hare AM, Plattner B, Pisoni R, Port FK, Rao P, Rhee CM, Sakhuja A, Schaubel DE, Selewski DT, Shahinian V, Sim JJ, Song P, Streja E, Kurella Tamura M, Tentori F, White S, Woodside K, Hirth RA: US Renal Data System 2015 Annual Data Report: Epidemiology of Kidney Disease in the United States. *Am J Kidney Dis* 2016;67:Svii, S1-305.
- 4 Jadoul M, Thumma J, Fuller DS, Tentori F, Li Y, Morgenstern H, Mendelssohn D, Tomo T, Ethier J, Port F, Robinson BM: Modifiable practices associated with sudden death among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. *Clin J Am Soc Nephrol* 2012;7:765-774.
- 5 Moroi M, Tamaki N, Nishimura M, Haze K, Nishimura T, Kusano E, Akiba T, Sugimoto T, Hase H, Hara K, Nakata T, Kumita S, Nagai Y, Hashimoto A, Momose M, Miyakoda K, Hasebe N, Kikuchi K: Association between abnormal myocardial fatty acid metabolism and cardiac-derived death among patients undergoing hemodialysis: results from a cohort study in Japan. *Am J Kidney Dis* 2013;61:466-475.
- 6 Converse RL, Jr, Jacobsen TN, Jost CM, Toto RD, Grayburn PA, Obregon TM, Fouad-Tarazi F, Victor RG: Paradoxical withdrawal of reflex vasoconstriction as a cause of hemodialysis-induced hypotension. *J Clin Invest* 1992;90:1657-1665.
- 7 Huang JC, Kuo IC, Tsai YC, Lee JJ, Lim LM, Chen SC, Chiu YW, Chang JM, aChen HH: Heart Rate Variability Predicts Major Adverse Cardiovascular Events and Hospitalization in Maintenance Hemodialysis Patients. *Kidney Blood Press Res* 2017;42:76-88.
- 8 Jimenez ZN, Silva BC, Reis LD, Castro MC, Ramos CD, Costa-Hong V, Bortolotto LA, Consolim-Colombo F, Dominguez WV, Oliveira IB, Moyses RM, Elias RM: High Dialysate Calcium Concentration May Cause More Sympathetic Stimulus During Hemodialysis. *Kidney Blood Press Res* 2016;41:978-985.
- 9 Paoletti E, Specchia C, Di Maio G, Bellino D, Damasio B, Cassottana P, Cannella G: The worsening of left ventricular hypertrophy is the strongest predictor of sudden cardiac death in haemodialysis patients: a 10 year survey. *Nephrol Dial Transplant* 2004;19:1829-1834.
- 10 Malhis M, Al-Bitar S, Farhood S, Zaiat KA: Changes in QT intervals in patients with end-stage renal disease before and after hemodialysis. *Saudi J Kidney Dis Transpl* 2010;21:460-465.
- 11 Khosoosi Niaki MR, Saravi M, Oliaee F, Akbari R, Noorkhomami S, Bozorgi Rad SH, Fallahpoor K, Ramezani MS: Changes in QT interval before and after hemodialysis. *Caspian J Intern Med* 2013;4:590-594.
- 12 Georgianos PI, Agarwal R: Blood Pressure and Mortality in Long-Term Hemodialysis-Time to Move Forward. *Am J Hypertens* 2017;30:211-222.
- 13 Elias MF, Crichton GE, Abhayaratna WP: Interactions between plasma homocysteine and arterial stiffness in chronic kidney disease in community-dwelling individuals: The Maine-Syracuse Study. *J Hum Hypertens* 2015;29:726-731.

- 14 Oike M, Inoue Y, Kitamura K, Kuriyama H: Dual action of FRC8653, a novel dihydropyridine derivative, on the Ba²⁺ current recorded from the rabbit basilar artery. *Circ Res* 1990;67:993-1006.
- 15 Morimoto S, Takeda K, Oguni A, Kido H, Harada S, Moriguchi J, Itoh H, Nakata T, Sasaki S, and Nakagawa M: Reduction of white coat effect by cilnidipine in essential hypertension. *Am J Hypertens* 2001;14:1053-1057.
- 16 Grassi G: Sympathomodulatory Effects of Antihypertensive Drug Treatment. *Am J Hypertens* 2016;29:665-675.
- 17 Sakata K, Shirotani M, Yoshida H, Nawada R, Obayashi K, Togi K, Miho N: Effects of amlodipine and cilnidipine on cardiac sympathetic nervous system and neurohormonal status in essential hypertension. *Hypertension* 1999;33:1447-1452.
- 18 Konda T, Enomoto A, Aritomi S, Niinuma K, Koganei H, Ogawa T, Nitta K: Different effects of L/N-type and L-type calcium channel blockers on the renin-angiotensin-aldosterone system in SHR/Izm. *Am J Nephrol* 2009;30:155-61.
- 19 Robles NR, Fici F, Grassi G: Dihydropyridine calcium channel blockers and renal disease. *Hypertens Res* 2017;40:21-28.
- 20 Takahara A, Nakamura Y, Wagatsuma H, Aritomi S, Nakayama A, Satoh Y, Akie Y, Sugiyama A: Long-term blockade of L/N-type Ca²⁺ channels by cilnidipine ameliorates repolarization abnormality of the canine hypertrophied heart. *Br J Pharmacol* 2009;158:1366-1374.
- 21 Cao X, Nakamura Y, Wada T, Izumi-Nakaseko H, Ando K, Sugiyama A: L/N-type Ca²⁺ channels blocker cilnidipine ameliorated the repolarization abnormality in a chronic hemodialysis patient. *Heart Vessels* 2016;32:105-108.
- 22 Grassi G, Vailati S, Bertinieri G, Seravalle G, Stella ML, Dell'Oro R, Mancia G: Heart rate as marker of sympathetic activity. *J Hypertens* 1998;16:1635-1639.
- 23 Bleyer AJ, Hartman J, Brannon PC, Reeves-Daniel A, Satko SG, Russell G: Characteristics of sudden death in hemodialysis patients. *Kidney Int* 2006;69:2268-2273.
- 24 Morimoto S, Yano Y, Maki K, Iwasaka T: Renal and vascular protective effects of cilnidipine in patients with essential hypertension. *J Hypertens* 2007;25:2178-2183.
- 25 Konoshita T, Makino Y, Kimura T, Fujii M, Wakahara S, Arakawa K, Inoki I, Nakamura H, Miyamori I: A new-generation N/L-type calcium channel blocker leads to less activation of the renin-angiotensin system compared with conventional L type calcium channel blocker. *J Hypertens* 2010;28:2156-2160.
- 26 Kannel WB, Kannel C, Paffenbarger RS, Jr, Cupples LA: Heart rate and cardiovascular mortality: the Framingham Study. *Am Heart J* 1987;113:1489-1494.
- 27 Fujiura Y, Adachi H, Tsuruta M, Jacobs DR, Jr, Hirai Y, Imaizumi T: Heart rate and mortality in a Japanese general population: an 18-year follow-up study. *J Clin Epidemiol* 2001;54:495-500.
- 28 Takahara A: Cilnidipine: a new generation Ca channel blocker with inhibitory action on sympathetic neurotransmitter release. *Cardiovasc Ther* 2009;27:124-139.
- 29 Thamcharoen N, Susantitaphong P, Wongrakpanich S, Chongsathidkiet P, Tantrachoti P, Pitukweerakul S, Avihingsanon Y, Praditpornsilpa K, Jaber BL, Eiam-Ong S: Effect of N- and T-type calcium channel blocker on proteinuria, blood pressure and kidney function in hypertensive patients: a meta-analysis. *Hypertens Res* 2015;38:847-855.
- 30 Klimas J, Kruzliak P, Rabkin SW: Modulation of the QT interval duration in hypertension with antihypertensive treatment. *Hypertens Res* 2015;38:447-454.
- 31 Coats A, Jain S: Protective effects of nebivolol from oxidative stress to prevent hypertension-related target organ damage. *J Hum Hypertens* 2017;31:376-381.
- 32 Nie Y, Zou J, Liang Y, Shen B, Liu Z, Cao X, Chen X, Ding X: Electrocardiographic Abnormalities and QTc Interval in Patients Undergoing Hemodialysis. *PLoS One* 2016;11:e0155445.
- 33 Genovesi S, Dossi C, Vigano MR, Galbiati E, Prolo F, Stella A, Stramba-Badiale M: Electrolyte concentration during haemodialysis and QT interval prolongation in uraemic patients. *Europace* 2008;10:771-777.
- 34 Pun PH, Lehigh RW, Honeycutt EF, Herzog CA, Middleton JP: Modifiable risk factors associated with sudden cardiac arrest within hemodialysis clinics. *Kidney Int* 2011;79:218-227.
- 35 Pun PH, Horton JR, Middleton JP: Dialysate calcium concentration and the risk of sudden cardiac arrest in hemodialysis patients. *Clin J Am Soc Nephrol* 2013;8:797-803.